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Review

Hepatitis E Virus: Epidemiology, Clinical Aspects, and Its Significance as a Major Pregnancy Risk

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Abstract: HEV is a single-stranded, positive RNA virus. The hepatitis E virus (HEV) is the causing agent of hepatitis, with a high prevalence rate in low-income countries due to poor sanitary conditions. It can exhibit acute, continuous, or extrahepatic consequences in immunocompromised individuals such as those undergoing organ transplantation and having HIV infection. HEV infection is either self limiting (silent), meaning the patient will possibly recover on his own, or symptomatic, causing acute liver injury or fulminant hepatitis and may eventually cause death. It can also cause chronic hepatitis that can progress to cirrhosis or recovery. Pregnancy-related HEV infection has an incidence rate of 30%. HEV escape from innate immunity, hormonal imbalances, defective monocyte–macrophage function, downregulation of the T-cell-mediated immune system, high cytokine production, nutritional factors, and socioeconomic conditions may play fundamental roles in the prevalence of HEV infection. It is necessary to take particular measures to reduce the incidence burden of HEV infection in high endemic locations as the incidence data, not the prevalence data, is more accurate at estimating disease dynamics. The purpose of this study is to throw light on several aspects of the hepatitis E virus and to discuss the incidence of HEV infection concerning other diseases. HEV molecular features, clinical features, epidemiology, extrahepatic manifestations, and multiple available diagnostics and treatment strategies for HEV are debated in the current review.

Keywords: hepatitis E virus (HEV); molecular organization; symptoms; diagnosis; extrahepatic manifestations; pregnancy; treatments

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1. Introduction

The hepatitis E virus (HEV) is one of the causal agents of hepatitis [1]. It typically results in 0.5% to 3% terminal illness in young adults, rising to 30% in expecting women [2]. HEV can exhibit acute hepatitis and continuous or extrahepatic consequences. HEV infects the liver and other organs and may get damaged indirectly. Chronic HEV infection is typically linked with immunocompromised individuals such as those undergoing organ transplantation or individuals with HIV infection or leukemia. Figure 1 shows various routes of HEV transmission.

Hepatitis E was once thought to be a water-borne virus that spread through the fecal–oral pathway or contaminated water, mainly with fecal material [3]. However, occasional cases of hepatitis E with zoonotic origin have also been documented recently in developed nations as a result of genetic similarity between human and animal isolates, and meat

consumption and blood or organ transplantation can also be traced as the source of infection [3,4]. Although the direct transfer of HEV from one person to another is rare, it is essential to recognize the possibility of vertical transmission [5]. Vertical transmission refers to viral transmission from parents to their offspring during delivery or via breastfeeding.

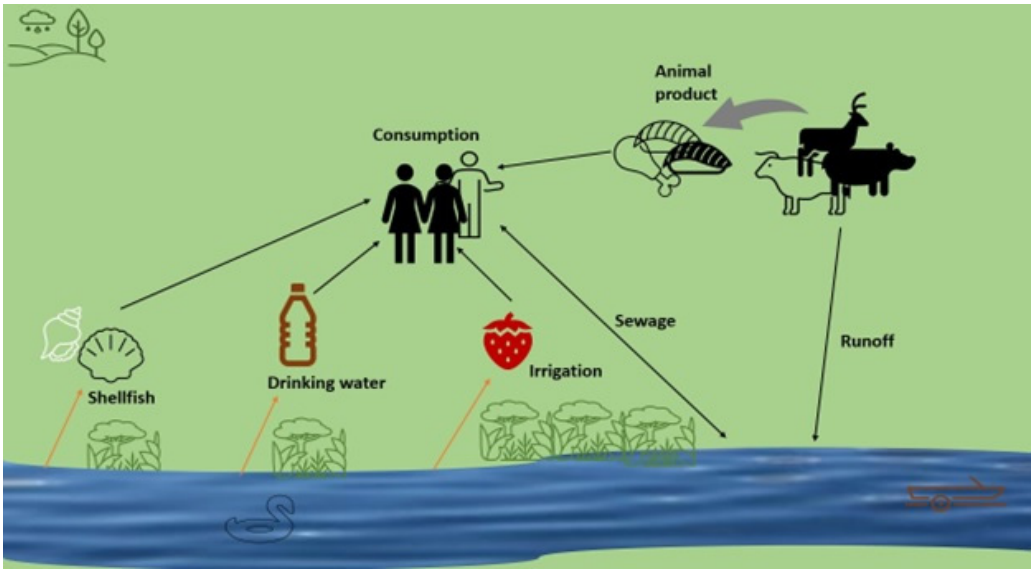

Figure 1. Circulation of HEV infection. The diagram depicts various routes of HEV transmission.

The incubation period lasts an average of 6 weeks and varies from 15 to 64 days. Hemodialysis and plasmapheresis are additional routes of HEV transmission. Anti-HEV IgG levels in hemodialysis patients are high in a few investigations with unclear origins [6].

The exact source of chronic HEV infection remains unknown. Additionally, comprehensive data on extrahepatic symptoms regarding HEV is lacking. A recent study revealed that human-derived monocytes (HMOs), human-derived macrophages (HMACs), and human bone marrow-derived macrophages (BMDMs) are tolerant to the hepatitis E virus. These cells mainly cause persistent and repeated infection in those patients with compromised immunity. The life cycle of HEV in human bone marrow-derived macrophages may be connected to hematological conditions that present extrahepatic manifestations [7]. Figure 2 illustrates a diagrammatic representation of HEV outcomes.

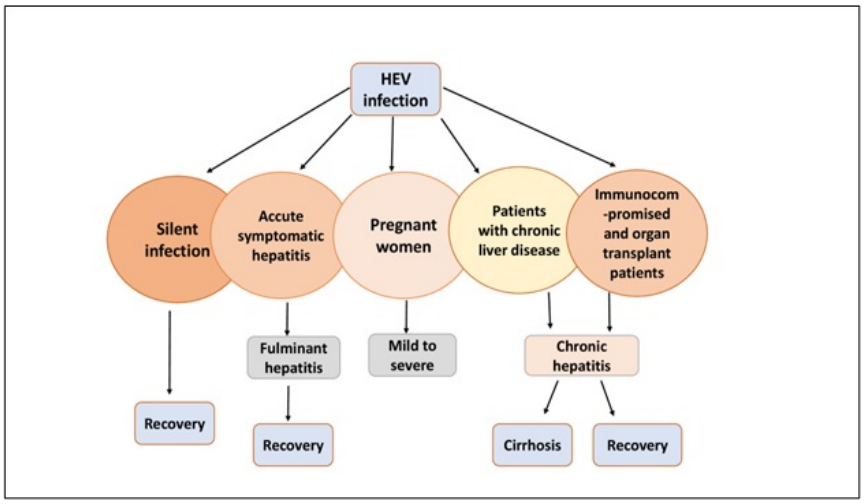

Figure 2. Diagrammatic presentation of HEV outcomes.

