Hepatology Snapshot

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Hepatitis E virus infection: Multiple faces of an underestimated problem

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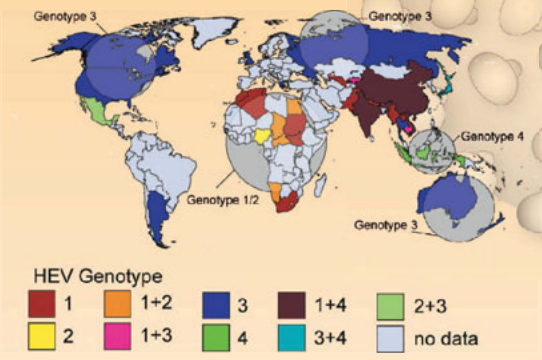
Key facts

- HEV is a relevant clinical problem also in industrialized countries
- In addition to waterborne infections, zoonotic and blood-borne transmissions of HEV occur, HEV may cause chronic infections in immunocompromised patients and can be associated with extrahepatic symptoms
- Antiviral therapies against HEV are available and a prophylactic vaccine has been developed

HEV basics

- Spherical positive-stranded RNA virus
- Hepevirus within the family of *Hepeviridae*
- One serotype but 5 different genotypes (1-4 humopathogenic)
- Thermal stability: 70 °C

Epidemiology

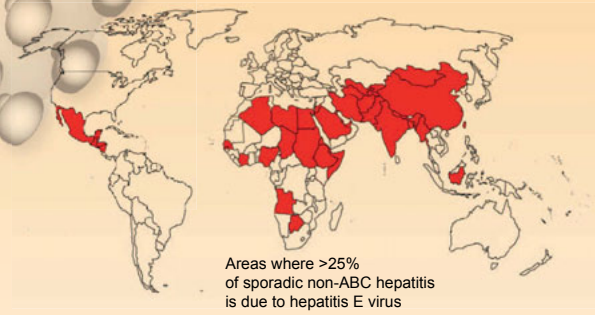


Transmission

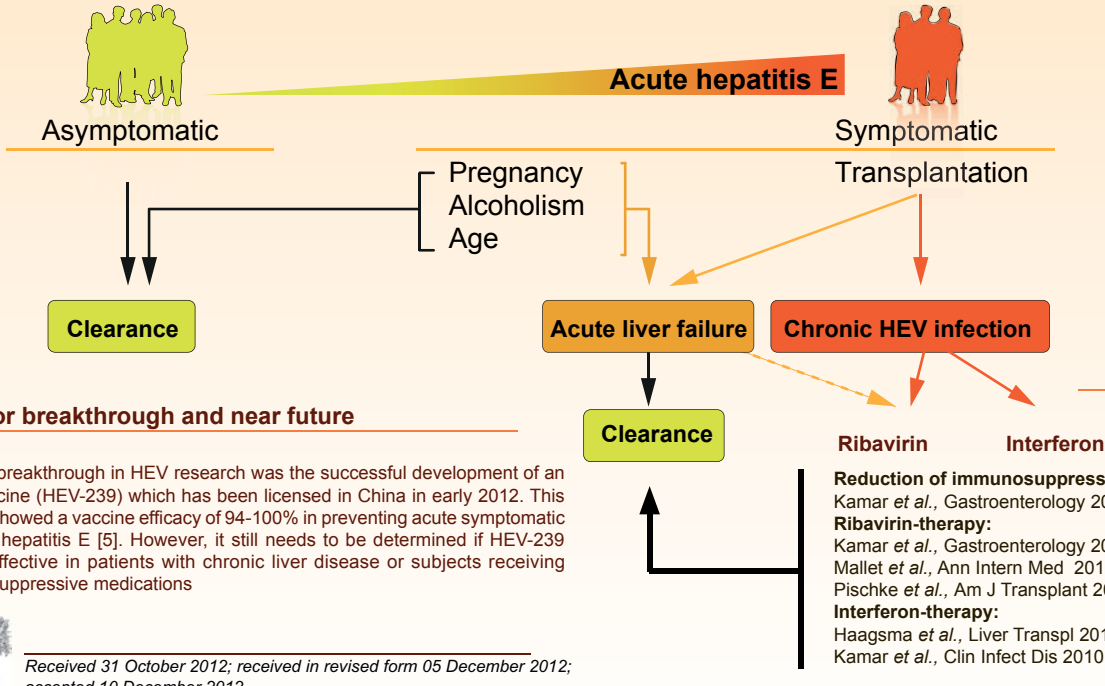
Hepatitis E virus

Diagnosis

Hepatitis E is frequently diagnosed by the detection of HEV antibodies followed by testing for HEV RNA in blood or stool. However, serological assays show a wide variability in sensitivity and specificity and HEV antibodies may be negative in immunocompromised individuals. Thus, direct testing for HEV RNA is advised in all patients [1]



Clinical course of exposed individuals



Therapy

Ribavirin **Interferon**

Reduction of immunosuppression
Kamar *et al.*, Gastroenterology 2011
Ribavirin-therapy:
Kamar *et al.*, Gastroenterology 2012
Mallet *et al.*, Ann Intern Med 2010
Pischke *et al.*, Am J Transplant 2012
Interferon-therapy:
Haagsma *et al.*, Liver Transpl 2010
Kamar *et al.*, Clin Infect Dis 2010

Major breakthrough and near future

A major breakthrough in HEV research was the successful development of an HEV vaccine (HEV-239) which has been licensed in China in early 2012. This vaccine showed a vaccine efficacy of 94-100% in preventing acute symptomatic cases of hepatitis E [5]. However, it still needs to be determined if HEV-239 is also effective in patients with chronic liver disease or subjects receiving immunosuppressive medications

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For more than two decades, medical students have learned that hepatitis E virus infection causes self-limited acute hepatitis, occasionally progressing to fulminant liver failure in distinct risk groups. However, emerging data generated during the last five years, clearly showed that various aspects of textbook knowledge on hepatitis E have to be revised. It became evident that HEV infection has multiple faces with respect to chains of infection and during the course of disease.

