Saudi Journal of Medicine and Public Health

https://saudijmph.com/index.php/pub

https://doi.org/10.64483/jmph-133

Hepatitis E Virus: Comprehensive Virological Insights, Diagnostic Strategies, and Laboratory Management for Clinical and Research Specialists

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Abstract

Background: Hepatitis E virus (HEV) is a major global cause of acute viral hepatitis, with significant morbidity and mortality in high-risk populations. It is a non-enveloped, single-stranded RNA virus transmitted primarily via the fecal-oral route, though zoonotic transmission is increasingly recognized.

Aim: This review provides a comprehensive update on HEV for clinical and research specialists, covering its virology, diagnostic strategies, and laboratory management to improve detection and patient care.

Methods: The synthesis is based on a detailed analysis of HEV's virological characteristics, including its genotypes and their distinct epidemiological patterns. Diagnostic approaches are evaluated, comparing serological assays (anti-HEV IgM/IgG) and molecular methods (PCR for HEV RNA) for acute and chronic infection.

Results: HEV genotypes 1 and 2 cause waterborne outbreaks in developing regions, while genotypes 3 and 4 are zoonotic and responsible for sporadic cases in developed countries. Infection is often self-limiting but can lead to fulminant hepatitis in pregnant women and chronic infection in immunocompromised individuals. Diagnosis relies on a combination of serology and PCR, with the latter being essential for confirming chronic infection in immunosuppressed patients where antibody responses may be blunted.

Conclusion: HEV is a complex pathogen with a variable clinical presentation. Accurate diagnosis requires an understanding of its virology and the strategic use of laboratory tests. Enhanced surveillance, targeted testing in high-risk groups, and a multidisciplinary approach are crucial for effective management and prevention.

Keywords: Hepatitis E Virus, HEV Genotypes, Zoonotic Transmission, HEV RNA PCR, Chronic Hepatitis E, Fulminant Hepatitis..

1. Introduction

Hepatitis E virus (HEV) represents the primary etiological agent of acute viral hepatitis on a global scale. Despite its widespread prevalence, the condition frequently remains underdiagnosed due to its nonspecific clinical manifestations and generally self-limiting course. HEV is classified within the genus *Orthohepevirus* of the family *Hepeviridae*. Structurally, it is a nonenveloped virus exhibiting icosahedral symmetry and possesses a single-stranded, positive-sense RNA genome. The virion measures approximately 27 to 34 nanometers in diameter, reflecting its compact architecture and capacity for efficient transmission [1][2][3]. Transmission of HEV occurs predominantly through the fecal-oral route, often resulting in acute, self-resolving hepatitis among immunocompetent hosts. In contrast, individuals with compromised immune systems, including organ transplant recipients and patients undergoing immunosuppressive therapy, may experience chronic

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Receive Date: 15 September 2025, Revise Date: 30 September 2025, Accept Date: 14 October 2025

infection. Mortality associated with HEV surpasses that observed with hepatitis A virus (HAV), particularly among vulnerable populations such as pregnant women, immunosuppressed individuals, and recipients of solid organ transplants. The higher mortality in these groups underscores the clinical significance of early recognition and monitoring [1][2]. The recognition of HEV as a distinct entity emerged from epidemiological observations during a waterborne outbreak of hepatitis in Kashmir, India, in the late 1970s. Dr Mohammad Sultan Khuroo, an Indian gastroenterologist, contributed significantly to its identification by demonstrating that affected individuals lacked serological markers of acute HAV infection, suggesting the involvement of an uncharacterized viral agent [4]. In 1983, Mikhail S. Balayan, a Russian virologist, further substantiated the existence of HEV through a self-experimentation study, ingesting stool extract from an infected patient and subsequently developing symptomatic hepatitis. This experiment provided definitive evidence of HEV as an enterically transmitted virus and clarified its distinction from other forms of viral hepatitis [1].

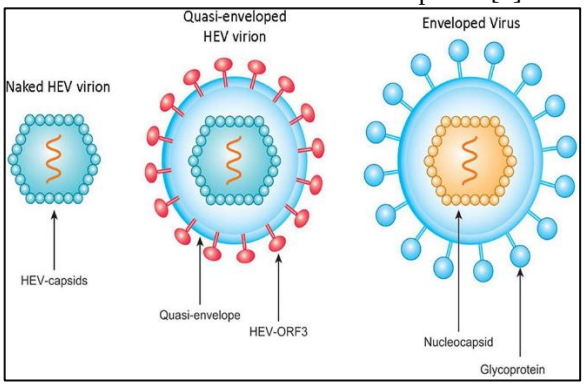

Figure-1: Hepatitis E Virus Structure.