2. Classification and Molecular Characteristics of HEV

Hepatitis E virus (HEV) belongs to the *Hepeviridae* family of viruses, which consists of two genera. The genus *Piscihepevirus* comprises the cutthroat trout virus, whereas the genus *Orthohepevirus* consists of all avian and mammalian hepatitis E virus isolates. There are four distinct species within the genus *Orthohepevirus*, namely *A*, *B*, *C*, *D* [8]. Species *A* comprises HEV isolates from human, deer, wild and domestic pigs, rabbits, camels, and mongoose. Species *B* consists of all avian HEV isolates from birds. Species *C* consists of all HEV isolates from greater bandicoots, rats, Asian musk shrews, minks, and ferrets. Species *D* comprises HEV isolates from bats. All HEV isolates that are infectious to humans belong to species *A*, which comprises eight genotypes, as shown in Figure 3. Genotype 1 HEV (majorly Asian isolates) and genotype 2 HEV (Mexican and some African isolates) only infect humans. Genotype 3 (human, rabbit, pig, mongoose, deer) and 4 isolates infect humans and a few other animal species. Genotype 5 and 6 HEVs infect wild boars. Genotype 7 HEV infects camels and, reportedly, humans, while genotype 8 HEV infects Bactrian camels [9].

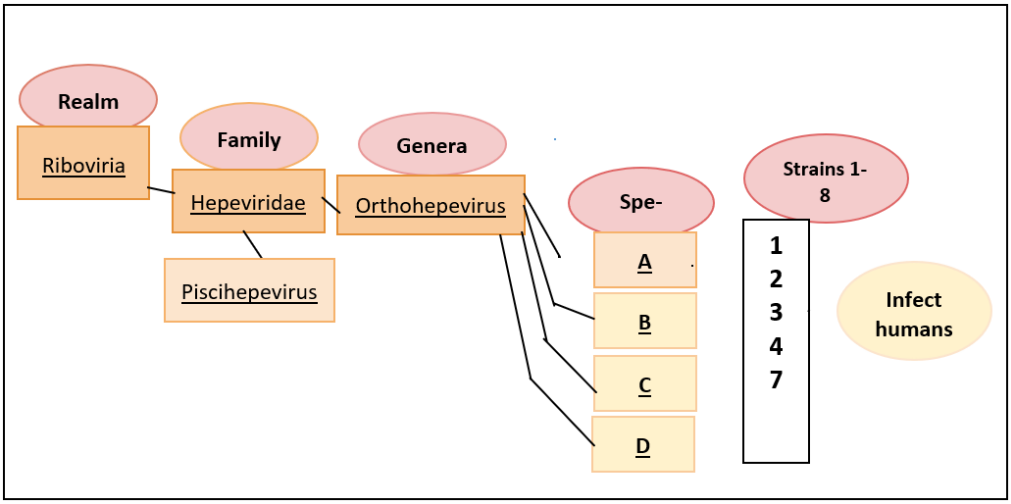

Figure 3. HEV classification. The family *Hepeviridae* has the genera '*Orthohepevirus*'. It has four species, of which species A contains eight viral genotypes. Genotypes 1, 2, 3, 4 and 7 mainly infect humans [9].

HEV is a nonenveloped virus that measures between 27 and 34 nanometers in diameter (nm). It comprises a single-stranded RNA genome (positive) and measures about 7.2 kb in length. Virological and hepatological characteristics of HEV are comparable to those of the hepatitis A virus (HAV). HEV is known to be present in blood with a coating of the lipid membrane, but it is not known to be encased in bile, and its primary source is fecal contamination. The HEV genome comprises a 5′ short non-coding region (NCR), ORF1, ORF2, ORF3, and ORF4 (specific to genotype 1) [9]. The non-coding regions of the viral genome are involved in non-structural proteins. The ORF3 region is responsible for encoding a small multipurpose protein, and ORF2 is related to the transcription of the viral coat protein. A poly adenosine tail of around 150–200 bases is present at the 3′ terminal (3′′ non-coding region of the genome). The ORF1 region of the HEV genome comprises the fourth open reading frame (ORF4) [10]. When endoplasmic reticulum stress occurs, ORF4 will take part and encodes a protein of 20 kDa. This protein regulates the viral RNA-dependent RNA polymerase activity via host–viral protein interactions. However, ORF4 is only expressed in HEV strains of genotype 1, even though it is present in all strains [11]. The functional domains of HEV are illustrated in Figure 4.

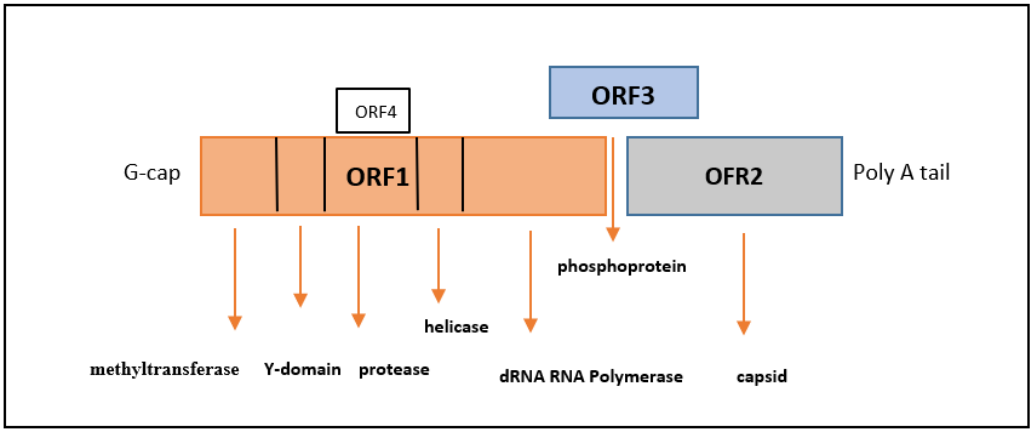

Figure 4. Functional domains of the HEV genome: methyltransferase domain, a Y domain, a PCP enzymatic domain, RNA helicase, phosphoprotein domain (ORF3), capsid-coding ORF2 region, and RNA-dependent RNA polymerase [10].

2.1. Life Cycle of HEV

Additionally, the blood-oriented bottom side of the hepatocytes also allows the release of enveloped hepatitis E virus (eHEV) particles into circulation. As a result, enveloped HEV can be identified in blood and urine, while naked HEV (without an envelope) can only be present in bile and feces [12,13]. The eHEV membrane is most likely derived from the trans-Golgi network.

The existence of the trans-Golgi network suggests that enveloped hepatitis E virus derives its envelope from the intracellular membrane [14]. The replication of HEV genotype 1 and genotype 3 has recently been demonstrated in primary intestinal cell cultures, and the intestinal crypts of a patient with chronic infection have demonstrated the presence of HEV RNA and ORF2-specific antigens. These results imply that HEV utilizes the digestive tract to replicate before it invades hepatocytes and causes hepatitis [15].

NHEV uses heparan sulphate proteoglycan (HSPG), even though enveloped HEV (EHEV) attachment is not dependent on HSPG [13]. Enveloped and nonenveloped HEV virions require clathrin-mediated (vesicular trafficking) and dynamin-2-dependent endocytosis for entry [16]. Not much is known about the precise uncoating mechanism; however, in general, it is followed by the discharge of the nucleic acid into the cytosol, where it acts as the model for ORF1 translation. Since translation is cap-dependent, it requires a 7-methylguanosine (m7G) cap at the 5′ end of the HEV genome that recruits protein factors to assemble pre-initiation complexes. This structure is necessary for the recruitment of the 40S ribosomal subunit [17].

To create the negative sense intermediate RNA, RdRp must attach to the viral genomic RNA (3′ UTR). The progeny positive-sense viral genomes are generated using this intermediary RNA as a template [18]. The brefeldin A-resistant guanine nucleotide exchange factor 1 (GBF1), Golgi-specific, plays a vital role in the complex activity of HEV replication complexes. GBF1 is not likely recruited to replication sites, as it does not co-localize with the ORF1 protein and its subcellular distribution is unaltered by viral infection or the overexpression of viral proteins. Replication inhibition occurs when the ubiquitin–proteasome system is inhibited [19]. Evidence shows that this system contributes to HEV replication through acidifying endosomes to favor uncoating and virus entry. The viral encapsidation and assembly are initiated after interaction between the capsid and the 76 nucleotide region on the 5′ terminal of the viral genome [20]. The vascular transmission process of HEV is illustrated in detail in Figure 5.