The far majority of HEV infections occur in developing countries due to waterborne transmission of HEV genotype 1 or 2 [1, 2]. In contrast, HEV genotype 3 and 4 infections are mostly foodborne with various animal species serving as potential zoonotic reservoirs [1]. Pig meat has been identified as a major source of HEV infections in industrialized countries and various studies detected HEV RNA in food products purchased in grocery stores [1]. In addition, HEV has been detected in deer, rats, shellfish, and also on strawberries. HEV is temperature sensitive and loses its ability to infect target cells after exposure to more than 70 °C. It is therefore strongly recommended that people at risk should avoid consuming raw meat or other food products potentially exposed to HEV. Moreover, close contact with certain animals may represent a risk factor for HEV. Patient to patient transmission of HEV has also been reported. Of note, sewage samples from different European countries and the United States tested positive for HEV RNA. A largely under-recognized cause of HEV infection may be transmission by HEV contaminated blood products. Plasma products analyzed in Germany tested HEV RNA positive in 10% of cases [3]. In single cases, HEV may even be transmitted by solid organ transplantation [4].

In many centres, diagnostic algorithms of hepatitis E testing rely on detection of HEV antibodies, followed by testing for HEV RNA in blood or stool. However, serological assays show a wide variability in sensitivity and specificity and HEV antibodies may be negative in immune compromised individuals. Thus, direct testing for HEV RNA is advised in all patients, if HEV infection is suspected as the cause of hepatitis that cannot be explained by other reasons [1].

HEV infection shows a wide spectrum of clinical manifestations. In most settings, less than one out of hundreds of infections lead to clinically symptomatic acute hepatitis [5]. More severe courses of acute hepatitis E have been described in individuals with pre-existing chronic liver disease, elderly men and pregnant women. In the latter, distinct genetic polymorphisms may contribute to the severity of hepatitis [6]. The WHO estimates that more than 3 million individuals suffer from acute symptomatic hepatitis E each year, leading to about 70,000 annual deaths [7].

Immune competent individuals almost always clear the infection within 6 weeks. In immunosuppressed patients, including organ transplant recipients and HIV-infected subjects, HEV infection may take a chronic course, leading to progressive liver disease in some patients. The severity of chronic hepatitis E has been highlighted by various case reports of HEV-associated liver cirrhosis followed by organ failure. HEV specific adaptive immunity has been correlated with the control of HEV infection, and the level of immunosuppression increases the risk of chronicity [8]. The use of distinct immunosuppressive compounds may also influence the likelihood of HEV clearance. While one retrospective study associated the administration of tacrolimus with chronicity [9], another prospective investigation suggested more frequent recoveries in a small series of heat-transplanted patients treated with mycophenolate [10]. However, these findings are still preliminary and further studies are required to investigate whether specific immunosuppressive drugs alter the course of HEV infection.

Different options to treat chronic hepatitis E have been proposed, including reduction of immunosuppressive medication (if possible), administration of interferon alpha or usage of ribavirin monotherapy [1, 2]. The optimal dose and duration of ribavirin therapy still need to be defined, but 600-1000 mg daily for 3-5 months was suggested. Shorter therapies and dose reductions have been associated with virological relapses or breakthroughs [1, 2, 10], and thus, should be avoided.

An unexpected and possibly frequently overlooked face of HEV infection is the association with various extrahepatic disorders. Immune phenomena have been described both during the acute and chronic viraemic phases and after recovery of infection. Specifically, cases of Guillaune Barre, glomerulonephritis and cryoglobulinemia occurred in the context of HEV infections. However, the frequency of extrahepatic manifestations of hepatitis E is completely unknown and the underlying pathomechanisms are not defined yet [1].

A major breakthrough in HEV research was the successful development of an HEV vaccine, which has been licensed in China in early 2012. The vaccine HEV-239, which is based on recombinant HEV genotype 1 antigen, showed a vaccine efficacy of 94-100% in preventing acute symptomatic cases of hepatitis E [5]. The vaccine also showed cross-genotype efficacy, since genotype 4 infections were prevented with a genotype 1-based vaccine. However, it still needs to be determined whether HEV-239 is also effective in patients with chronic liver disease or subjects receiving immunosuppressive medications. Moreover, the long-term safety and immunogenicity need to be determined. HEV 239 will hopefully become available also outside of China in the near future; in particular as no alternative HEV vaccine program has reached phase 3 clinical trials.

In summary, the overall relevance of HEV infection has been underestimated for many years. Clinical textbooks need to be updated and should consider recent advances:

(i) HEV is a relevant global health problem and also occurs in industrialized countries
(ii) In addition to waterborne infections, zoonotic and blood-borne transmission of HEV occurs
(iii) HEV may cause chronic infections in immune compromised patients and can be associated with extrahepatic symptoms
(iv) Antiviral therapies against HEV are available and a prophylactic vaccine has been developed

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Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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