Initially classified under the broader category of non-A, non-B hepatitis (NANBH), the virus was subsequently designated Hepatitis E to align with standardized nomenclature. This classification reflected advances in virological understanding and facilitated the differentiation of HEV from other hepatotropic viruses with similar clinical presentations. The early epidemiological and virological investigations laid the foundation for ongoing research into HEV pathogenesis, transmission dynamics, and clinical management, emphasizing the importance of laboratory-based diagnosis and molecular characterization in both clinical and research settings [1][4]. The cumulative evidence highlights HEV as a critical pathogen in global public health, necessitating heightened awareness among clinicians and laboratory specialists. Its variable clinical course, potential for severe outcomes in high-risk populations, and capacity for chronic infection in immunocompromised individuals make it a subject of considerable relevance for virological investigation and diagnostic vigilance. Continued research into HEV's molecular biology, epidemiology, and immunopathogenesis remains essential to inform prevention strategies, enhance diagnostic accuracy, and guide therapeutic interventions [2][3].

Etiology:

Hepatitis E virus (HEV) is a nonenveloped virus exhibiting icosahedral symmetry, with a single-stranded, positive-sense RNA genome and a particle diameter ranging between 27 and 34 nanometers. Four distinct genotypes of HEV have been identified, designated as genotypes 1 through 4, each demonstrating unique epidemiological and clinical characteristics [5]. Genotypes 1 and 2 are strictly human pathogens transmitted predominantly via the fecal-oral route, often through ingestion of contaminated water. These genotypes are endemic to developing regions, including parts of Africa, Asia, Central America, and the Middle East. Epidemiological data indicate that outbreaks associated with genotypes 1 and 2 frequently affect young adults between 15 and 40 years of age. In immunocompetent individuals, infection with these genotypes typically results in an acute, self-limiting hepatitis that resolves without progression to chronic disease. However, certain populations, such as pregnant women and patients with pre-existing chronic liver conditions, demonstrate increased susceptibility to severe disease. In these high-risk groups, infection may precipitate fulminant hepatic failure, leading to significant morbidity and mortality [5]. The transmission dynamics in these regions are closely linked to inadequate sanitation, limited access to clean water, and high population density, which collectively facilitate rapid viral spread during outbreaks.

In contrast, genotypes 3 and 4 exhibit a predominantly zoonotic pattern, circulating in animal reservoirs and transmitted to humans primarily through the consumption of undercooked or raw meat, including pork and deer. These genotypes are more frequently reported in developed countries, such as the United States, Australia, Japan, and China. Infections caused by genotypes 3 and 4 are often sporadic rather than outbreak-driven and primarily affect adults over the age of 40. While these infections can present as acute hepatitis in otherwise healthy individuals, there is a documented risk of progression to chronic hepatitis in immunocompromised patients. This risk is particularly pronounced in individuals receiving immunosuppressive therapy following solid organ transplantation and in patients living with human immunodeficiency virus (HIV). The clinical course in these patients may be complicated by persistent viral replication, elevated liver enzyme levels, and progressive hepatic fibrosis, highlighting the importance of early detection and monitoring [5]. The differentiation between these genotypes carries significant implications for public health strategies and clinical management. Genotypes 1 and 2

necessitate interventions aimed at improving sanitation, access to clean water, and outbreak control measures in endemic regions. Conversely, genotypes 3 and 4 require awareness of foodborne transmission risks, particularly the proper handling and cooking of meat products. Understanding the etiological diversity of HEV, including genotype-specific transmission routes, epidemiology, and clinical outcomes, is critical for laboratory specialists, epidemiologists, and clinicians. This knowledge underpins the development of targeted diagnostic protocols, preventive measures, and management strategies for both sporadic and epidemic HEV infections, ensuring timely intervention in at-risk populations and mitigating the public health burden associated with the virus [5]. Overall, HEV represents a complex pathogen with genotype-dependent variation in transmission, population susceptibility, and clinical severity. Continued research into the molecular virology, host-pathogen interactions, and epidemiological patterns of each genotype is essential to inform effective surveillance, preventive measures, and clinical guidelines, particularly in regions where the virus imposes significant morbidity and mortality.