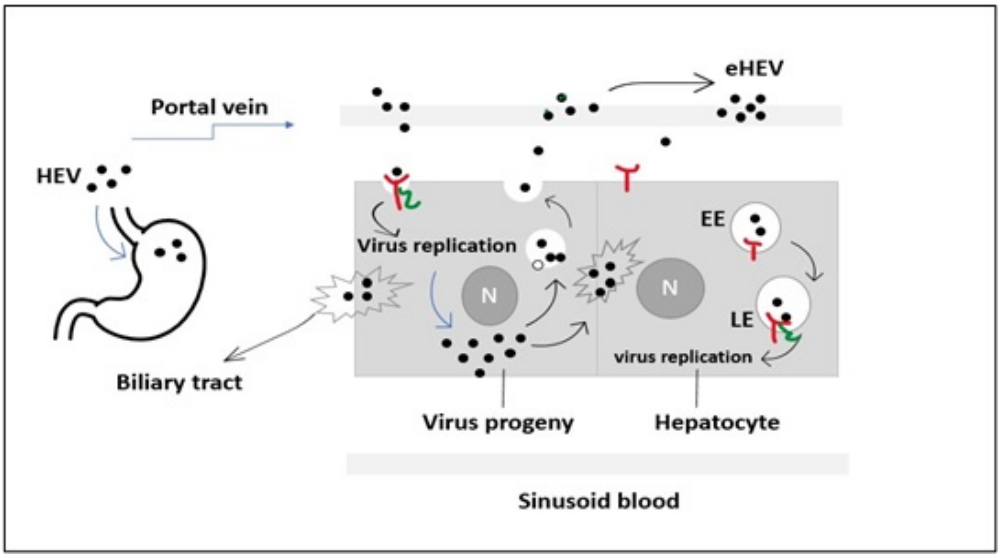

Figure 5. Vascular transmission of HEV. Viral genome assembly occurs in the cytoplasm, and the genome is encapsidated, along with ORF3. Then, multivesicular bodies take the assembled viruses and discharge them via the exosome system of cells. The apical side of the hepatocytes releases HEV particles as enveloped HEV into the biliary canaliculi, where the bile enzymes convert the enveloped hepatitis E virus (eHEV) to the naked hepatitis E virus (NHEV). These HEV particles can cause infection.

2.2. HEV Escapes from Innate Immune Response

Although the host has strong immune defences, HEV has evolved several ways to circumvent these defence mechanisms, resulting in pathological conditions. These mechanisms include the inhibition of Toll-like and RIG-like receptors, suppressing the production of IFNs and pro-inflammatory cytokines, and reducing the expression of MHC-1 molecules, as indicated in Figure 6.

It is vital to understand the relationship between the host immune system and hepatitis E viral proteins to understand the infection potential of HEV and disease-promoting components. IFNs are responsible for directing the antiviral adaptive immune response. Research data from chimpanzees demonstrated that HEV causes a more robust IFN response as compared to hepatitis A virus (HAV) and hepatitis C virus (HCV). Examining rhesus macaque liver gene expression revealed different profiles based on the genotype (gt1 or gt3), suggesting that all HEV genotypes cannot be described as equivalents [21]. In short, 25% of the interferon-responsive genes, including IRF3 and IRF7, or ISG15, were negatively regulated during the initial stages of viremia after an HEV gt1 infection. During HEV gt3 infection, however, these identical genes were positively regulated. Variations in virus protein sequences that change the virus–host signaling relationship are likely responsible for genotype-dependent host immune gene expression variations [22].

Although HEV genotype 1 contains at least one site in the RdRp region targeted for microRNA, neither gt1 nor gt3 disrupts the synthesis of microRNA-122. MicroRNA-122 supports HEV (genotype 1 and 3) replication in human hepatoma and non-hepatoma cells. HEV (gt1, gt3) replication was significantly decreased when microRNA-122 molecules were inhibited but may negatively affect liver homeostasis. MicroRNA 122 has a protective role in cardiac fibrosis and liver homeostasis; therefore, there is a need for more research on its therapeutic implication [23].

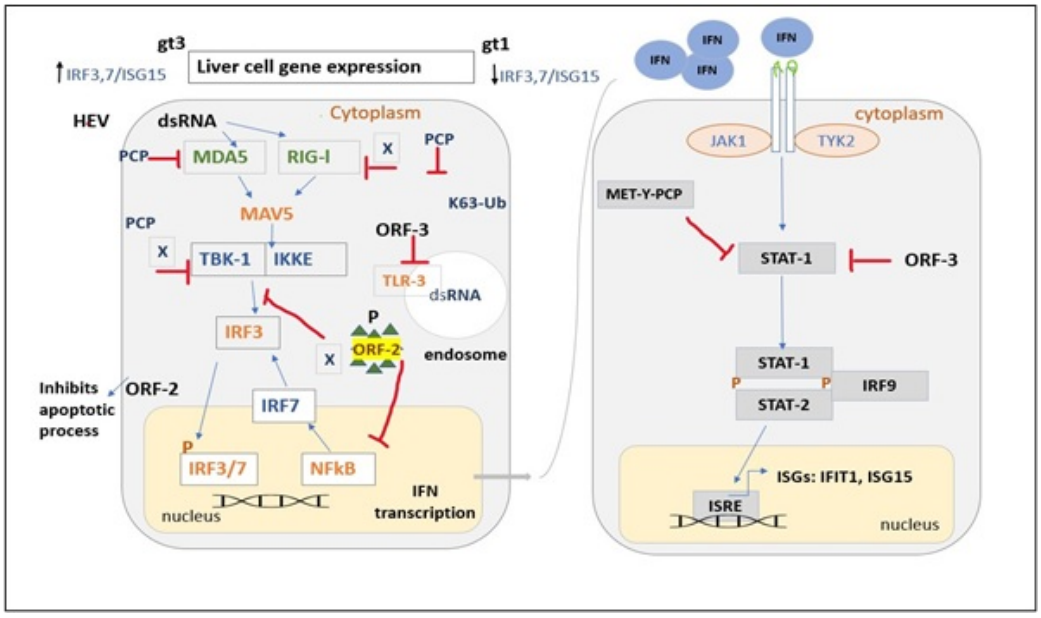

Figure 6. Innate immune escape by HEV. The gene expression of liver cells revealed that different genes are activated in infected cells, particularly following genotype 1 and genotype 3. The detection of the double-stranded (ds) HEV RNA results in the generation of type 1 and type 2 interferons (IFNs) via the retinoic acid-inducible gene I (RIG-) and melanoma differentiation-associated protein 5 (MDA5). The endosomal compartment's Toll-like receptor 3 (TLR3) recognizes HEV RNA. The ORF1 protein's protease domain (PCP) limits IFN induction and inhibits signaling via RIG-TBK-1 through dissociating ubiquitin from RIG- and TANK-binding kinase 1. Methyltransferase (MET) inhibits the release of ferritin, decreasing the inflammatory response. IFN-regulating protein 3 is prevented from being phosphorylated (P) by the X domain and ORF3 (IRF3) infection. It has been demonstrated that ORF2 inhibits the apoptotic process and NF-k activity. Through RIG, ORF3 promotes the synthesis of type I INF while inhibiting the synthesis of TLR3. Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) and ISG15 expression of ISGs are all inhibited due to ORF1 (MET-Y-PCP) and ORF3 binding to STAT1. This binding prevents its phosphorylation and the upregulation of the downstream cascade [22].

