Review Article

Global Burden and Evolving Understanding of Hepatitis E Virus

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Hepatitis E virus (HEV) is the leading cause of acute viral hepatitis worldwide, recognized as a significant global public health concern. Recent advancements in understanding the natural history of HEV infection have shed light on its epidemiology and clinical implications. The primary mode of HEV transmission is fecal-oral, occurring through contaminated water or food. Parenteral transmission, particularly through blood transfusions, was initially overlooked but has been increasingly recognized in both developing and industrialized countries. Acute HEV infection typically manifests as self-limiting jaundice, particularly in immunocompetent individuals. However, recent data suggest that acute infection can progress to a chronic form in various immunosuppressive conditions, including solid organ transplantation, hematological malignancies, and human immunodeficiency virus (HIV) infection. Chronic HEV can lead to cirrhosis, which may progress rapidly in some cases. Extrahepatic manifestations, particularly neurological complications, have also been reported. HEV remains underdiagnosed globally due to a lack of awareness among healthcare providers in many regions. Advances in serological and molecular assays have facilitated reliable diagnosis, both in immunocompetent and immunocompromised patients. Ribavirin monotherapy has proven effective in treating chronic HEV infection in immunosuppressed individuals and is currently widely recommended. However, its efficacy in acute HEV remains inconclusive. In 2011, an effective and well-tolerated HEV vaccine was developed and approved in China. This vaccine holds promise for high-risk populations, particularly individuals with cirrhosis and travelers to endemic regions.

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I. Introduction

Hepatitis E virus (HEV) is the leading cause of acute viral hepatitis worldwide [1]. It remains a major public health problem, especially in developing countries. The World Health Organization estimates that 2.3 billion people have already been infected with hepatitis E virus (HEV), 20 million cases are recorded each year, of which more than 3 million are acute cases causing approximately 44,000 deaths [2]. The mortality rate ranges from 1-4% in the general population. Severe forms are more common in pregnant women and subjects with chronic liver disease. A particular excess mortality of up to 15-20% has been classically described in pregnant women during outbreaks[3]. The perception of different aspects of hepatitis E has changed radically over time. It has long been considered an infection contracted only during a stay in an endemic area in developing countries. Currently, the improvement of virological tools has demonstrated that many cases of hepatitis E belong to a sporadic form acquired in industrialized countries, defining the emerging nature of this infection in this so-called non-endemic area[4]. Historically, fecal-oral transmission has been the main mode of transmission. In recent years, other routes of contamination, including transfusional transmission, have come to light and differ depending on the species considered [1]. In addition, HEV is distinguished from other hepatitis viruses by the presence of an animal reservoir, which characterizes the zoonotic potential of the virus[5]. In most cases, HEV is responsible for an acute, self-limiting form with rapid viral clearance. However, the course of the disease can progress to a chronic form in various immunosuppression situations (organ transplantation, malignant hematopathy, and human immunodeficiency virus infection), which can be complicated by cirrhosis that is sometimes rapidly progressive [6]. IFN alpha and ribavirin are the two effective antiviral therapies recommended for immunocompromised patients with chronic hepatitis E [7]. The high endemicity of HEV in developing countries and the potential severity of the disease in pregnant women warrant active prevention measures[2].

II. Background

Historical jaundice outbreaks with the epidemiological characteristics of hepatitis E, including high mortality among pregnant women, have been documented in Europe since the 18th century. These epidemics spread to Eastern Europe, Central Asia, and South Asia in the 1930s. During the following decades, they were widely reported in the Middle East and North Africa. The advent of serological tests in the 1980s ruled out hepatitis A and B as the causative agents of these epidemics, which were then labeled

"NANB," and a different etiological agent was suspected. It was not until 1983 that this agent was visualized using electron microscopy[8]. In 1990, thanks to advances in molecular biology, the causative agent was isolated, cloned, and named "hepatitis E virus." The discovery of porcine HEV in the United States in 1997 raised concerns about the zoonotic risk [9]. In 2008, HEV was recognized as a potential cause of persistent infection in immunocompromised patients [10].

III. Epidemiology

Hepatitis E virus, identified in 1983, represents the fifth human hepatitis virus [5]. It is distinguished by its unique virological, epidemiological, and pathogenic characteristics, which are primarily manifested in pregnant women.

