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# Transmission, Diagnosis, and Treatment of Acute and Chronic Hepatitis E

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**Abstract**

Hepatitis is the liver inflammatory disease that is caused by chemicals, drugs, or by the infection with different kinds of viruses. Hepatitis E infection is a disease that affects the liver and is caused by hepatitis E virus (HEV), a virus that can infect both animals and humans. The HEV infection can cause acute liver failure, chronic hepatitis, and liver cirrhosis that remain a clinical challenge and still account for high mortality. It is the main cause of enterically transmitted hepatitis in humans worldwide. Among weakened immune patients it can lead to chronic hepatitis that may result a life-threatening illness, such as fulminant liver failure. There are eight genotypes: HEV 1-8; and genotypes 1 and 2 infect humans exclusively. The virus is transmitted mainly through the fecal-oral route of contaminated food and water. Active screening, reducing misdiagnosis, improving patient management, proper medications, supportive treatments, and timely antiviral therapy for severe and chronic cases are important measures to reduce the morbidity and mortality due to hepatitis E. This study focuses on the transmission, management, and treatment of HEV infection.

**Keywords:** HEV, acute and chronic hepatitis, screening, antiviral therapy, ribavirin, pregnancy

## 1. Introduction

Hepatitis E virus (HEV) is the most common cause of acute viral hepatitis globally that is responsible for the major liver infection and may develop in people who have a suppressed immune system. Hepatitis E occurs as both sporadic and epidemic outbreaks of acute hepatitis in developing countries, leading to a self-limiting disease (Pilot et al., 1987). In most cases HEV (where E for epidemic) infections are mild or asymptomatic, but in some cases slightly symptomatic and the disease is rarely fatal (Kamar et al., 2012). Infection with the HEV may be related to acute illness, chronic hepatitis, liver cirrhosis, and liver failure (Guerra et al., 2017). The HEV also shows extrahepatic manifestations, such as pancreatitis, neurological symptoms, renal injury, hematological disorders, glomerulonephritis, and mixed cryoglobulinemia (Nimgaonkar et al., 2018). It affects more men than women, with a ratio of 2:1 in developing countries and more than 3:1 in developed countries (Kamar et al., 2014).

The first well-documented epidemic acute hepatitis named non-A, non-B viral hepatitis was occurred in 1955 in New Delhi, India that was affected 29,000 people, which occurred due to fecal contamination of drinking water (Wong et al., 1980). Hepatitis E was first identified by Indian physician Mohammad Sultan Khuroo as non-A, non-B viral hepatitis during an epidemic of hepatitis, which occurred in Kashmir Valley, India in 1978 that affected over 50,000 inhabitants of which almost 1,700 died (Kumar et al., 2013). In 1983, the Russian virologist Mikhail Surenovich Balayan visualized the virus through electron microscopy when examining his own feces after self-administration of contaminated material (Meng, 2011; Mikhailov et al., 2021). The HEV was discovered in 1983 by Russian virologists investigating an outbreak of unexplained hepatitis using immunoelectron microscopy among Soviet soldiers serving in Afghanistan. In 1989, the viral genome was

successfully sequenced and this pathogen was formally designated as HEV (Izopet et al., 2014). In 1991, American virologist Albert W. Tam and his team have succeeded in cloning and sequencing the genome of the virus and it is named “hepatitis E virus (HEV)” (Tam et al., 1991).

Hepatitis E is water-borne disease that spreads by the HEV contamination with the fecal material ingestion. The HEV infection may prove to be dangerous in pregnant women, especially during the third trimester; older people; and people who have existing chronic liver disease (Polley et al., 2022). In severe stage, the disease is associated with a clinical syndrome called fulminant liver failure, with death rates about 20% (Ali, 2018). Sometimes for adverse effects on the mother may happen, such as preterm delivery, abortion, low birth weight, stillbirth, and neonatal death (Patra et al., 2007). The prevalence is highest in East and South Asia. Also, Bangladesh, India, China, Middle-East, Mediterranean region, Ethiopia, Mexico, South America, and Kenya carry the highest burdens of HEV infection (Zeng et al., 2021).

From 1990 to 2019, the incidence rates of HAV, HCV, and HEV infection have remained stable (Zeng et al., 2021). Every year there are an estimated 20 million HEV infections globally with 3.3 million symptomatic cases, 3000 stillbirths, and 44,000–70,000 HEV-related deaths per year (WHO, 2020). The HEV seroprevalence is high in developing countries, such as in India and Southeast Asia, ranging from 27% to 80% (Guerra et al., 2017).