3. Manifestations of HEV Infection

After being exposed to HEV for two to nine weeks, patients begin to experience clinical symptoms such as:

- Myalgia;
- Arthralgia;
- Anorexia;
- Hepatomegaly;
- Fever;
- Weakness;
- Vomiting;
- Jaundice.

HEV can occasionally result in abrupt liver failure. Although chronic cases are rare, they are evident in immunocompromised people, and at the same time, acute hepatitis is more frequent in adults [24].

Even though the infection may not induce symptoms in some people, it may also cause clinical illness in another group. Notably, the clinical disease begins to manifest 15–60 days (on average, at 40 days) after HEV infection. At first, these symptoms are nonspecific and include restlessness, anorexia, nausea, fatigue, myalgia, and abdominal pain. Later, acute hepatitis symptoms include jaundice, dark urine, pale stools, and the appearance of hepatomegaly.

When it becomes symptomatic, IgM antibodies against HEV are elevated in the sera of infected persons and are detectable over 14 days to 12 weeks, with a sensitivity of 99.4% and specificity of 74.3%. IgG antibodies, which show a prior HEV infection in sick persons, develop in later stages and last for many years after the virus has dissipated. According to laboratory studies, HEV infection is responsible for high bilirubin levels in serum and a significant increase in enzymes in the liver [25]. The typical incubation time is 40 days (15–60 days). Most acute infections spontaneously subside after 4–6 weeks without traceable symptoms. However, pregnant women in underdeveloped countries are most frequently affected by acute HEV infection that drastically affects liver function. In the West, acute HEV infection can cause significant acute liver damage, but it seldom results in acute liver failure. Both gt1 and gt2 are linked to the emergence of decompensated liver disease and acute or chronic liver failure.

4. Incidence Rate of HEV in Developing and Developed Nations

The rapidly spreading HEV causes acute viral hepatitis and is the leading cause of acute hepatitis infection in adults in Central Asia, the Indian subcontinent, and Southeast Asia. After hepatitis B, it is the second most common cause of acute hepatitis infection in the regions of the Middle East and North Africa. According to global estimates, over 20 million new cases of HEV infections occur yearly, of which 3.4 million are symptomatic [26]. The WHO reported 44,000 fatal HEV cases, roughly representing 3.3% of all deaths caused by viral hepatitis [27]. The frequency of HEV infection ranges from 7.2% to 35% in impoverished nations with generally poor health conditions. The prevalence rate, however, is approximately 3% in developed countries. The death rate for this virus, which is often self limiting, ranges from 1% to 3% and increases in cases of pregnant women [28].

Several variables, including varied degrees of virus exposure, different living standards in distinct regions, and various modes of viral transmission, can impact the distribution of HEV infection within a state. In nations with inadequate sanitation systems, gt1 and gt2, as human pathogens, can cause HEV endemics or epidemics [29].

In developed nations, food-borne zoonosis is thought to be the most typical method of HEV transmission. The discovery of HEV in pigs with high similarity to HEV strains reported in people was the first source of proof for HEV zoonosis. Pigs, deer, rabbits, mongooses, cattle, sheep, and horses are among the animals that can contract genotypes 3 and 4 [30]. In multiple case reports, food-borne strains of HEV are described. Undercooked or raw pork, pig liver, sausages, shellfish, green vegetables, and strawberries have recently been recognized as significant risk factors for human HEV infection [31]. Soft fruits and infected seafood are also acknowledged as potential food-borne transmission routes.

Until now, only one incidence of genotype 7 infection has been reported in humans. The infected person is from the United Arab Emirates who frequently consumed camel milk and meat products and experienced a liver transplant. Therefore, paying more attention to the prevalence of camel-based zoonotic HEV in that region is essential [32]. The coliform tract is associated with HEV spread, like other viruses. HEV is self-limiting in young women indicating a low infectious load (0.1–4%). However, HEV persisted in underdeveloped countries for a long time due to poor sewage systems, causing endemic situations and affecting several individuals with liver disease.

Manifestations of gastrointestinal hepatitis are distributed differently worldwide, with genotype 1 being more widespread in Asia, Africa, and Latin America and genotype 2 being more widespread in sub-Saharan Africa and Mexico. Both vulnerable and healthy populations can contract genotypes 3 and 4, which are primarily found as sporadic cases in developed countries [26]. Viral hepatitis A (HAV) and HEV coinfection generally showed a higher prevalence in the summer, autumn, and winter (December to May).

Hepatitis E is an "emerging infection" in developed nations. It would be more accurate to call it locally acquired hepatitis E in these nations. The prevalence of IgG antibodies against HEV infection in developed countries was reported to be 5% in many early investigations, and therefore, hepatitis E is not a significant health concern in these areas.

The seroprevalence for anti-HEV is approximately 0.6-52% in the Europe [33], 3–16% in the U.K., and up to 50% in some French hyper-endemic regions. The number of confirmed symptomatic cases of locally acquired HEV infection in England has progressively escalated in the last 14 years, from 124 in 2003 to 958 (2015). About 80,000–100,000 HEV asymptomatic infections are reported annually in England. Non-travel HEV infection is not a mild condition; patients with underlying chronic liver disease have mortality rates as high as 27% [34]. In France, there is significant regional diversity in the seroprevalence of genotype 3, and the southwest and northeast of the nation all have incredibly high seroprevalence rates. IgM seroprevalence of 1% and 22.4% overall IgG seroprevalence have been reported in blood donors. South France self-reported that patients who consumed sausage made from pork liver, pate, and wild boar meat had the most significant IgM seroprevalence [35].

Recently, HEV genotype 4 infection instances have been documented in Western nations like Belgium, Germany, and France. This genotype is highly prevalent in endemic in China, Japan, and Indonesia [36]. In 2011, Italy faced an epidemic of genotype 4 [37]. Since this endemic was not specific to travel-borne or food-borne illnesses from imported products, new strains are more likely to emerge. The most reported symptom in this outbreak was fatigue, which only affected male patients (mean age: 59 years). Children between 3 and 18 years old from low socioeconomic backgrounds have a 50% to 90% greater prevalence of HEV than their socioeconomically better-off peers. Young adults (15–39 years) have the highest infection rates, affecting both sexes equally.

Hepatitis E cases have been recorded in large numbers from Pakistan, Iraq, and India. A study comparing Tehrani inhabitants of different age groups has shown that HEV prevalence rates are higher than in Pakistan and lower than in Turkey during 2017–2018. In Pakistan, acute HEV infection was discovered in the middle of the 1950s for the first time. In the early era of the disease, the virus was first incorrectly attributed to other viral hepatitis. However, it was later found that HEV was just the cause of a small fraction of diseases. The majority of people in Pakistan are still affected by HEV. Several bacteria have recently been found in Pakistan, and these microbes appear to be associated with indicator microorganisms in sewage systems. Karachi city experienced a severe epidemic of active disease, spurred on by HEV in 1994 and January 1995, prompting considerable public concern. According to a study conducted in 2015, overall prevalence of HEV in pregnancy was 0.19% [38]. According to Butt et al. (2016), the seroprevalence of IgG antibodies in healthy-appearing individuals was 14–26% [39]. Patients who drank non-filtered water had an incredible prevalence rate of over four times more (19.38%) than those who drank filtered water (4.62%).