1. Virological Characteristics

Morphology and Classification: Hepatitis E virus is a small, spherical, single-stranded RNA virus with icosahedral capsid symmetry, approximately 27-34 nm in diameter. It is enveloped by membrane fractions in the blood of patients, while viral particles are naked in feces [11]. HEV belongs to the Hepeviridae family. Since 2015, this family has been divided into two genera: Orthohepevirus and Piscihepevirus. Orthohepevirus is further subdivided into four species, A to D. Species A includes viruses mostly infecting mammals. Group B comprises avian strains identified in chickens. Group C is identified in rodents, and Group D in bats. The Piscihepevirus genus was recently isolated from trout [12].

Genetic Diversity: Significant genetic diversity exists within HEV. Mammalian HEV isolates have been grouped into four major genotypic groups, designated VHE-1, VHE-2, VHE-3, and VHE-4. Despite this nucleotide divergence, these four genotypes belong to a single serotype. Other genotypes, such as VHE-5, VHE-6, VHE-7, and VHE-8, have been recently documented in animals, which are considered potential virus reservoirs [13].

2. Animal Reservoir and Cross-Species Transmission

Animal Reservoir: Hepatitis E virus stands out from other hepatitis viruses due to the existence of an animal reservoir in addition to the natural human reservoir. Cross-species transmission has been demonstrated in animal models [14]. Genotypes 1 and 2 are restricted to humans and hyper-endemic regions. Genotype 3 is found worldwide in various hosts, including pigs, wild boars, deer, mongooses, and macaques. Genotype 4 is primarily found in China and Southeast Asia, infecting pigs, wild boars, and

sheep. Recently, genotypes 5 and 6 have been isolated from wild boars, and genotypes 7 and 8 from camels. Additionally, more distantly related HEVs have been identified in birds, bats, rats, ferrets, and fish. Molluscs are recognized as vectors of enteric viruses. Sequences of HEV have been found in mussels but also in oysters. Shellfish, particularly filter feeders like oysters and mussels, are recognized as vectors of enteric viruses, including HEV. HEV RNA sequences have been detected in various shellfish species, including mussels, oysters, and clams [14].

Modes of Transmission

Hepatitis E virus transmission occurs primarily via the fecal-oral route. The virus is mainly carried by surface water contaminated with fecal matter. Humans are infected either directly or indirectly by consuming raw and poorly washed vegetables or through shellfish [15]. Transmission through direct contact with zoonotic reservoirs is possible in certain high-risk populations (such as farmers, hunters, and veterinarians). Animal-to-human transmission is also linked to the consumption of food products from zoonotic reservoirs (pigs, wild boars, deer, and recently dromedaries, through meat or milk)[14]. Parenteral transmission from blood or its components is possible during transient viremia during the prodromal phase[16]. Human-to-human transmission through direct contact is possible but rare due to poor hand hygiene [15]. There is a risk of vertical transmission with sometimes fatal consequences for the newborn [17]. The predominant mode of transmission differs in each area depending on the level of hygiene and the circulating virus reservoir [5].

3. Environmental Resistance and Survival of Hepatitis E Virus

Thermal Resistance: Thermal resistance is a crucial factor in preventing foodborne transmission of HEV. At 56°C (the minimum cooking temperature), all strains remain virulent. An internal temperature of 71°C for 20 minutes is necessary to completely inactivate HEV. The virus exhibits moderate stability at 4°C. However, it can be detected by PCR after more than 10 years of freezing at -20°C [18].

Environmental Stability: Like other non-enveloped enteric viruses, HEV demonstrates relative resistance in the environment. It is susceptible to common enteric virus disinfectants, including chlorine. The virus tolerates moderate pH fluctuations, allowing it to survive in the gastrointestinal tract and wastewater. HEV is sensitive to ultraviolet and infrared radiation[19].

4. Geographic distribution

Endemic Regions: In endemic regions such as Asia, Africa, and Central America, HEV is a leading cause of large-scale outbreaks of acute hepatitis, primarily waterborne and associated with fecal contamination [3]. Cross-connections between potable water and wastewater systems have been implicated in most outbreaks reported in countries with low levels of sanitation. This was the case for the first hepatitis E outbreak described in 1955-1956 in New Delhi and in several outbreaks in Chad, Sudan, Somalia, and Algeria [3].

HEV is responsible for over 50% of acute hepatitis cases in India, nearly a quarter of cases in Africa, and around 15-20% in Middle Eastern countries. Seroconversion occurs predominantly in young adults, and seroprevalence ranges from 25 to 80% [20].