## 2. Literature Review

In any type of research, literature review is an introductory area, where works of previous researchers are included (Polit & Hungler, 2013). It deals with secondary research sources and does not think about coming research work (Gibbs, 2008). Silvia E. Tritz and her coauthors have investigated zoonotic transmission of HEV in rural settings of Lao People’s Democratic Republic where humans are in close contacts with ruminants and where pigs are rare. They have highlighted on the need to raise the awareness of the rural population about water- and food- borne pathogens, and about the role of cattle as a possible source of infection (Tritz et al., 2018).

Chia-Yu Chiu and his coauthors have studied the cancer patients with HEV infection. They have observed that cancer patients with hematologic malignancies may be at risk for HEV viremia and chronic infection refractory to antiviral treatment (Chiu et al., 2022). Qiumin Luo and her coworkers have focused on the clinical presentation, management, and prevention of hepatitis E to reduce worldwide morbidity and mortality (Luo et al., 2024). Danielle M. Yugo and Xiang-Jin Meng have studied the current understanding of HEV transmission routes with emphasis on food and environmental sources and the prevalence of HEV in animal species with zoonotic potential in humans (Yugo & Meng, 2013).

Chunchen Wu and her coworkers have shown that the HEV causes self-limiting viral hepatitis, and among pregnant women the infection can be severe that has been associated with up to 30% mortality in the third trimester. They have also indicated that in pregnancy HEV is also associated with high rates of preterm labor and vertical transmission. They have summarized the current knowledge about HEV infection during pregnancy that focuses on the epidemiology, clinical manifestations, and mechanisms underlying severe liver injury; and also management and prevention of HEV infection during pregnancy (Wu et al., 2020).

Toni L. Meister and her coauthors have described various approaches to cultivate HEV in cellular and animal models, and have indicated how these systems are used to study HEV infections and evaluate anti-HEV drug candidates (Meister et al., 2019). Subrat Kumar and his coworkers have reviewed the currently available information with regard to the molecular biology, pathobiology, and epidemiology of HEV infection. They have also reviewed the current therapeutic interventions and strategies being used to control HEV infection, with emphasis on possible approaches that could be used to develop an effective vaccine against HEV (Kumar et al., 2013).

## 3. Research Methodology of the Study

All academicians take the research as a challenging work to lead in academic world (Pandey & Pandey, 2015). A well-built outline of the study and an efficient understanding are crucial to reach the goal of a research (Tie et al., 2019). Methodology is a guideline to perform good research that helps the researchers to increase the trust of a reader in the research findings (Kothari, 2008). Research methodology is the science and philosophy behind all researches that provide the principles for organizing, planning, designing and conducting good research (Legesse, 2014).

To prepare this article we have used secondary data that are collected from both published and unpublished data sources (Mohajan, 2024a-j; Mohajan & Mohajan, 2023a-d). The published data are collected from various sources, such as websites, national and international journals and e-journals, books and handbooks of famous authors, internet, etc. (Mohajan, 2017, 2018, 2020).

## 4. Objective of the Study

Main objective of this article is to discuss the infectious disease that is associated by hepatitis E virus (HEV), which is responsible for the major liver damage. The HEV is related to acute illness and also chronic hepatitis. It can be transmitted via the fecal-oral route, zoonotic route, and blood transfusion route. Common symptoms of it are jaundice, fever, tiredness, loss of appetite, etc. The disease is self-limiting and treatment is palliative and supportive. Other minor objectives of the study are as follows:

1) to focus on the virology of HEV,

2) to highlight on the symptoms and transmission of HEV, and

3) to indicate the diagnosis and treatment of HEV.

**5. Virology of HEV**

The HEV is a small, icosahedral, non-enveloped, single-stranded, positive-sense RNA virus with genome of 7.2 kb and 27-34nm in diameter that is highly unstable due to the lack of a lipid membrane (Mayr et al., 2018). It consists of short 5′ non-translated region (NTR) with 7-methylguanylate cap, 27-35 nucleotides in length and the 3′ non-translated region (NTR) is 65-74 nucleotides in length, terminated with a poly end with 150-200 nucleotides in length. The 3′ end of the chain is polyadenylated and the 5′ end is structurally characterized by the capping (Vasickova et al., 2007). It contains three open reading frames (ORF): ORF1, ORF2 and ORF3 (Figure 1). The ORF1 is the largest, containing several conserved domains, and encodes non-structural proteins that is about 1693 amino acids long with at least four putative functional domains (Kenney & Meng, 2019), the ORF2 encodes the viral 660 amino acids capsid protein that has been divided into three domains (Yin et al., 2018), and the ORF3 encodes a 113 or 114 amino acids phosphoprotein, depending on the genotype (Ding et al., 2017).

