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HEV and transfusion-recipient risk

VHE et risque receveur

J. Izopet [a,b,*], S. Lhomme [a,b], S. Chapuy-Regaud [a,b], J.-M. Mansuy [a], N. Kamar [b,c], F. Abravanel [a,b]

[a] *Department of virology, National reference center for hepatitis E virus, CHU Purpan, IFB, 330, avenue de Grande-Bretagne, TSA 40031, 31059 Toulouse, France*
[b] *Inserm UMR 1043/CNRS UMR 5282, CPTP, center for pathophysiology of toulouse-Purpan, Toulouse university Paul-Sabatier, 31024 Toulouse, France*
[c] *Department of nephrology and organ transplantation, CHU Rangueil, 31059 Toulouse, France*

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Abstract

HEV infections are mainly food- and water-borne but transfusion-transmission has occurred in both developing and developed countries. The infection is usually asymptomatic but it can lead to fulminant hepatitis in patients with underlying liver disease and pregnant women living in developing countries. It also causes chronic hepatitis E, with progressive fibrosis and cirrhosis, in approximately 60% of immunocompromised patients infected with HEV genotype 3. The risk of a transfusion-transmitted HEV infection is linked to the frequency of viremia in blood donors, the donor virus load and the volume of plasma in the final transfused blood component. Several developed countries have adopted measures to improve blood safety based on the epidemiology of HEV.

Keywords: HEV; Transfusion; Genotype 3; Blood donors; Blood safety

Résumé

Le VHE est transmis principalement par voie alimentaire et hydrique. Des cas de transmission par transfusion ont cependant été décrits aussi bien dans les pays en développement que dans les pays industrialisés. L'infection est habituellement asymptomatique mais des hépatites fulminantes peuvent survenir chez des patients ayant une hépatopathie chronique sous-jacente et chez la femme enceinte dans les pays en développement. Chez les patients immunodéprimés, l'infection par le VHE de génotype 3 conduit dans environ 60 % des cas à une hépatite chronique avec fibrose progressive et cirrhose. Le risque de transmission du VHE par transfusion est influencé par la fréquence de la virémie chez les donneurs de sang, la charge virale du donneur infecté et le volume de plasma résiduel dans le produit transfusé. Plusieurs pays industrialisés ont adopté des mesures visant à améliorer la sécurité transfusionnelle en fonction de l'épidémiologie du VHE.

Mots clés : VHE ; Transfusion ; Génotype 3 ; Donneurs de sang ; Sécurité transfusionnelle

Hepatitis E virus (HEV), the causal agent of hepatitis E, is mainly transmitted by the fecal-oral route but parenteral transmission from blood and its components has been reported in both developing and developed countries. All four major HEV genotypes have been involved. HEV-1 and -2 are found only in humans and predominant in Asia, Africa and Central America where transmission is mainly due to the consumption of food or water contaminated with human fecal material. Transfusion-transmission has also been reported in these countries where HEV is endemic [1,2]. HEV-3 and -4 are zoonotic and predominant in developed countries. The large animal reservoir of these strains, including pigs, wild-boar, deer and rabbits, ensures that transmission occurs mainly through the consumption of uncooked or undercooked contaminated pork and game.

* Corresponding author. Department of virology, National reference center for hepatitis E virus, CHU Purpan, IFB, 330, avenue de Grande-Bretagne, TSA 40031, 31059 Toulouse, France.
E-mail address: izopet.j@chu-toulouse.fr (J. Izopet).

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HEV infections can also be due to eating other food products, including shellfish, fruits and vegetables that have been contaminated by pig effluent or irrigation water. Lastly, HEV-3 and -4 can be transmitted by direct contact with infected animals. Transfusion-transmission has been reported in Japan (HEV-3 and HEV-4) [3–5] and in several European countries (HEV-3) including France [6–10], the UK [11,12], Germany [13], and Spain [14].

In this context, the transfusion-recipient risk as well as measures taken by developed countries to improve blood safety require particular attention.

1. Characteristics of HEV

HEV is a small RNA virus with an icosahedral capsid. There are two forms of fully infectious particles. One form of virion is shed in the feces. These unenveloped particles are 27 to 34 nm in diameter, and have a density of 1.22 g/cm^3 on iodixanol gradients. The second form, virions circulating in the blood, are cloaked in host cell membranes; their size is around 50 nm and their density is 1.08 g/cm^3. The host-derived membranes protect the virus from neutralizing antibodies and may play an important role in cell tropism [15].

