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Hepatitis E: A Multi-Facets Viral Disease

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Introduction

The hepatitis E virus (HEV) is the cause of hepatitis E, an inflammatory liver disease: In many tropical nations with poor sanitary standards in the 1980ies, this infection was said to be endemic. It has been believed for more than 20 years to be a travel-related, acute, self-limiting liver illness that only affects certain, high-risk individuals and results in fulminant hepatic failure [1]. According to a recent estimate by the WHO (2014), HEV infection results in roughly 56,000 fatalities annually worldwide. In the past ten years, occasional occurrences of HEV infections have also been reported in industrialized nations, with genotype 3 of the virus accounting for the majority of these cases [2]. clinically undetectable seroconversion or acute, self-limiting liver inflammation. HEV infection has been linked to cases of fulminant liver failure in both pregnant women and people who already have chronic liver disorders [2]

Additionally, in various cohorts of immunocompromised people, persistent HEV infection cases linked to progressive liver disease have been reported. In this situation, testing for HEV-specific antibodies may not be sensitive enough to diagnose HEV infection; instead, HEV RNA detection should be used [3]. A

stem cell derived cell culture system has been constructed to explore the *in vitro* replication of HEV and potential Inhibitors. Where in, the effectiveness of Interferon and was investigated ribavirin and interferon was investigated [34].

Human liver chimeric mice have also been developed as a model of chronic HEV for testing novel therapeutic trials [4]. In addition, mounting data suggests that T-lymphocyte-mediated immune responses aid in the suppression of HEV infection [5] Furthermore, HEV-specific T lymphocytes responses without discrete immunodominant areas have been described as targeting the whole HEV genome [6].

Interferon therapy [7]. immunosuppressive medication decrease [8], or ribavirin therapy [9] are all possible treatments for chronic hepatitis E. Recent studies have demonstrated that the hepatitis C treatment sofosbuvir, a direct acting antiviral (DAA) agent, can be used effectively in treatment of HEV infection both in vitro and, to a lesser extent, in vivo. [10] [11] [12] [13].

According to [14], this vaccination demonstrated a >90% efficiency in avoiding acute hepatitis E symptoms. It is not yet clear if or when this vaccination will be made available.

Genetic characteristics of HEV

According to Wedemeyer [15], the hepatitis E virus is a single-stranded, non-enveloped RNA virus. The viral family Hepeviridae includes HEV as a member of the species Orthohepevirus A. Rodents and bats

are just two examples of the many mammalian species that are infected by other species in this family (Orthohepevirus B-D). It is still debatable whether these species are relevant to humans.

Previously, 24 subtypes (HEV GT 1a–1e, 2a–2b, 3a–3j, and 4a–4g) and 4 distinct classical HEV-genotypes (HEV GT 1-4) had been identified [16]

However, a fresh categorization that divided 8 HEV-genotypes and numerous subtypes has been established based on the discovery of HEV-strains from rabbits, wild boars, and camels [17]. Three open reading frames (ORF 1) are surrounded by two brief non-coding sections in the HEV genome.

These ORFs hold the genetic material for numerous proteins required for HEV infection, viral replication, and capsid formation.

One of the Hepatitis E viral proteins, ORF 4, which is recently shown to be associated with HEV GT 1 was recently regarded as a novel viral replicative marker. [18]HEV genotype 1 causes endemic and pandemic infections in Asia and Africa, whereas genotype 2 is prevalent in Mexico and Western Africa (Figure 1). These genotypes are typically spread fecal-orally and are water-born in unsanitary environments. The likelihood of HEV genotype 1 infecting swine has only been discussed in one study [19]. For this genotype, there are no known more reports of zoonotic transmission.

HEV genotype 3 on the other hand, is present in both humans and animals in Europe, the United States, and Asia [20]It has been widely shown that this genotype can spread by contact with infected animals, foodborne transmission, and zoonotic transmission.