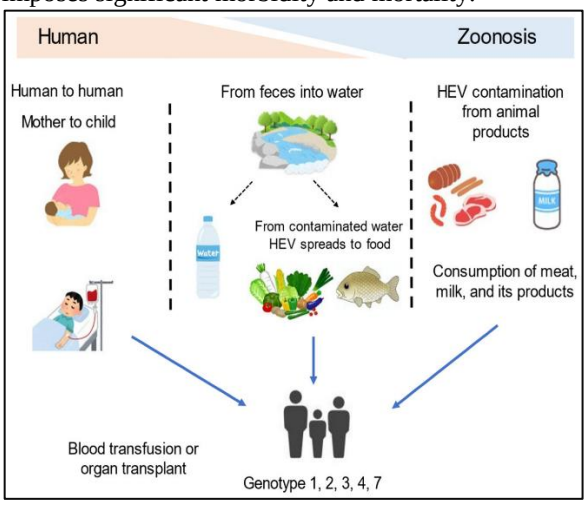

Figure-2: Hepatitis E Etiology.

Epidemiology:

Hepatitis E virus (HEV) infection represents a significant public health challenge worldwide. According to the World Health Organization (WHO), HEV accounts for approximately 20 million new infections annually and over 55,000 deaths each year. The infection demonstrates a global distribution, yet its incidence is disproportionately higher in developing regions. The highest burden of disease is observed across Asia, Africa, the Middle East, and Central America [6][7][8]. In these regions, HEV constitutes the second most common cause of sporadic hepatitis, particularly in North Africa and the Middle East [9]. While historically HEV was associated predominantly with developing countries, sporadic cases have increasingly been reported in Western nations, largely among travelers returning from endemic areas [10][11][12]. In the United States, seroepidemiological studies conducted between 2009 and 2010 indicated an overall HEV seroprevalence of approximately 6% [13]. Analysis of risk factors revealed a higher likelihood of seropositivity among older individuals, persons born outside the United States, Hispanic populations, and individuals consuming meat more than ten times per month. These findings suggest that HEV exposure in high-income countries may occur through dietary habits, particularly consumption of meat products that may carry zoonotic strains. Historically, HEV was regarded as confined to low-income regions, but emerging evidence has redefined its status as a zoonotic pathogen in high-income countries, particularly across Europe, where the virus is commonly transmitted through pigs [14]. This shift in epidemiological understanding underscores the need for heightened surveillance and diagnostic vigilance in regions previously considered low-risk.

HEV infection can be broadly classified into two epidemiological patterns: endemic and sporadic. The endemic form is predominantly observed in developing countries and is characterized by waterborne outbreaks driven by HEV genotypes 1 and 2. HEV1 is widely endemic in Asia and select regions of Africa, where it circulates among human hosts and causes substantial outbreaks, often affecting young adults. HEV2 demonstrates similar epidemiological characteristics but is geographically more restricted, occurring primarily in Africa and parts of Latin America. In contrast, genotypes 3 and 4 are largely zoonotic, infecting various mammalian hosts, particularly pigs, and are responsible for sporadic hepatitis E cases rather than large-scale outbreaks. HEV3 exhibits a global distribution, whereas HEV4 is predominantly reported in East Asia [15]. The epidemiology of HEV thus varies according to genotype, and its patterns are influenced by transmission pathways, regional environmental factors, dietary habits, and the availability of diagnostic infrastructure. Particular attention is warranted for HEV infection during pregnancy, especially in the third trimester, due to its association with severe maternal and fetal complications [16]. Pregnant women infected with HEV are at markedly increased risk of fulminant hepatic failure, with maternal mortality rates reported between 15% and 25% [17]. This risk is significantly higher than in nonpregnant women, highlighting the heightened vulnerability during gestation [18]. Fetal outcomes are similarly affected, with increased rates of preterm birth, stillbirth, and neonatal mortality. Vertical transmission from mother to child, though relatively uncommon, has been documented, leading to neonatal hepatitis E and complicating postnatal management [19][20]. The mechanisms contributing to the amplified severity of HEV infection during pregnancy remain incompletely understood but are hypothesized to involve immunological modulation and hormonal changes that compromise the host's antiviral response.