In the Mediterranean region, several HEV outbreaks have been reported. In Morocco, an outbreak was reported in the south in 1994, and nearly 70% of non-A non-B hepatitis in adults and adolescents is attributed to HEV [21]. In Tunisia, a relatively high prevalence of 12.1% was found among pregnant women in the Sousse region in 2009 [22]. In Egypt, 42% of acute non-A non-B hepatitis diagnosed in 1996 had positive markers for HEV [23]. Outbreaks of non-A enteric hepatitis, formerly known as A-like hepatitis, have been reported in Algeria, with particular severity observed in pregnant women. Following a major outbreak in Sétif in spring 1967 with 1300 cases, 474 cases were reported in Mostaganem in 1980, and 964 cases in Médéa in 1981 [24]. In 1983, another waterborne outbreak occurred in Constantine [25]. The most recent outbreak, reported in 1986, was in Tanefdour, Jijel, with 247 cases [26].

Developed Countries: In several industrialized countries in Europe and America, HEV is now the leading cause of acute viral hepatitis. The prevalence has long been underestimated, particularly among blood donors. Immunoglobulin G (IgG) antibodies are found in 1-20% of adults [27].

IV. Pathogenicity

Several factors contribute to the pathogenesis of HEV infection, including host factors such as pregnancy, chronic liver disease, and immunosuppression, as well as viral factors. Based on epidemiological, clinical, and experimental observations, HEV 1 and 2 are considered more virulent than HEV 3 and 4. However, HEV 4 appears to be associated with more severe manifestations than HEV 3[28].

1. Special Case of Pregnant Women

Several pathophysiological hypotheses have been proposed to explain the severity of HEV infection in late pregnancy. An immunological hypothesis has been put forward, suggesting an imbalance in the Th1/Th2 cell-mediated immune response, with an increase in the Th2 response and a decrease in the Th1 response, not observed in non-pregnant women. Additionally, hormonal level fluctuations (increased progesterone, estrogen, and human chorionic gonadotropin) promote lymphocyte apoptosis and viral replication [17]. Alongside immunological factors, virological factors may also play a role. Higher viral loads are found in pregnant women with fulminant hepatitis compared to pregnant women with uncomplicated forms. [17].

2. Mechanisms of HEV Persistence in Immunocompromised Individuals

Host Factors: Available data suggest that the level of immunosuppression plays a crucial role in HEV persistence. However, the specific nature of the impaired innate or adaptive immune responses that lead to chronicity remains to be elucidated. Studies are ongoing to investigate the role of anti-HEV CD4/CD8 T cell responses, neutralizing antibodies, and genetic determinants in HEV persistence [29].

Viral factors: Chronic evolution has been almost exclusively caused by HEV 3 and 4. Persistent infections due to HEV 7 have been described more recently. Subtype-specific differences may exist within HEV 3. Most described cases of chronic HEV hepatitis involve subtypes 3f and 3c. However, this may simply reflect the predominance of these subtypes in Europe [30].

V. Clinical Presentation

1. Acute forms

The clinical presentation of acute hepatitis E resembles that of acute hepatitis caused by other hepatotropic viruses. In endemic areas, hepatitis E primarily affects adolescents and young adults. In non-endemic areas, it mainly affects adults over 50 years of age, where it is often misdiagnosed as autoimmune or drug-induced hepatitis [31]. The incubation period ranges from 15 to 60 days. The common icteric form is present in 10 to 50% of cases, presenting as acute cytolytic hepatitis that often resolves favorably after 2 to 4 weeks. Clinical and biochemical recovery usually occurs within six

months [31]. Reinfections appear to be common and can lead to the development of a new infection. Relapses are exceptional [32].

2. Fulminant forms

In 1 to 2% of cases, acute hepatitis E progresses to a fulminant form with acute liver failure. This leads to massive destruction of liver parenchyma with hepatocyte necrosis and liver atrophy, putting the patient's life at risk in the absence of liver transplantation [5]. The incidence rate of these fulminant forms is significantly increased in pregnant women during the third trimester of pregnancy, reaching 20%. The mortality rate is between 20 and 40% [17]. In industrialized countries, fulminant hepatitis has not been observed in pregnant women but occurs with a high frequency (approximately 10%) in individuals with underlying liver disease [4].

3. Special situations

Hepatitis E and chronic liver disease: HEV can exacerbate pre-existing chronic liver disease. Several studies have documented the exacerbation of liver injury upon HEV superinfection, regardless of whether the primary liver damage is caused by alcohol or other hepatotropic viruses (HBV, HCV) [33]. This exacerbation is most often characterized by a marked elevation of liver enzyme levels and, in some cases, severe decompensation manifested by ascites and varying degrees of hepatic encephalopathy [31]. In the absence of liver transplantation, the prognosis is poor, with a mortality rate of 70% in HEV-infected patients [33] Ribavirin-based therapy can, in some cases, prevent the need for liver transplantation [32].