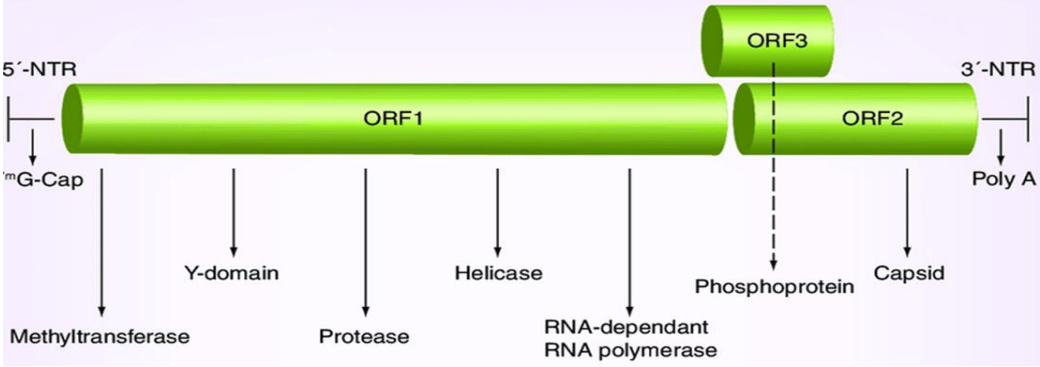


Figure 1. Genomic structure of the HEV. Source: Olyaee et al. (2009).

The HEV replicates in the cytoplasm of cells and also can replicate in hepatocytes, small intestine and colon cells, and lymph nodes (Kamar et al., 2014). It is classified into the family Hepeviridae, which is divided in two genera, Orthohepevirus and Piscihepevirus. The genus Orthohepevirus encompasses all mammalian and avian HEV variants, and is subdivided into four species: A-D (Pérez-Gracia et al., 2017).

At present HEV can be clustered genetically into 8 genotypes (GTs); HEV 1-8 that recognize with distinct differences in geographic distribution (Sridhar et al., 2017). It is classified into different subtypes, such as 1a-e, 2a-b, 3a-j, and 4a-g (Meng et al., 1999). The GTs 1 and 2 are endemic and restricted to humans, and are associated with large outbreaks through the fecal-oral route with contaminated water. The GT1 can be classified into 5 subtypes, such as 1a-e that have been isolated from tropical and several subtropical countries in India, Nepal, China, and North Africa (Song, 2010). The GT2 can be classified into 2 subtypes, such as 2a-b that have been isolated from Mexico, Nigeria, and Chad (Pelosi & Clarke, 2008). These are often associated with epidemics in developing countries due to poor hygiene and sanitation (Nimgaonkar et al., 2018).

The GTs 3 and 4 are zoonotic and have been detected in various mammalian species (swine viruses) worldwide and occasionally infect humans (as accidental hosts) that are autochthonous in several industrialized countries (Shrestha et al., 2015). These are associated with food-borne transmission, linked to the consumption of raw or undercooked infected meat from wild animals, such as deer and boar, and other game meats; watery non-mammals, such as shellfish and crabs; and domestic animals, such as pig and rabbit (Guerrant et al., 2011). These are prevalent in industrialized countries and are associated with sporadic and clustered cases of hepatitis E in these regions (Khuroo et al., 2016). The GT3 can be classified into 10 subtypes, such as 3a-j and is widespread in developed countries across Europe, Oceania, the Americas, Japan and Korea (Lu et al., 2006). The GT4 are classified into 7 subtypes, such as 4a-g and is endemic to China and Southeast Asia but has emerged in

indigenous cases in Europe over the past decade (Boyer et al., 2012).

**6. Symptoms of HEV**

Some HEV infected people have no symptoms but can still spread the virus to others. Symptoms usually start 3-6 weeks with an average 40 days after the HEV infection; some cases symptoms may occur from 15-64 days after infection (Heymann, 2015). The symptoms of hepatitis E are jaundice, fever, tiredness, loss of appetite, malaise, anorexia, nausea, vomiting, abdominal pain, joint pain, hepatomegaly, pruritus, dark urine, pale stools, and arthralgia (Mirazo et al., 2014). An altered immune status, hormonal levels, and viral factors may be related to the severity of the disease. The HEV can cause acute liver failure that can lead to death. The HEV infection can cause fulminant hepatitis failure, such as cerebral edema, disseminated intravascular coagulation (DIC), and encephalopathy at a higher rate with a mortality rate of up to 30% (Wu et al., 2020).