5. Incidence Rate of HEV in Pregnant Females

According to studies, pregnant women demonstrate more significant signs of viral infection. Growing evidence shows that genotype 1 HEV infection, during the third trimester of pregnancy, is an important cause of maternal death in South Asia. A more severe infection that can occasionally lead to fulminant hepatitis is a hallmark of hepatitis E infection during pregnancy, especially in the third trimester, which raises morbidity and death rates for both mother and fetus [40].

Higher HEV rates have been associated with increased pregnancies in recently industrialized areas like Egypt, China, Pakistan, Nigeria, and Sudan. It is unclear which factor—viral pathogenicity, viral variations, immunological state, socioeconomic status, or a gap in prompt and effective care—is responsible for the catastrophic outcome of vaginal birth in each location. Pregnancy increases the risk of death for unknown reasons, especially during the second phase [41]. A very contagious HEV is known to cause severe liver damage during pregnancy, with a 30% survival rate. The incidence of liver failure was higher in prenatal treatment in India, Iran, and Northern Africa. Although 50% of individuals continued to transmit the virus to family members, women with hepatitis had a 100% survival rate. The virus in pregnant females is critical for comprehending the

illness caused by the virus and formulating a strategy for its prevention and eradication. Researchers are looking for evidence that HEV can be associated with sexual transmission.

The prevalence of fulminant hepatitis is more common in pregnant women. A recent study demonstrated for the first time that pregnant women had greater hepatitis E incidence and fulminant rates than non-pregnant women and males. Lower progesterone receptor expression, greater interleukin, a higher viral load, and a poorer CD4/CD8 cell ratio are some of the mechanisms causing fulminant hepatitis during pregnancy [42]. According to narrative reviews of observational research, pregnant women with HEV are more prone to experience poor maternofetal outcomes, especially during the second and third trimesters.

The prevalence rate of HEV infection was higher in symptomatic women than in asymptomatic ones, as described in a multivariable meta-regression model. Maternal mortality, low birth weight, truncated gestational age, intrauterine deaths, and miscarriages were all linked to HEV infection. HEV during pregnancy was linked to several other outcomes, including a three-fold increase in intrauterine fetal immaturity, a two-to-three-fold increase in intrauterine fetal mortality, and additional effects.

The prevalence of HEV in the general population (women aged between 15 to 45 years) was between 5 and 22%, as predicted in earlier modelling research. Pregnant women are more susceptible to HEV infection than other hepatitis viruses such as A, B, and C [43]. The evidence suggests that hepatitis E contributes to pregnancy-related jaundice.

Another critical factor is the increased level of IgM in the serum of HEV-symptomatic women. In thirteen African countries, the ratio of immunoglobulin was higher in pregnant women in rural areas than in other demographics, with 0 to 84% HEV seroprevalence.

According to a study by Shahid Ahmed Khan involving 115 multiple pregnancies, all HEV cases are admitted during the first trimester of pregnancy. The fulminant liver failure led to the death of three of twenty-one HEV-infected women. Every three months, the rate of HEV infection in pregnant women rises and worsens, eventually resulting in death in the last three months. According to a study from India, 63% of HEV infections result in hepatitis during the second or third trimester [44].

Regarding pregnancy outcomes, HEV infection in newborns delivered by HEV-positive mothers is generally harmful. However, children may typically survive without suffering a severe disease. Following a report from the Emirates, most children born to mothers who had HEV were either minimal, diagnosed with hepatitis, or passed away within a few hours of being born. However, the death of two newborns happened among HEV-infected mothers; one was due to an IUD and the other to an abortion (10%), which was 5% more than the rate among babies born to uninfected mothers. The incidence rate was significant in Ethiopia, with 14 IUDs and 10 preterm births in 40 pregnant women with chronic infection during the epidemic. In Nepal, a similar situation, particularly regarding medical loss, has been observed, where 40% of thriving babies of infected mothers died within two weeks after birth [44].

Another crucial factor is the likelihood of vertical transmission of HEV infection from the mother to the fetus. Hospital-based research conducted during a Delhi outbreak found that HEV infection during pregnancy was linked to perinatal death, stillbirth, or miscarriage in 56% of cases. According to a recent study, antenatal maternal deaths are often linked to additional fetal deaths, and in developing countries, HEV infection may cause 2400–3000 stillbirths each year [45]. Pregnant women with HEV infection have a high risk of preterm delivery and poor neonatal survival rates. In two independent studies from India, the mortality rate for the newborns of infected mothers ranged from 15% to 50% within a week of delivery. In addition, 14 intrauterine deaths and 9 preterm births occurred among 39 HEV-infected pregnant women during an outbreak in Sudan from 2010 to 2011.

Despite the colostrum's anti-HEV antibodies and HEV genome presence, breastfeeding is safe in asymptomatic HEV-infected women. However, it is worrisome if the mother has high virus exposure or severe hepatitis. In these situations, formula feeding is suggested due to the danger of transfer from contaminated breast milk or from lesions on the nipple [46]. Some studies, however, have shown that all children born to HEV-infected mothers

were healthy. On the contrary, numerous studies have demonstrated significant regional and local variations in children's health in HEV-infected females, including congenital disabilities, birth complications, uterine perforations, and fetal or preterm death.

6. Relation of HEV with the Immune System during Pregnancy

Though the exact cause of liver damage is unknown, the interaction of hormones and the immune system probably occurs during pregnancy with a high HEV load. It makes the pregnant woman more susceptible to infection. Pregnant women are more prone to HEV infection because of immunological changes made during pregnancy to support the maintenance of the fetus in the maternal environment through reducing T-cell-mediated immunity.

It is believed that there is a synergy between hormonal (estrogen and progesterone receptor expression) and immunologic changes in T-cell immunity during pregnancy, together with a high viral load, even though the physiopathology of HEV infection in pregnancy and its effects are still poorly known [40]. Only abortion was not the cause of HEV infection in cases of fetal non-survival. All phases of fetal development are affected by physiological changes in the hormone level and immunological interactions, which should favor pregnancy development in a healthy pregnancy.

Over the course of 5 months of pregnancy, the level of cytokines in the plasma starts to decline. Due to this gradual decrease in cytokine levels, there is a low concentration of cytokines in the plasma in late pregnancy, which lowers overall immunity. This explains why an elevated risk of unfavorable fetal infections in late pregnancy is linked to HEV infection. According to one study, HEV infection increases the risk of death during pregnancy by a factor of seven [42].

6.1. T-Cell-Mediated Immune System

The adaptive immune system (T-cell mediated) is compromised during pregnancy to maintain the antigenic fetus inside the mother [47]. The ratio of T-helper type 1 and type 2 cells is changed, with a clear shift toward Th2 cells [48]. Most cytokine levels continue to lower until 20 weeks of gestation, a critical stage for the fetus's survival. Through limiting cell-mediated immunity, cytokines, including TGF, IL-4, and IL-10, are released by the placenta, and immunological tolerance is aided by trophoblasts. According to Bose et al., a more excellent IL-12/IL-10 ratio, a lower progesterone receptor and PIBF expression, and a high HEV burden are all linked to a higher death rate in HEV-infected pregnant women and associated fetus [49].

6.2. Defective Monocyte-Macrophage Function

Compared to HEV-induced acute liver injury, pregnant patients have impaired monocyte–macrophage function accompanied by decreased Toll-like receptor 3 and 7 expressions and reduced downstream signaling. Thus, an inadequate trigger for the innate immune response affects the severity and development of HEV-induced acute liver failure during pregnancy [50].