Hepatitis E and pregnancy: Observational studies have demonstrated that among pregnant women, HEV exhibits a higher rate of fatal liver failure compared to other known viral hepatitis agents [31]. Fetal and/or maternal mortality is contingent upon the viral load and the severity of clinical presentation. It has been estimated that HEV infection could be responsible for 2,400 to 3,000 stillbirths annually, in addition to fetal deaths associated with maternal mortality. Preterm delivery, low birth weight, and neonatal death are observed in 25% to 56% of cases [17].

4. Chronic Hepatitis E

The transition to chronic hepatitis E, defined by the persistence of viremia for more than six months, has recently been demonstrated in various immunosuppression settings: solid organ transplantation (kidney,

liver, kidney-pancreas), including in children [10] hematological malignancies [34], HIV infection, especially in cases of CD4 lymphopenia [35].

The infection is asymptomatic and is most often discovered during the detection of a moderate and fluctuating elevation of transaminases. Testing for HEV RNA in blood and stool should therefore be systematically performed in case of suspected chronic hepatitis E, even in the presence of a subnormal and fluctuating level of transaminases, and even in the absence of anti-HEV IgG and IgM [29].

Progression to cirrhosis can be rapid and more severe than HCV infection, within 12 to 36 months, and may then necessitate re-liver transplantation in previously transplanted patients [10].

Risk Factors for Chronic HEV Infection: Solid organ transplant recipients, particularly kidney and liver transplant recipients, represent the primary risk group for chronic HEV infection. Acute HEV infection progresses to chronic infection in approximately two-thirds of these patients. Risk factors for chronicity include a short interval between transplantation and HEV infection, low platelet and lymphocyte counts, particularly CD2, CD3, and CD4 lymphocytes, and the use of tacrolimus as an immunosuppressant (vs. cyclosporine) [29].

The development of chronic HEV infection has been described in several patients with lymphomas. The combined effects of the malignancy and its treatment (high-dose corticosteroids, rituximab) are likely responsible for this progression [34].

The first two cases of chronic HEV infection in HIV-infected individuals were reported in 2009. Since then, additional cases have been reported. The infection is often asymptomatic and is discovered during liver function test abnormalities or in the presence of CD4 lymphopenia. Progression can be complicated by rapid-onset cirrhosis. Spontaneous clearance of HEV can be achieved after several months of effective antiretroviral therapy concomitantly with immune restoration [35].

5. Extra hepatic manifestations

Extrahepatic manifestations have been described during both acute and chronic HEV infections. Neurological manifestations are reported in 5.5% of cases. These include Guillain-Barré syndrome, meningoencephalitis, and neuritis. A large case-control study confirmed that 5% of patients with Guillain-Barré syndrome had acute hepatitis E [36].

Several cases of pancreatitis have been reported [37]. Cases of thrombocytopenia and haemolytic anaemia have also been described [38]. Cases of acute polyarthritis revealing hepatitis E have also been

reported [39].

VI. Virological Diagnosis

1. Indirect Virological Diagnosis

Indirect virological diagnosis involves detecting the humoral immune response. The presence of anti-HEV IgM antibodies is the key marker of acute infection. They appear on average 2 to 3 weeks before the first clinical signs. Their serum concentration reaches a maximum titer at the time of the ALT peak, i.e., during jaundice. Then, IgM antibodies gradually disappear over a period of 2 to 3 months (sometimes 4 to 6 months) [6]. Anti-HEV IgG antibodies appear shortly after IgM antibodies. Their titer increases at the end of the clinical phase and then tends to decrease slightly during convalescence, and they usually persist for several years [6]. Immunoenzyme assays (ELISA and western blot) are the most commonly used methods for the serological diagnosis of HEV infection. Recent studies have demonstrated that commercially available assays have excellent sensitivity (>97% in immunocompetent individuals and >85% in immunocompromised individuals) and specificity (>99.5%) [40]. The detection of anti-HEV IgG antibodies alone cannot confirm the recent nature of the viral infection but indicates contact with the virus. Theoretically, a positive IgM-IgG association found after an initial test that showed only isolated positivity for anti-HEV IgM antibodies is strongly suggestive of acute hepatitis E [31].