The HEV patient has a higher risk of fulminant hepatitis and may cause acute liver failure in a few days. It causes acute hepatitis that recovers completely without causing any longstanding chronic hepatitis (Lewis et al., 2010). Acute hepatitis is marked by sudden and massive death of the hepatocytes over a short period of time. It creates a lifelong immunity following natural infection. Clinical symptoms are usually concurrent with increases in liver enzyme levels markedly, such as bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) (Hoofnagle et al., 2012).

**7. Transmission of HEV**

The HEV can be transmitted via the fecal-oral route, zoonotic route, and blood transfusion route. The infection in pregnancy is also associated with vertical transmission with significant perinatal morbidity and mortality (Wu et al., 2020). The HEV is usually spread from animals to humans through the consumption of undercooked and processed pork, deer, camels or shellfish. It can also be spread directly through handling animals. Direct spread of HEV from person to person through blood transfusions is very rare (Grierson et al., 2015).

The HEV can spread from person to person by swallowing foods and drinks that is contaminated with feces from the HEV infected person (Weston et al., 2016). People who live in, or travel to, countries with poor sanitation are at most risk. Most people get hepatitis E from drinking water contaminated with sewage. The transmission of HEV is similar to HAV, and is by the oral-fecal route (enterically), but it may develop into acute liver failure and is associated with higher mortality (Mayr et al., 2018). Other routes of transmission are consumption of contaminated food, such as raw or undercooked meat derived from infected animals and through transfusion of infected blood (Lewis et al., 2010).

Hepatitis E can be spread through the eating food or drinking water in countries with poor sanitation, eating undercooked meat, venison (deer) and wild boar, eating raw shellfish that has been contaminated by sewerage, eating food prepared by an infectious person, direct contact with infectious animals, transmission from a pregnant woman to her baby (Patra et al., 2007). It can be spread through the direct contact with an infected person, such as a household member or sexual partner, or in childcare or healthcare settings (Mirazo et al., 2014).

**8. Diagnosis of HEV**

Diagnosis can be made indirectly by detecting antibodies against HEV in the serum, or directly by detecting the genome of the virus in blood or other body fluids (Kamar et al., 2014). Diagnosis of hepatitis E depends on clinical and epidemiologic features to detect IgM and IgG anti-HEV in serum. Anti-HEV IgG antibodies are detectable by 3 weeks post immunization and persist for at least 8 weeks (Meng et al., 1997). Serologic tests for IgG against HEV are insufficient to identify HEV infection. Chronic HEV infection is defined as an HEV viremia for more than 3 months with prolonged cholestasis and hematological malignancy. This condition has mainly been reported for HEV-3 and 4, leading to life-threatening liver fibrosis and cirrhosis (Lhomme et al., 2020).

**9. Treatment of HEV**

The HEV infections are usually self-limiting and asymptomatic in immunocompetent individuals. Prevention is the most effective policy to protect HEV (Wedemeyer et al., 2012). No effective and specific treatments against HEV infection have been developed yet, and also there is no HEV vaccine available, and treatment is palliative and supportive (Mirazo et al., 2014).

Current therapeutics used to treat HEV infection are the nucleoside analog ribavirin and pegylated interferon-α (PEG IFN-α) (Kamar et al., 2014). The broad-range antiviral ribavirin inhibits the replication of various RNA and DNA viruses. It is the only recommended treatment option for patients in whom reversal of immunosuppression is not successful and for other patients suffering from severe acute hepatitis E or liver failure (Kamar et al., 2010). The IFN-α is generally contraindicated after transplantation of most organs and is only recommended in liver transplant patients who do not respond to ribavirin (Kang et al., 2018). A Chinese

vaccine has been demonstrated to be protective against HEV in the general population and seems to be safe in pregnancy; however, its safety and efficacy is not determined (Wu et al., 2020).

**10. Conclusions**

From this study, we have observed that the HEV infection is a significant cause of acute and chronic viral hepatitis worldwide. It is now recognized as an important global health problem in both developing and industrialized countries for numerous morbidity and mortality. Still, it poses several challenges and is not fully understood. The disease is potentially preventable by simple improving hygiene and sanitary measures, and clean and healthy food intake, avoiding consumption of undercooked meat, improving prognosis and avoiding other existing difficulties. Moreover, it can be treated with medications, therapies, and nutrition supports.

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