The HEV genome is a single-strand, positive-sense RNA approximately 7.2 kb long. It has a short 5′ noncoding region that is capped with 7-methyl-guanosine, three open reading frames (ORFs), ORF1, ORF2, and ORF3, and a short 3′ noncoding region that ends in a poly-(A) tail. ORF1 encodes a nonstructural protein about 1700 amino acids long that is involved in HEV RNA replication. ORF2 encodes the 660 amino acid virus capsid protein. Immunological and structural studies of this protein have contributed to the development of a hepatitis E vaccine. ORF3 encodes a small protein, 113 residues in HEV-3 and 114 residues in HEV-1, -2, and -4, that is essential for virus egress.

HEV is a member of the *Hepeviridae*, a family that consists of two genera, *Orthohepevirus* and *Piscihepevirus*. Only one HEV serotype is recognized. The genus *Orthohepevirus* contains three species that infect mammals (*Orthohepevirus* A, C and D), and one that infects birds (*Orthohepevirus* B). The *Orthohepevirus* A species, which includes strains that infect humans, contains seven genotypes (HEV-1 to HEV-7). Despite the lack of robust criteria, subgenotypes have been identified within the four major HEV genotypes (5 for HEV-1, 2 for HEV-2, 10 for HEV-3, and 7 for HEV-4). Complete reference genome sequences are available to facilitate genotyping and molecular epidemiology studies [16].

2. Virological tools

HEV infections can be diagnosed indirectly by detecting anti-HEV antibodies in the serum or directly by detecting HEV RNA or capsid antigen in the blood or other body fluids. An initial incubation period of 2 to 6 weeks usually precedes the IgM response, which is detected around the time the alanine aminotransferase activity increases, and persists for 6–9 months. The IgG response can be delayed; it persists for several years although the exact duration of this response remains uncertain. HEV RNA becomes detectable in the blood and stools during the incubation period and persists for around 4 (blood) and 6 weeks (feces). Capsid antigen persists in the blood for about the same time.

2.1. Serology

Both conventional microplate and rapid immunochromatographic commercial assays have been developed. The presence of anti-HEV IgM in the serum is a key marker of an acute infection while the presence of anti-HEV IgG alone indicates a past infection. The limits of detection of commercial anti-HEV IgG assays vary from 0.25 WHO units/mL to 2.5 WHO units/mL. The use of a specific, sensitive assay (detection limit: 0.25 WHO unit/mL) provides a clear picture of HEV epidemiology.

2.2. Viral RNA detection and characterization

HEV RNA can be detected and quantified in the blood, stools, and other body compartments using nucleic acid amplification technologies with primers targeting regions of the genome that are conserved between HEV genotypes. Most real-time PCR assays, including commercial assays, target ORF3. A transcription-mediated amplification (TMA) assay performed on a fully automated platform is well adapted for high throughput testing. Conversely, loop-mediated isothermal amplification (LAMP) assays provide a one-step, single-tube, amplification of HEV RNA without any special equipment. The assays based on nucleic acid amplification must all be validated using the WHO international reference panel for HEV RNA genotypes. The limit of detection of current assays is 7 to 80 IU/mL. This feature is relevant not only for diagnosis but also for defining an optimal strategy for blood screening. HEV RNA can be characterized by sequencing different regions of the HEV genome such as ORF2 or OFR1. This can then be used to determine the HEV genotype/subgenotype and for tracing the source of infection using phylogenetic analyses and an appropriate panel of HEV sequences.

2.3. Antigen detection

HEV infections can be diagnosed by detecting the HEV capsid antigen using a commercial sandwich EIA. One study found that the specificity was excellent but the lowest HEV RNA concentration detected was 800 to 80,000 IU/mL using serial dilutions [17]. Although HEV RNA testing is the gold standard, testing for HEV capsid antigen is technically simpler and less expensive.

3. HEV markers in blood donors

HEV seroprevalence and HEV viremia in blood donors in industrialized countries have turned out to be higher than expected, indicating that zoonotic HEV infections are very common in the general population. A single sensitive validated IgG assay was used to test samples from blood donors living in