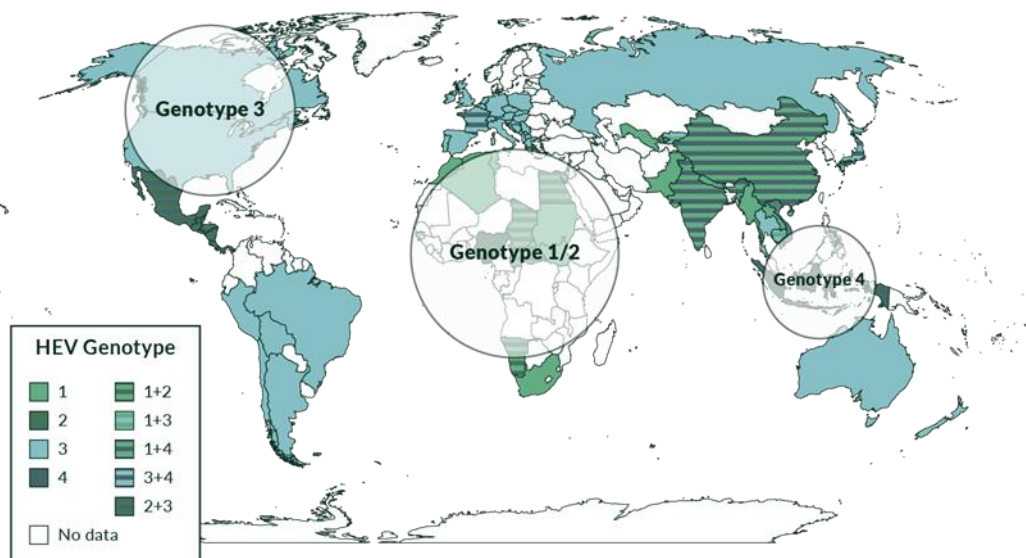


Figure 1. Worldwide distribution of the four classical human pathogenic HEV genotypes (GT1–4)

Transmission of HEV

Transmission of HEV is via oral-fecal route. However, direct patient-to-patient infection is extremely uncommon, but it has been reported from hematological wards in Europe [20]and from a significant outbreak in Northern Uganda [21] . HEV blood-borne transmission was hypothesized as early as the late 1990s [22]. Blood transfusions were verified as a potential source of HEV infection in later research from Hong Kong, Japan, Great Britain, and France According to a German study that looked at 1019 blood donors, 0.35 percent of them underwent seroconversion within a year [23]. Another sizable research of 18737 German blood donors found that 0.1% of them tested positive for HEV RNA The bulk of the viremic donors' sources of infection were found to be consumption of raw pig meat. Thirteen out of 40,176 blood donors were shown to harbor HEV particles, according to a Dutch study [24]. According to these numbers, one blood donation every day in the Netherlands is HEV positive. With 0.035% of blood products being HEV-viremic, a sizable English investigation involving 225,000 blood

products established blood transfusions as a potential source for HEV transmission [25]. A lack of HEV antibodies and a high viral load in the blood product were linked to post-transfusion infections. Among 18,829 tested donors in the US, a study found two HEV RNA positive samples [26].

Subclinical HEV infections in seemingly healthy blood donors. A recent study from Germany on 27 HEV-containing blood found a median time period for proven HEV RNA viral clearance of 55 days [27], which is consistent with these findings. Three of these donors had persistent viremia that lasted more than 100 days. At the time of donation, serological testing was unable to distinguish amongst viremic donors since 70.4% of them lacked any detectable antibody response. In antibody-naïve donors, it took an average of 53 and 57 days before anti-HEV IgM or IgG was discovered.

Only three instances of organ transplant-borne HEV infection (liver or kidneys from a patient with occult hepatitis E) have been reported, in contrast to blood-borne HEV infection [28] .

It has been assumed that zoonotic transmission of HEV is the main contributor to HEV infections in developed countries (Figure 2). Ingesting infected food or coming into close contact with sick domestic animals are two ways that HEV can be transmitted. Commercial food products like pig meat may carry HEV, according to studies from the Netherlands, France, and Germany [29][30] .