6.3. HEV-Induced Acute Liver Injury

In pregnant HEV-infected females with acute liver failure, it has been discovered that myeloid interactions and Toll-like receptor signaling are both compromised. As a result, the onset and intensity of hepatotoxicity brought on by HEV infection may be due to a deficiency of innate immunologic signals [50]. The DNA-binding activity of nuclear factor kappa B was considerably higher in pregnant patients with HIV-induced FHF compared to non-pregnant women and women with acute viral hepatitis (AVH) without FHF. These instances either had no p65 activation at all or had significantly less of it [51].

6.4. High Level of Cytokines

High levels of cytokines like TNF, IL-6, IFN, and TGF-1 may also be linked to worse pregnancy outcomes. HEV capsid protein decreases NF-B activity in the cell through blocking the UB-mediated proteasomal degradation of IκBα in human hepatic tissue, extending the viability of infected liver cells [52].

6.5. Hormonal Imbalance in HEV-Positive Pregnancy

Many steroid hormones are produced during pregnancy. These steroid hormones may inhibit CD4 cells while promoting virus replication. Women with acute liver failure infected with HEV have higher CD8 counts than CD4. Furthermore, compared to pregnancy without HEV or healthy pregnant women in the control group, expecting females with HEV-induced acute liver failure exhibited more significant estrogen, progesterone, and B-HCG levels [53]. In situations of pregnancy-related liver injury, fulminant hepatic failure and, ultimately, mortality are more likely due to the interaction between infectious agents and host immunological and hormonal variables.

Hormone levels in the control group were physiologically high but considerably higher in childbearing females with HEV infection, indicating a direct relationship between HEV and the immune system. While estrogen and ESR2 levels are biomarkers for maternal death during pregnancy with HEV infection, estrogen may also be a biomarker for preterm delivery [54]. Through the activation of the adaptor protein (ORF3 of HEV), the host factors induced by low immunity and hormonal imbalances are thought to harm cellular immunity and facilitate viral proliferation, leading to fulminant hepatitis during pregnancy.

Bose et al. found a strong relationship between severe and adverse pregnancy complications in HEV-infected pregnant females and high levels of HEV viral load as well as low levels of progesterone receptor expression, PlBF, and PROGINS carriers. It was discovered that estrogen levels in pregnant HEV-infected women were significantly linked with fetal death and may be used as a diagnostic biomarker for preterm delivery [49]. The reduction in progesterone may be responsible for preterm labor.

According to in vitro research, Tamoxifen, an estrogen antagonist, suppresses HEV replication, while estradiol analogues (17-estradiol and diethylstilbestrol, or DES) promote it. HEV infection is known to suppress the Ras-Raf-MEK-ERK signaling pathway, the cAMP-PKA-CREB, the PI3-AKT-mTOR [55], and other signaling pathways, which ultimately affect estrogen signaling pathways. Studies based on protein–protein interactions show that the estrogen receptor (E.R.) and the HEV helicase interact to suppress the expression of the E.R. [56].

6.6. Antibody-Mediated Hepatitis E Severity in Pregnancy

These results show a definite correlation between antibody levels and hepatitis E severity and imply antibody-mediated liver injury, as indicated in Figure 7. While IFNa levels declined in HEV-infected pregnant women in the later trimesters and were independent of healthy pregnancies, subclinical IFNa levels were higher, raising the question of whether these higher levels are responsible for the asymptomatic infection. The levels of four cytokines—CXCL10, IL10, sIL2RA, and IL6—and IgM-anti-HEV titers were correlated with ALT levels, and maternal females' anti-HEV immunoglobulin was associated with how sick they were. Even if the relevant gene expression in the PBMCs is increased, the illness in pregnancy was linked to a considerable decrease in plasma cytokines [42].

HEV recurrence in severe patients is linked to virus-related factors. HEV permanence is related to more significant quasispecies variability in the ORF1 and ORF2 domains during the acute stage of infection. Low quantities of the M domain protein of the virus are present in chronic HEV patients. The presence of T lymphocyte autoantigens in the M domains further emphasizes the significance of the cell-mediated immune response in eradicating HEV as well as HEV is inhibited via IRF-3 phosphorylation with help of X-domain [57]. The Ka/Ks ratios of viral parts are one indicator of selection pressure on quasispecies.

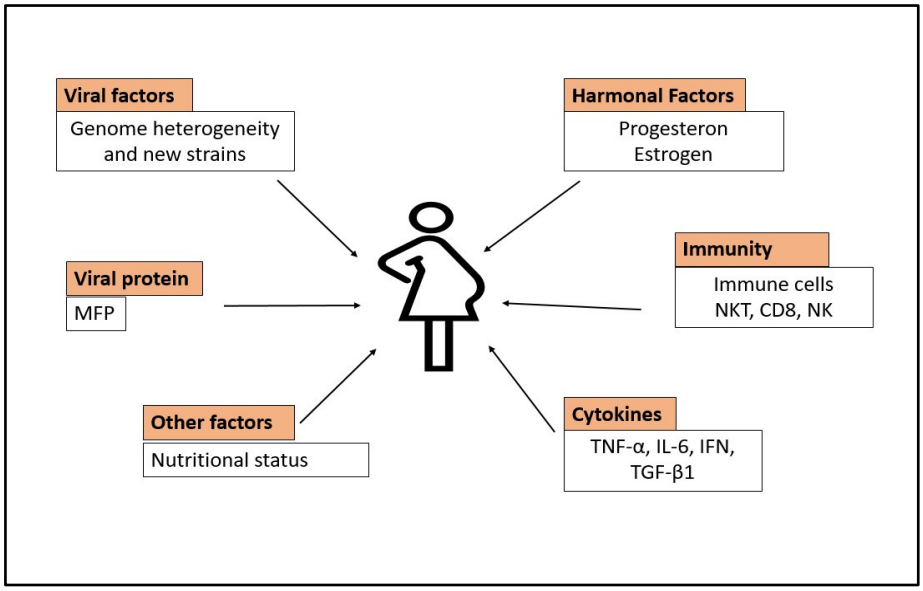

Figure 7. Diagrammatic illustrations of HEV-induced liver injury during pregnancy. Various viral factors, hormonal factors, immunity, and nutritional status of a woman can play prominent roles during pregnancy. Several theories support that host factors, including immunological status, hormone levels, dietary imbalances, and viral factors, cause poor outcomes of HEV infection during pregnancy. Unfortunate pregnancy and birth outcomes are often linked to poor maternal nutrition. Micronutrient deficits, insufficient diet, and exposure to infectious disease results in immunologic compromise, diminished mucosal immunity, and altered cytokine expression that eventually increase the risk of HEV spread [42].

Additionally, prolonged HEV infection was linked to increased quasispecies variants, a weak inflammatory response, and enhanced blood concentrations of the inflammatory mediators involved in leukocyte activation and trafficking in acute hepatitis. Patients undergoing solid organ transplantation (SOT) and suffering from severe HEV infection eventually develop cirrhosis. Within three to five years, over 10 percent (14.3%) of the total SOT recipients with HEV infection develop cirrhosis [58].

7. Extrahepatic Manifestations of HEV

Over the past few years, our awareness of HEV-induced pathogenesis has greatly expanded. Hematological cancers, age, and prior liver condition are risk factors in the general population for developing fulminant hepatic failure (FHF) due to HEV gt1. Acute, non-travel-related hepatitis E is associated with HEV genotype 3,most prevalent in animals which can manifest as fulminant hepatitis with encephalopathy and coagulation issues [59].