Overall, the epidemiology of HEV is shaped by a combination of geographic, environmental, and host-related factors. High-incidence regions reflect deficiencies in sanitation and safe water access, whereas sporadic cases in developed countries emphasize zoonotic transmission and dietary exposure. The differential clinical impact of HEV across populations, particularly among pregnant women and immunocompromised individuals, underscores the necessity of genotype-specific surveillance, preventive measures, and targeted public health interventions. Understanding these epidemiological nuances is essential for guiding laboratory diagnostics, shaping public health strategies, and informing clinical management protocols to reduce both morbidity and mortality associated with HEV infection globally.

Pathophysiology:

Hepatitis E virus (HEV) primarily spreads through the fecal-oral route, typically via contaminated water sources, which accounts for the frequent occurrence of large waterborne outbreaks, particularly in developing countries [21]. Although less common, HEV can also act as a zoonotic pathogen transmitted through fecal contamination from infected animals. Person-to-person transmission is relatively rare, but the virus can be transmitted via blood transfusions, posing a significant risk in endemic regions where blood screening may be limited [22]. Vertical transmission from infected pregnant women to their infants has been documented, contributing to substantial perinatal mortality and fetal loss [23]. Evidence regarding transmission through breast milk is limited; however, HEV has been isolated in breast milk with viral serum titers comparable to maternal viremia, suggesting a potential risk of postnatal exposure [24]. The incubation period for HEV infection ranges from 28 to 40 days. Following ingestion, the virus crosses the gastrointestinal mucosal barrier and enters the portal circulation, ultimately reaching the liver, which serves as the primary site of viral replication. In hepatocytes, the HEV virion attaches to cell surface receptors, likely mediated by interactions with heparan sulfate. Subsequent internalization occurs through clathrin-mediated endocytosis, leading to uncoating of the viral particle and release of its RNA genome into the cytoplasm [25][26]. This sequence of events initiates the viral replication cycle, allowing HEV to exploit host cellular machinery for the synthesis of viral proteins and replication of its genome.

The HEV genome consists of positive-sense single-stranded RNA, which can be directly translated into the open reading frame 1 (ORF1) polyprotein. ORF1 encodes multiple nonstructural proteins essential for viral replication, including helicase, RNA-dependent RNA polymerase, and protease domains. During replication, the virus generates negative-sense RNA intermediates that serve as templates for the synthesis of new genomic and subgenomic positive-sense RNAs. Subgenomic RNAs are particularly important for the translation of structural proteins, including the capsid protein encoded by ORF2 and the small multifunctional protein encoded by ORF3, both of which are critical for virion assembly and egress. The fully assembled virions are then released into the bile and subsequently excreted in feces, facilitating continued fecal-oral transmission and contributing to environmental contamination in endemic regions. The pathophysiology of HEV infection also explains its variable clinical outcomes. In immunocompetent individuals, viral replication is typically controlled by the host immune response, resulting in self-limiting acute hepatitis. In contrast, immunocompromised patients, including organ transplant recipients and those with chronic immunosuppressive therapy, may experience prolonged viral replication and progression to chronic hepatitis. Similarly, the heightened severity of HEV infection during pregnancy, particularly in the third trimester, is linked to altered immune regulation and hormonal changes that compromise viral clearance and increase the risk of fulminant hepatic failure.

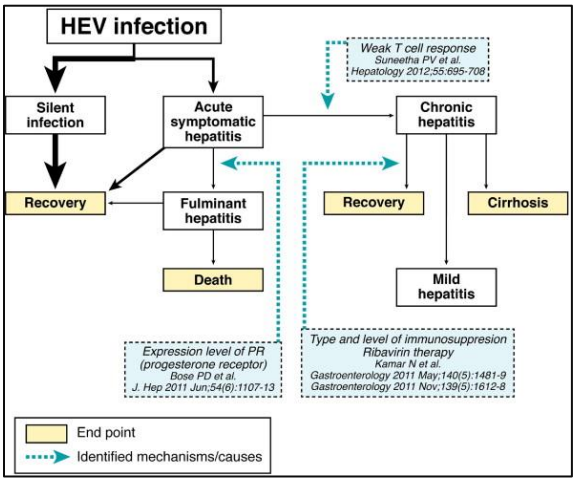

Figure-3: Hepatitis E pathophysiology.