2. Direct Diagnosis

Direct diagnosis of HEV infection relies on conventional or real-time RT-PCR. Strain sequencing enables a molecular epidemiology approach. In vitro virus culture on cell lines is limited to specialized laboratories due to its restricted feasibility. Recently, the detection of viral antigens has allowed for the identification of HEV 1 and 4 capsid proteins [27]. The primary limitations to virus detection include a narrow detection window or intermittent excretion [41]. Conversely, molecular biology can facilitate the diagnosis of serologically silent hepatitis E cases in immunocompromised and sometimes immunocompetent individuals [27]. In endemic areas, HEV infection should be considered in any case of acute cytolytic hepatitis that is negative for hepatitis A, B, and C. The diagnosis is primarily serological. These areas correspond to developing countries, where serological tests are significantly less expensive than molecular biology techniques and therefore more affordable [42]. In industrialized countries, the diagnosis was traditionally guided by clinical presentation, the epidemiological context, or a recent

history of travel to an endemic area. It should now be considered for any case of acute hepatitis of unexplained origin, even in the absence of a known travel history to an endemic area. In immunocompetent individuals, the detection of anti-HEV IgM antibodies typically allows for the diagnosis of acute hepatitis E. Since the sensitivity of serological tests is lower in immunocompromised individuals, the detection of viral RNA in plasma or stool is essential. [42].

VII. Treatment

Treatment of Acute Hepatitis E in Immunocompetent Individuals: In the majority of immunocompetent individuals, acute hepatitis E resolves spontaneously. Therefore, treatment is primarily supportive and focuses on managing symptoms. It is crucial to avoid any additional hepatotoxic factors, particularly acetaminophen, corticosteroids, and estrogen-progestin therapy [7]. In developing countries, with limited access to qualified medical care, patients often use medicinal plants to treat jaundice. However, these treatments are generally ineffective and may even worsen the disease course [43]. Severe cases of acute hepatitis E require management in an intensive care unit. Supplementation with N-acetylcysteine, a glutathione precursor, can be considered, especially if the patient has taken acetaminophen (common during the prodromal phase). This is supported by positive outcomes observed with N-acetylcysteine treatment in improving transplant-free survival in non-acetaminophen-induced severe acute hepatitis [44]. Liver transplantation has revolutionized the prognosis of hepatocellular failure in severe cases of HEV infection. However, the decision for transplantation should be made on an individual basis, taking into account the specific circumstances of each case [45]. The impact of fetal extraction on the course of maternal HEV infection remains unclear due to insufficient research [17].

Management of Chronic Hepatitis E

Immunosuppression Reduction: In cases of chronic hepatitis E, reducing immunosuppression, when feasible, can lead to HEV clearance in approximately 30% of patients [10]. If this strategy is not possible or is ineffective, two antiviral therapies have been successfully employed: pegylated interferon alpha [46] and ribavirin [47]. These treatments achieve a sustained virological response in 80% of patients. However, the use of interferon is limited due to the risk of graft rejection. Therefore, ribavirin is often the preferred treatment option [46][47].

Sofosbuvir as a Potential Alternative: Sofosbuvir has demonstrated in vitro activity against HEV and could potentially serve as an alternative to ribavirin [48].

Prevention of Hepatitis E

In developing countries, hepatitis E prevention primarily focuses on improving sanitation and hygiene practices. This includes ensuring access to clean water, proper wastewater treatment, and strict adherence to personal and food hygiene guidelines, particularly for pregnant women [49]. In developed countries, specific dietary recommendations are advised for individuals with immunocompromised conditions or underlying liver disease. These recommendations emphasize limiting the consumption of high-risk foods, such as raw or undercooked meat. Thorough cooking (at a temperature of >70°C for at least 20 minutes) is essential to eliminate the virus [7]. Strict adherence to hygiene and dietary guidelines is crucial for individuals traveling to endemic areas *Compliance with dietary hygiene rules is essential for people travelling to endemic areas*[49]. This includes avoiding contaminated water and food, practicing proper hand hygiene, and avoiding raw or undercooked meat products.

HEV 239 (Hecolin®) Vaccine

The HEV 239 (Hecolin®) vaccine represents a significant breakthrough in hepatitis E prevention. It is the first and only licensed hepatitis E vaccine, approved in China since 2011 [50]. The vaccine is well-tolerated, even in pregnant women. The World Health Organization (WHO) recommends the use of the HEV 239 vaccine in developing countries to reduce the frequency of epidemics and mitigate the incidence of hepatitis E in high-risk groups, including pregnant women and individuals with chronic liver disease. In non-endemic regions, the vaccine is recommended for travelers planning to visit endemic areas [51].

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