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Updates on hepatitis E virus

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Hepatitis E virus (HEV) is the causative agent of hepatitis E. Globally, it is estimated that 20 million HEV infections with 3.3 million symptomatic cases occur annually, and the mortality rate is 0.5% to 3% in general population. Although hepatitis E is commonly considered as an acute, self-limited disease, HEV infection can be chronic in immunocompromised patients and related with high mortality rate and poor pregnancy outcomes in pregnant women.[1]

Characteristics of HEV: HEV is a single-stranded, positive sense RNA virus with genomic length ranging from 6.6 to 7.2 kb with three open reading frames (ORFs): ORF1 encodes non-structural protein associated with HEV RNA replication; ORF2 encodes the capsid protein and a secreted form of ORF2 protein[2]; and ORF3 encodes a small protein related with the release of HEV.[3] The virus particle is icosahedral and has a diameter of 27 to 32 nm. HEV is non-enveloped in feces and bile but contains a lipid envelope in blood and cell culture supernatant, and hence HEV is declared to be a quasi-enveloped virus.[2] Robust cell culture system for HEV is still lacking, and suitable animal models for HEV include non-human primates, swine, rabbits, and human liver chimeric mice. Given the small size and zoonotic potential for rabbit HEV, rabbits could be an important model in HEV studies.

Classification and host range of HEV: HEV was classified in the family *Hepeviridae*. The most studied HEV genotypes belong to species *Orthohepevirus* A and are subsequently divided into eight genotypes. HEV genotypes 1 and 2 are known to be exclusively infectious to humans and are mainly prevalent in developing regions due to relatively poor sanitary conditions, leading to large-scale outbreaks or epidemics. HEV genotypes 3 and 4 are zoonotic and mainly cause sporadic cases in developed regions and China. HEV genotypes 3 and 4 have various animal hosts, including rabbit, deer, mongoose, goat, pig, and wild boar. Zoonotic cases reported are mostly caused by HEV strains in pigs or wild boars.[4] Rabbit HEV was first isolated in farmed rabbits in China in 2009,[5] and numerous cases of humans infected by rabbit HEV have been reported subsequently.[6,7] HEV genotypes 5 and 6 were isolated from wild boars in Japan, and no zoonotic cases have been reported, but HEV genotypes 5 is reported to be able to experimentally infect cynomolgus macaques using a recently established reverse genetics system.[8] HEV genotypes 7 and 8 were isolated from dromedary camels and Bactrian camels, respectively.[9,10] HEV genotype 7 has been reported to lead to chronic infection in immunosuppressed patient, and HEV genotype 8 could experimentally infect cynomolgus macaques.[11] Avian HEV strains belong to the genera *Orthohepevirus* B and lead to big liver and spleen disease and hepatitis-splenomegaly syndrome. *Orthohepevirus* C was isolated in several regions, and its animal hosts include rat, shrew, ferret, and mink. Rat HEV was thought to be unable to infect humans, but recently cases have reported that rat HEV can infect not only immunosuppressed patients but also immunocompetent patients and cause severe acute hepatitis.[12,13]*Orthohepevirus* D consists of bat HEV strains and has no evidence of zoonotic potential. *Piscihepevirus* A represents HEV isolated from trout.

The host range of HEV has been expanded recently and seroprevalence of HEV antibody has recently been detected in multiple other species including raccoon, cattle, dog, cat, and sheep. HEV RNA can also been detected in small mammals, including rodents and bats. Hepe-like virus, distantly related with HEV, have been detected recently in white-backed planthopper[14] and farmed prawn[15], indicating a broader host range of HEV. Predictably, the host range of HEV will continue to expand over the years and provide us better understandings for the origin and evolution of HEV.

Transmission of HEV: HEV is transmitted mainly via fecal-oral route. HEV genotypes 1 and 2 often spread through contaminated water and lead to large outbreaks or epidemics in developing regions. While in industrialized or developed regions where HEV genotypes 3 and 4 dominated, HEV mainly transmits to humans via

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contaminated animal products, for example, uncooked meat or liver. Apart from fecal-oral route, other transmission routes have also been discovered recently.

HEV particles and HEV capsid protein were found in the urine of HEV-infected rhesus macaques as well as immunocompromised patients. Monkeys were successfully infected by inoculating with urine of HEV-infected monkey, indicating the urine-oral route for HEV trans-mission.[16,17]

Blood-borne HEV infection has drawn attention worldwide. Sporadic cases of HEV infection through transfusion have been widely reported and could lead to chronic hepatitis E in immunosuppressed patients. So far test for HEV in blood donors has been introduced in some regions including England, France, Germany, Ireland, Scotland, Netherlands, and Japan but is under discussion and still lacking in most regions.[18]

Vertical transmission of HEV can occur and are caused predominantly by genotype 1 HEV. HEV genotypes 3 and 4 could also vertically transmit in animal models such as rabbits or rhesus macaques.[19,20] Vertical transmission of HEV can lead to jaundice at birth and mainly self-limited disease for infants with no prolonged clinical course, but it can also cause death within 48 h due to severe hypothermia, hypoglycemia, or fulminant hepatic failure. Recently, HEV RNA was detected in the semen samples from patients chronically infected with HEV, and hence the sexual transmission of HEV demands further studies.[21]

Donor-derived HEV infection cases in organ transplantation were also reported in 2019.[22] Since organ recipients are immunosuppressed, HEV infection can be chronic and lead to persistent hepatitis E. Screening of HEV is thus recommended for organ donors.