Understanding the pathophysiology of HEV is essential for laboratory diagnosis, therapeutic development, and public health interventions. The virus's replication dynamics, hepatotropism, and excretion patterns highlight the critical role of the liver in disease manifestation, the potential for widespread environmental contamination, and the importance of early identification in high-risk populations. The interplay between viral replication mechanisms and host immune responses ultimately determines the clinical severity, duration of infection, and potential for chronicity, emphasizing the need for continued research into HEV biology and host-pathogen interactions [15][21][26].

Histopathology

Hepatitis E virus (HEV) infection induces a range of morphologic alterations in hepatic tissue, which may resemble patterns seen in both cholestatic

and classic acute hepatitis; however, these histopathologic features are not specific enough to establish a definitive diagnosis of hepatitis E [27]. The liver changes observed during HEV infection vary considerably depending on the host's immune status, underlying hepatic pathology, and the phase of infection. In many cases, histopathological examination reveals minimal portal or lobular inflammation, often characterized by a modest infiltration of lymphocytes and occasional neutrophils within portal tracts. Lobular involvement may include scattered hepatocyte apoptosis and focal necrosis, reflecting the acute hepatocellular injury induced by viral replication and immune-mediated cytotoxicity [28]. In addition to inflammation, some patients demonstrate steatohepatitis, which may represent a secondary response to viral infection or pre-existing metabolic or alcoholic liver conditions exacerbated by HEV. Hepatocyte necrosis can occur in varying stages, ranging from focal single-cell necrosis to more extensive confluent necrosis, particularly in patients with severe disease or those with comorbid chronic liver disorders. Bile duct damage is another reported finding, manifesting as ductular proliferation, epithelial degeneration, or cholestasis. These alterations contribute to the occasional cholestatic pattern observed in some HEV-infected patients and may correlate with laboratory evidence of elevated bilirubin or cholestatic liver enzyme profiles. Although histopathologic examination provides insight into the hepatic response to HEV infection, it lacks specificity and must be interpreted alongside serological and molecular diagnostic results. The variability in liver pathology underscores the influence of host factors, such as immune competence, pregnancy, or pre-existing hepatic disease, on the extent and pattern of tissue injury. Consequently, histopathology serves primarily as an adjunctive tool to understand disease mechanisms and assess hepatic damage rather than as a standalone diagnostic criterion for hepatitis E [27][28].

History and Physical

Hepatitis E virus (HEV) infection most commonly presented as an acute illness that is clinically indistinguishable from other forms of acute viral hepatitis. The majority of patients remain asymptomatic or experience mild, self-limiting disease. When symptoms do appear, they mirror those seen in infections caused by other hepatotropic viruses, including hepatitis A and hepatitis B. HEV should be considered in any patient presenting with features of acute hepatitis, particularly if they reside in or have recently traveled to regions with high incidence or endemicity. The disease demonstrates a higher prevalence in adults compared with children, and pregnant individuals are at increased risk of severe clinical manifestations. In immunocompetent hosts, HEV infection is typically self-limiting and resolves without long-term sequelae [29]. The clinical spectrum of HEV infection ranges from subtle constitutional symptoms to overt hepatic dysfunction and less common extrahepatic complications. Jaundice is the most consistent and frequently observed symptom, occurring in approximately two-thirds of cases. Non-specific prodromal symptoms often precede the development of jaundice and include malaise, fatigue, fever, anorexia, and myalgia. Gastrointestinal complaints, such as nausea and vomiting, are also common and can contribute to patient morbidity during the acute phase of infection. While extrahepatic involvement is less frequent, it represents a clinically significant component of the disease. Neurological complications, including neuropathies and encephalopathic manifestations, are reported in roughly 8% of infected patients, reflecting HEV's capacity for systemic effects beyond the liver [29].