Recent research has demonstrated the presence of the ORF4 domain in genotype 1 HEV, which has been postulated to be a causal component in stillbirths and fetal abnormalities. This is further corroborated by the finding that HEV gt3 infection in expecting females did not result in fatal pregnancy and is possibly related to the absence of ORF4, while other potential differentiating variables remain to be determined.

Extrahepatic manifestations of HEV might be age dependent. HEV-highviral load in pregnant women may develop jaundice to neurological disease [60]. Moreover, a study from Pakistan said that neurological disorders were more prevalent among women (56.6%) with age of 30 to 50 years [61]. The majority of the patients were between the ages of 31 and 40. A related Indian study found that prevalence of neurological disorder is higher among women than men [62]. It is further reported that the most common symptom seen in twenty-eight (82%) patients is itching, which is followed by jaundice in twenty-seven (79%), nausea or vomiting in twenty-five (74%), neurological disease in eighteen (53%)

cases, and damage to the gums or anterior naris in two cases. Eleven patients experienced sudden internal organ failure that caused sudden death.

There have been neurological symptoms associated with HEV genotypes 1 and 3. Patients who experienced neurological symptoms while infected with HEV had HEV RNA in their cerebrospinal fluid. Several studies have demonstrated a higher occurrence of HEV infection among Guillain–Barre syndrome (GBS) patients, and many of them have documented co-occurrence of acute hepatitis E with GBS. According to a study from the Netherlands (n = 201), 5% of patients with GBS also had an acute HEV infection. Other neurological conditions include transverse myelitis, cranial nerve palsies, and neuralgic amyotrophy. Pancreatitis, renal impairment with cryoglobulinemia, and hematological abnormalities are additional recognized extrahepatic symptoms associated with HEV infection [63].

Brachial neuritis or neuralgic amyotrophy (N.A.), also recognized as Parsonage–Turner syndrome, is a neurological ailment described by abrupt, severe pain in the shoulder, tailed by severe weakness. A European study compared 61 patients with HEV-NA to 61 patients without HEV-NA and found that HEV-NA more frequently causes bilateral irregular involvement (80.0% vs. 8.6%) and causes significant brachial plexus damage. At the same time, damage associated with the extra brachial plexus is also more evident in HEV-NA patients [63,64].

HEV-associated membranoproliferative glomerulonephritis and membranous nephropathy are documented complications in kidney transplant cases. Kidney function and histology assessment in 51 SOT patients positively diagnosed with HEV genotype 3 infection showed a statistically noteworthy decline in glomerular filtration. Interestingly, cryoglobulinemia was cured, and renal function was amended along with improvement in proteinuria [65].

Several different types of anemia are associated with HEV infection; hemolytic anemia can impede acute hepatitis, with a 23% occurrence rate demonstrated in HEV patients. This frequency may increase to 70% in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Autoimmune hemolytic anemia (AIHA) and aplastic anemia are also common among HEV patients [66].

Another consequence linked to hepatotropic viruses, including HEV, is thrombocytopenia [67] which can result from hypersplenism, decreased liver thrombopoietin synthesis, or inhibited bone marrow. Antiplatelet antibodies have occasionally been discovered in cases of thrombocytopenia caused by HEV [68]. The majority of times, thrombocytopenia resolved on its own, but sometimes, patients required corticosteroids, intravenous globulin, or platelet transfusions.

Hepatic viruses are also implicated in acute pancreatitis, often resulting from edema of the ampulla of Vater, which prevents the flow of pancreatic fluid. Acute pancreatitis was the only observable cause in single-center research reported from France, where 2.1% (16/790) of patients exhibited evidence of recent HEV infection through serological testing.

It is well known that immunosuppressed people can have chronic HEV infection and cirrhosis. Patients with HIV infection, those with hematological malignancies [69] and recipients of solid organ transplants fall under this category and are frequently reported to have chronic HEV infection [70]. HEV is proven to harm the liver structurally, resulting in nodules, fibrotic alterations, and cirrhosis. It is further demonstrated that viral infection-related damage, including inflammation and structural liver damage, regresses after HEV is eliminated. It is unclear if HEV can lead to persistent infection in individuals with more severe humoral and cellular immune deficits, such as those with final-stage renal dysfunction and who need renal replacement therapy. A comprehensive list of HEV-induced extrahepatic manifestations is listed in Table 1.

Table 1. Extrahepatic manifestations associated with hepatitis E virus infection.

System	Manifestations	References
Neurological system	Guillain-Barré syndrome	[71]
	vestibular neuritis	[72]
	Meningoencephalomyelitis	[72]
	Mononeuritis multiplex	[73]
	severe myositis	[74]
	neurological injury	[75]
	Bell's palsy	[76]
	Neuralgic amyotrophy	[77]
	Seizure	[78]
	Pseudotumor cerebri	[79]
	Oculomotor palsy	[80]
	Polyradiculoneuropathy	[81]
Hematological system	Thrombocytopenia	[82]
	autoimmune hemolytic anemia	[83]
	Aplastic anemia	[84,85]
	Hemophagocytic syndrome	[86]
	CD30 (+) cutaneous T-cell lymphoproliferative disorder	[87]
	Thrombotic thrombocytopenic purpura relapse	[88]
Kidney	membranous nephropathy	[89]
	Cryoglobulinemia	[90]
	monoclonal gammopathy	[91]
Heart	Myocarditis	[92]
Pancreas	Acute pancreatitis	[93–95]
Thyroid	Autoimmune thyroiditis	[96]
	Subacute thyroiditis	[97]
Skeletal system	Polyarthritis	[98,99]
Vasculitis	Henoch-Schönlein purpura	[100]

8. Transmission Route of HEV

Numerous investigations have shown the parenteral mode of infection to be via blood transfusion [101], along with the oro-fecal route being the primary route for hepatitis E infection. Studies regarding the transmission of HEV via dialysis demonstrate a significant seroprevalence of hepatitis E in the patients who received hemodialysis [102,103]; dialysis duration, however, does not correlate with HEV infection. Persons with uremia may be more vulnerable to HEV infection than people with normal renal function. Also, erythropoiesis is impaired in patients with final-stage renal failure and often needs blood transfusion. Although it has been shown that direct infection through blood transfusions can occur, blood products are not checked for HEV in most countries. The lack of a correlation between receiving blood products and the presence of HEV in serum, however, raises the possibility that HEV infection acquired via transfusion may not be the cause of the elevated anti-HEV IgG seroprevalence observed in the hemodialysis group. There may be brief or occasional outbreaks of HEV infection occurring within the dialysis unit that went unnoticed or were simply subclinical. This theory is supported by a study in which the patients receiving hemodialysis had anti-HEV IgM antibodies, even though none had a detectable HEV RNA genome [104].

Heparin administration to dialysis patients could be one possible source of HEV. Heparin may cause HEV in dialysis patients since it is manufactured from the porcine small intestine, which frequently becomes infected after experimental pigs become infected. Past HEV infections that led to end-stage renal failure can probably help to explain, at least in part, the increased anti-HEV seroprevalence. If this is the case, one may have expected kidney transplant recipients to have a similar seroprevalence.

9. Clinical Diagnosis of HEV

There is still no international alliance for lab HEV testing, and there are several different HEV tests with varying levels of specificity and sensitivity. Clinically, it is impossible to distinguish between severe acute hepatitis caused by HEV infection and other causes. A direct or indirect diagnosis of the disease can be made using a quantitative RT-PCR reaction to find HEV RNA in serum [105], plasma, or stool samples. Anti-HEV immunoglobulin M is detectable after acute HEV infection but is undetectable in the 16–24 weeks before clinical disease manifests.