HEV infection: HEV infection mainly leads to self-limited acute hepatitis and cause clinical manifestations including anorexia, nausea, vomiting, malaise, abdominal pain and jaundice lasting <1 month. Although hepatitis E is commonly considered as an acute self-limited disease, chronic HEV infection can occur in mainly immunocompromised patients, e.g., recipients of solid-organ transplants, hematological malignancy patients and HIV-infected individuals. Chronic HEV infection is defined as persistence of HEV replication >3 months and is predominantly associated with HEV genotypes 3 and 4 infection in immunocompromised patients with a rapid development to cirrhosis. Cases of HEV chronic infection caused by HEV genotypes 7 and rat HEV have been reported recently[13,23] in immunosuppressed organ transplantation recipients. Elevation of liver enzymes was observed, and the patients progressed to acute-on-chronic liver failure. Besides, HEV infection is associated with a mortality rate of 20% to 30% in pregnant women with poor pregnancy outcomes including stillbirths and miscarriage.[24]

HEV infection can also cause multiple extrahepatic manifestations including mainly neurological symptoms and diseases and renal diseases. HEV infection has been proved to be associated with Guillain-Barré syndrome and the development of Parsonage-Turner syndrome. Renal disorders including membranoproliferative glomerulonephritis and cryoglobulinemia have also been found to be associated with HEV infection. Other extrahepatic manifestations related with HEV infection include hematological disorders, acute pancreatitis, myocarditis, arthritis, and autoimmune thyroiditis.[25]

Diagnosis, prevention, and treatment of hepatitis E: Incubation period of hepatitis E varies from 15 to 60 days, and HEV RNA can be detected in feces and serum sample from patients 3 weeks after infection. HEV RNA detection and quantification in blood, stool, or other body fluids remains the golden standard for current HEV infection.[26] Detection of anti-HEV antibodies, including anti-HEV IgG and IgM, also plays an important role in the diagnosis of hepatitis E, but immunosuppressed patients often showed negative results for serology due to low titer of anti-HEV antibodies. Positive results for anti-HEV IgM (with or without positive anti-HEV IgG) together with HEV RNA represents current acute infection and a single positive result for anti-HEV IgG represents past infection of HEV. Patients reinfected with HEV usually show positive result for anti-HEV IgG and HEV RNA but not anti-HEV IgM. Chronic hepatitis E is diagnosed when HEV infection lasts over 3 months.[26]

The prevention of HEV infection mainly depends on cutting off the transmission route of HEV, including drinking boiled water, consuming well-cooked animal products, and improving sanitation standard. HEV 239 vaccine (Hecolin), the only commercialized combination vaccine, is licensed in China but not in other regions, has shown protective effect against genotype 1 HEV, and showed cross-protection against genotype 4 HEV.[27] The vaccine showed 100% efficacy against hepatitis E for participants receiving three doses of HEV 239 and 96% efficacy for participants receiving at least one dose of the vaccine in phase III clinical trial. To date, HEV 239 vaccine has shown safety and immunogenicity in people > 65 years and in hepatitis B surface antigen-positive adults in clinical trials. Because HEV infection is often more severe in pregnant women or immunosuppressed patients, vaccination of high-risk population should be an important strategy for the prevention of HEV infection.[24]

No antiviral therapy is needed in most cases of acute HEV infection because hepatitis E is usually self-limited, but treatment is still needed for chronic hepatitis E patients or pregnant women. No drug is currently approved by FDA against HEV infection, and the most commonly used drugs include ribavirin (RBV) and pegylated-interferon-α (PEG-IFN-α).[26] RBV is used in most cases but it leads to viral clearance in only approximately 80% patients treated, possibly due to the mutations of HEV genome discovered recently in patients showing failure to clear HEV replication with RBV therapy.[28,29] PEG-IFN-α can be administrated only for the subset of liver-transplant recipients but cannot be used after kidney, heart, or lung transplantation. Sofosbuvir, known as a NS5B inhibitor used against HCV, has been proved to inhibit HEV replication *in vitro* and has additive effect when combined with RBV, but its effect in clinical cases remains controversial.[29,30]

Conclusion and perspectives: HEV has been neglected for a long time, but the understandings of HEV have changed greatly over the recent decade. HEV is being increasingly recognized as a major health concern globally in both developing and developed regions. The pathogenic mechanism of HEV remains unclear and deeper studies are required. In addition, owing to the zoonotic nature of HEV, studies on the animal hosts and the epidemiology of HEV remain significant. Robust cell culture system as well as more animal model is still urgently needed for studies of HEV.

The transmission route of HEV can be diverse, and it is still under discussion whether blood and organ donors shall be all tested for HEV to avoid HEV transmission through transfusion or organ transplantation. Moreover, the range and underlying mechanisms of HEV infection-associated extrahepatic manifestations warrant future studies. Screening for specific anti-HEV drugs and evaluations of new therapies are also urgently needed.

Conflicts of interest

None.

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