Meat should be cooked at a temperature above 70°C to prevent HEV infections from foodborne sources [31] [32] .It's interesting to note that a liver transplant patient who ate camel meat afterwards developed chronic hepatitis E [33] .Even though this will certainly have little impact in the US and Europe, it does suggest a fresh method of transmission in the Arab region.

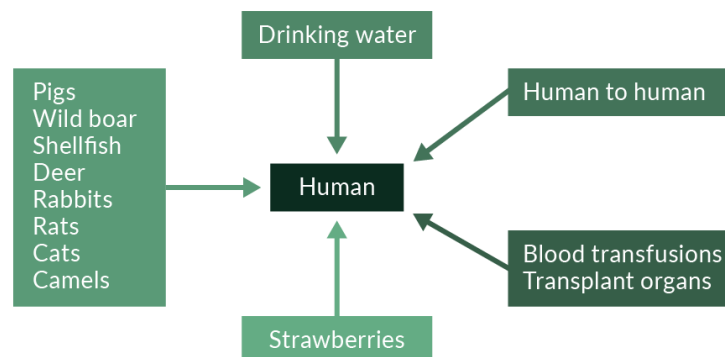


Figure 2. Possible sources of HEV infection

Acute hepatitis E in immunocompetent Individuals

Since 2008, chronic HEV infections have been reported in patients in Europe who have undergone liver or kidney transplants [34][35]. The first 14 cases of acute hepatitis E were found in patients from southwest France who had received kidney and liver transplants. Ten to eighteen months later, eight of them underwent a chronic course that resulted in consistently increased ALT levels, substantial histological activity, and fibrosis. Additional chronic HEV infections have since been identified in transplant patients, according to reports from several different organizations, proving that chronic hepatitis E can cause patients to develop liver illness after receiving an organ transplant[36].

To determine the prevalence of chronic HEV infections in liver transplant recipients in a low endemic nation, a German study looked at 226 liver transplant recipients and 129 patients with chronic liver disease [37]. HEV RNA and anti-HEV IgG tests were performed on all patients. In two individuals who

had liver transplants, persistent HEV infections were found. Within less than two years, one of them experienced substantial liver fibrosis. HEV genotype 3 infection was present in both cases. Infecting pigs with a patient's blood served as an experimental confirmation of the potential for reverse zoonotic transmission. The pigs' muscles and other organs all had HEV RNA. In light of the possibility that eating raw meat could lead to HEV infection, it is advised that organ transplant recipients avoid doing so in light of these findings. Collectively, 56 (66%) of the 85 total HEV infections were reported to have progressed to chronic hepatitis E. Notably, tacrolimus use, and a low platelet count were linked to chronicity [38]. However, it must be remembered that a single center had recruited the great majority of patients, and stories from different areas and transplant centers must be shared.

Heart transplant recipients have also been documented to experience chronic HEV infection [39][40]. According to a German study looking at cardiac patients with and without heart transplants, the seroprevalence of HEV-specific antibodies is five times higher in these patient groups than it is in control group [41]. It has been hypothesized that medical treatments, particularly those involving blood products, may be to blame for the observed variation in seroprevalence rates.

Additionally, lung transplant recipients from the Netherlands [42] and Germany [43] have been reported to have chronic HEV infections. Overall, unless other clear causes already explain hepatitis, all solid organ transplant recipients with increased liver enzymes should be screened for HEV RNA. Testing for HEV RNA should be used in immunosuppressed patients since antibody testing may not be sensitive enough.

Different immunosuppressive medications could either directly or indirectly impair HEV replication, hence this should be taken into account when managing organ transplant recipients [7]. Studies from Germany [44] and France [45] did not observe any cases of chronicity in stem cell transplant recipients, in contrast to solid organ transplant recipients, which led to the notion that this occurrence is uncommon in this patient population. However, 328 stem cell transplant recipients were the subject of a sizable Dutch investigation that discovered 8 cases (2.4%) of chronic HEV viraemia. While the other four patients recovered from HEV infection after a median of 6.3 months, four of these patients passed away after developing hepatitis. These findings support the relevance of chronic HEV infections in stem cell transplant recipients [46].