Following the rapid development of anti-HEV immunoglobulin M, anti-HEV IgG persists several times, occasionally even for the remainder of the patient's life [106]. Anti-HEV IgG is found in 95% of patients at their first clinical signs. Genomic DNA testing is essential to exclude active HEV infection due to the immunosuppressed group's subpar antibody response. Additionally, immunochromatography and enzyme immunoassay [107] can be used for screening. Immunocompetent people are more specific to this assay than immunosuppressed individuals. Nonspecific hepatitis can be readily attributed to an alternate cause. HEV Ag immune-histochemistry is required to confirm the diagnosis.

Standardizing diagnostic assays is crucial to identify as many cases of HEV infection as feasible. The World Health Organization is now working on developing reference materials for HEV serology that will eventually be accessible globally. A few years ago, an assay designed in China (Wantai) with 98% sensitivity was used commercially to recognize anti-HEV IgG. Due to insufficient sensitivity, the true seroprevalence has been grossly exaggerated, which has allowed HEV to "hide" at the population level. The estimations from more recent studies utilizing the Chinese assay are significantly higher than those from prior studies. The seroprevalence rates match those of HEV viremia in asymptomatic blood donors [108].

PCR is an efficient strategy to distinguish between viruses and HEV in water samples. Additionally, it is advised to use the current negatively charged membrane filters (Millipore, Burlington, MA, USA) with pore sizes ranging from 0.2 to 0.45 m. This approach is one of the best and most economical for concentrating various viruses from environmental samples [109].

10. Treatment Strategies for HEV Infection

The World Health Organization (WHO) published a strategic vision to limit the spread of viral hepatitis in 2016 [110]. This was accomplished to support the idea that persons with viral hepatitis must have access to adequate, inexpensive care, diagnosis, and therapeutic services. By 2030, this project hopes to treat 80% of those who qualify for treatment for viral hepatitis [111]., minimize hepatitis-related fatalities by 65%, and eradicate 90% of new cases of the disease.

Maintaining hygienic practices while visiting endemic areas is crucial to lowering the risk of developing HEV. Some destructive behaviours are avoiding ice cubes, drinking unpurified water, not washing your hands with clean water before handling food, and eating fruits and vegetables that have not been peeled. It is time to launch communication and social mobilization initiatives to reduce the HEV burden at the global level.

10.1. Vaccination Therapy

Ribavirin and pegylated interferon are two primary options for HEV medical treatment. Pegylated interferon and ribavirin both prevent HEV replication in culture. Since then,

pegylated interferon has been replaced with ribavirin as the primary medical therapy for acute and chronic HEV diseases. Focused investigations must clarify the ideal dosage and time length of ribavirin therapy [112]. Due to a high probability of acute repudiation, pegylated interferon is inappropriate in kidney transplant recipients. IFN-α is not advised for pregnant women [113].

It has been reported that some patients develop ribavirin tolerance and therapy inability, commonly attributed to a reduction in ribavirin dosage due to adverse effects, including anemia [114]. Ribavirin may cause viral clearance through applying mutagenesis pressure to the viral genome [115]; additionally, it changes the possibility of selecting resistant variations that do not respond. The viral polymerase variants Y1320H, K1383N, and G1634R are associated with resistance in addition to insertion in the hypervariable region. Because animal research showed that it has embryocidal and mutagenicity effects, therefore, pregnant women should not take ribavirin.

Recently, the Pregnancy Category B medication sofosbuvir has shown antiviral efficacy against HEV in both in vivo and vitro studies, suggesting that it may be an effective antiviral treatment for HEV in pregnancy. Sofosbuvir may be advised for HEV infection in pregnancy. More controlled research is required before its use in expecting women. Regarding potential antiviral possibilities, interferon λ1–3 has been demonstrated to limit HEV replication. There is still much work to be done on the other antiviral opportunities. Therefore, managing HEV infection in pregnancy requires thorough monitoring and intense care.

Childbearing females with HEV may be more inclined to use herbal remedies, which may also be a factor in the high mortality rates in some areas. High death rates among HEV-infected children under two have also been observed in Central Asia and Eastern Africa. HEV can sometimes be incorrectly diagnosed. Re-infection with HEV is also documented; it is recognized by a sharp rise in anti-HEV IgG levels and the appearance of HEV RNA [116].

One mTOR (mammalian target of rapamycin) inhibitor, everolimus, promotes HEV multiplication in vitro; it is well known that the calcineurin inhibitors tacrolimus and ciclosporin A have a pro-proliferative effect, in contrast to mycophenolate mofetil, which inhibits HEV replication in vitro [117]. For most patients, ribavirin monotherapy is the preferred course of action and reducing immunosuppression should be the first step in treating transplant recipients if possible [118]. Clinical studies were required to confirm the efficacy of sofosbuvir in curing HEV disease, especially in individuals who have not been able to overcome HEV with ribavirin therapy alone. Nucleic acid amplification testing must be implemented to confirm drug response.

Other drugs like rapamycin and everolimus promote HEV replication in vitro through blocking the mTOR, a molecular target of rapamycin, because the PI3K-PKB-mTOR pathway works as a cell limitation factor. As a result, when mTOR inhibitors are administered, increased HEV RNA amounts might be found in the blood [55].

Recent advancements in cell culture systems and techniques will enable the creation of novel approaches for investigating the biology of HEV, as well as specialized therapies and cures [119]. A unique therapeutic strategy may be provided through targeting viral polymerase with SOF, with profound genome technologies, it might be possible to pinpoint the patients who are more likely to experience a failed ribavirin therapy [120]. Conventional medicines can be replaced by T cell therapy [121] and its use in a "personalized medicine" approach to treat HEV infection may be essential. In China, a vaccine named Hecolin is liscenced [122] but its safety in pregnant females is still unknown [123].

'Future studies should emphasize the need for professionals to have a different threshold for HEV testing, particularly in immunocompromised individuals, and raise awareness of HEV infection in both developed and developing countries. Patients who could be at risk for chronic HEV infection also need to know the different ways the infection is disseminated and should be trained to stop it. Immunological research as well as preventative and therapy strategies must be improved shortly if the disease is to be brought under control.

Additionally, cost-effective immunization programs are necessary in nations where the disease is endemic.

10.2. Drug Development

Only 80% of patients treated with RBV experience viral clearance, and RBV is restricted in the significant-risk cohort of pregnant women, similar to pegIFN, highlighting the importance of novel therapy choices and clinical trials must be performed in the future. For the de novo discovery of drugs, screening libraries of compounds for their potential to interfere with viral lifespans can be used. It is necessary to have a molecular structure for the target to design antivirals for structure-guided development [124]. No matter the approach taken to uncover a prospective medicine, candidates must be evaluated in vitro and in vivo. In vitro models may include various cell culture models, hepatoma cell lines, primary human hepatocytes, and induced pluripotent stem cells [125], to name a few. Similar to this, there are several small animal models for the many HEV strains, such as rabbits, rats, ferrets, and birds, among others [126].

11. Conclusions

Due to unsanitary settings, HEV has a high prevalence rate in developing countries, which induces severe hepatitis infection. Humans are infected by genotypes 1 and 2, whereas genotypes 3 and 4 are animal-infection-causing agents. Pregnant women and others with impaired immune systems are seriously at risk. Because it is linked to undernourished populations and poor sanitation, HEV infection is understood to be a disease of poverty. Particular emphasis must be placed on reducing the burden of HEV infection in areas where HEV is highly endemic.

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