Association of HEV with HIV infection and other immunological deficiencies

In 2009, a patient with an underlying HIV infection was the first to have chronic hepatitis E described [47]. Less than 200 CD4 T cells were seen in this patient, who also had significant HIV RNA levels (>100,000 copies/mL). However, later research from Spain (n=93; [48]), Germany (n=123; [49]), and England (n=138; [46]) was unable to find any incidences of chronic hepatitis in HIV-infected people. In France, only one out of 184 HIV-positive people had HEV RNA detectable for more than 10 months [50].

This patient's CD4 count was notably low (50 cells/mm), in contrast to two other patients who had greater CD4 counts and were able to eradicate HEV on their own. As a result, people with HIV infection seldom experience persistent HEV infection. Although the immune systems of single HIV-infected patients have improved, it has been shown that HEV can still survive in these individuals [51] [52].

Chronic HEV infections in people who are not HIV positive Numerous immunosuppressive diseases, such as retroperitoneal fibrosis, granulomatosis, lupus erythematosus, or CD4 deficiency, have been observed [53] [54]. In contrast to these illnesses, a German cohort of 73 patients with common variable immunodeficiency (CVID) had no cases of persistent HEV infection. Regular immunoglobulin infusions may have eventually shielded these patients from infection, according to a theory [55]

Vaccination

A phase 2 study [56] that successfully evaluated a vaccine created by GSK and the Walter Reed Army Institute has not led to further research. Data from a hugely successful phase 3 vaccine experiment were

released by a Chinese organization [57]. Nearly 110,000 participants were enrolled in this study, and they either received the recombinant HEV vaccination ("Hecolin") or a placebo . After three doses, the vaccine had a 100% success rate in preventing symptomatic acute hepatitis. Early in 2012, this vaccination received approval in China. The availability of this vaccination outside of China is not yet known, nor is it when. The effectiveness of this vaccination also has to be examined in particular risk populations, such as people who are immunosuppressed or patients with end-stage liver disease. Also uncertain is if HEV 239 offers defense against HEV genotype 3 infection [58] However, it was found that only symptomatic hepatitis E infection may be prevented by the vaccine or naturally occurring, post-infectious antibodies [59]. Furthermore, it was demonstrated that pregnant women could utilize this vaccine without risk [60]. It is significant to remember that the vaccine does not result in sterilizing immunity and that asymptomatic infection happened in those who received the shot. There should be discussion and research towards the application of this vaccine in underdeveloped nations. In the future, this vaccination might aid in reducing the morbidity and death brought on by hepatitis (E) .

Conclusions and Recommendations

In populations with immune competence, HEV infection typically progresses in a self-limiting manner and presents clinically as acute hepatitis.

Hepatic failure could be more prevalent in some groups, such as pregnant women. Chronic cases have been documented in patients who have immunosuppression from a variety of causes.

Serological assays may not be sensitive enough to accurately diagnose HEV infection in organ transplant recipients. The gold standard for diagnosing HEV infection is the detection of HEV RNA by PCR in serum or feces.

Chronic HEV infection is uncommon in people who have received solid organ transplants, and this incidence is generally low in industrialized nations. However, chronic hepatitis E can arise and should be taken into account when determining the cause of graft hepatitis because it has been linked to the progression of graft hepatitis and the emergence of liver cirrhosis. All chronic HEV infections in transplant recipients that have been reported so far have been caused by HEV genotype 3 or 4. If genotypes 1 or 2 can also result in chronic hepatitis E is unknown. In order to prevent HEV infection, organ transplant recipients and other immunocompromised people should refrain from consuming raw meat. According to preliminary findings, ribavirin treatment for chronic hepatitis E (lasting 3 to 5 months) can successfully induce a prolonged virologic response in immunocompromised individuals. To prevent liver failure, this medication is only necessary in a small number of immunocompetent persons with acute HEV infection.

Further research is necessary to determine the significance of extrahepatic symptoms linked to acute or chronic HEV infection, particularly the links between autoimmune hepatitis, cryoglobulinaemia, and neurological symptoms and the presence of a positive anti-HEV serostatus.

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