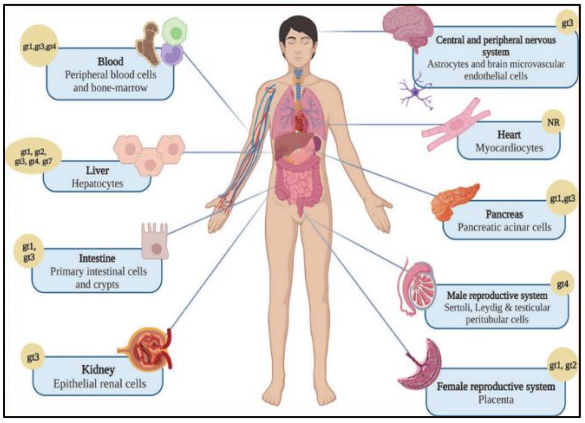

Figure-4: Hepatitis E Symptoms.

In immunocompromised individuals, particularly solid organ transplant recipients, acute HEV infection carries a higher risk of progression to chronic hepatitis. Immunosuppressive therapy impairs the host's ability to clear the virus, allowing for persistent viral replication and prolonged liver injury. Chronic HEV infection in these patients can eventually progress to cirrhosis, emphasizing the importance of early detection and close monitoring in immunocompromised populations [30]. Physical examination findings in acute HEV infection are typically nonspecific. Jaundice may be evident on inspection, and patients may appear generally unwell. Hepatomegaly and tenderness in the right upper quadrant are common, reflecting hepatic inflammation and cellular injury. In severe cases, fulminant hepatitis can develop, carrying a case fatality rate ranging from 0.5% to 3%. This severe form is particularly relevant in pregnant women, individuals with chronic liver disease, and other high-risk groups [31].

Extrahepatic manifestations of HEV infection contribute to the complexity of clinical evaluation and can affect multiple organ systems. Hematologic abnormalities such as thrombocytopenia, hemolysis, and aplastic anemia have been documented, while renal involvement may manifest as membranous glomerulonephritis. Endocrine complications, including acute thyroiditis, and

neurological syndromes such as acute transverse myelitis and septic meningitis, illustrate the virus's systemic potential and highlight the need for comprehensive patient assessment [32]. These extrahepatic effects, although less frequent than hepatic involvement, can influence clinical outcomes and require targeted interventions in specific cases. Pregnancy presents a unique clinical scenario in HEV infection. Women infected during the third trimester are at heightened risk of fulminant hepatitis, severe hepatic decompensation, and increased maternal mortality. Fetal and neonatal outcomes are similarly compromised, with higher incidences of stillbirth, preterm delivery, and neonatal hepatitis. The severity observed during pregnancy is believed to be influenced by immune modulation, hormonal changes, and altered hepatic metabolism, which together exacerbate viral replication and hepatocellular injury. Overall, the history and physical examination of patients with HEV infection reveal a broad clinical spectrum. Most cases are mild and self-limiting, but certain populations, including pregnant women and immunocompromised individuals, are at risk for severe disease, chronicity, and systemic complications. Accurate recognition of these patterns is essential for timely diagnosis, appropriate laboratory evaluation, and effective management to reduce morbidity and mortality associated with hepatitis E [29][30][32].

Evaluation

Accurate evaluation of hepatitis E virus (HEV) infection requires a high degree of clinical suspicion, particularly in patients presenting with symptoms of acute hepatitis or in those from endemic regions. The biochemical profile of HEV infection parallels that of other acute viral hepatitides, with elevations in serum transaminases reflecting hepatocellular injury. Following an incubation period of two to six weeks, HEV viremia can be detected in both blood and feces, providing a critical window for laboratory diagnosis. Detection of viral particles in these specimens is especially important in immunocompromised patients, who may fail to mount an adequate immune response and in whom serological markers alone may be insufficient for diagnosis [33]. As the virus replicates and enters the bloodstream, the host immune system responds by producing specific antibodies. Serum transaminases rise during this period, and anti-HEV immunoglobulins become detectable. Commercial assays are available to detect anti-HEV IgM and IgG; however, the diagnostic utility of these kits is limited by variability in sensitivity and specificity, resulting in occasional false-positive and false-negative results. In most clinical scenarios, the diagnosis of acute HEV infection is established by detecting serum anti-HEV IgM in the appropriate clinical context. Concurrent testing for other viral hepatitides, including hepatitis A, B, and C, is recommended to exclude alternative causes of acute liver injury and ensure an accurate differential diagnosis [33].

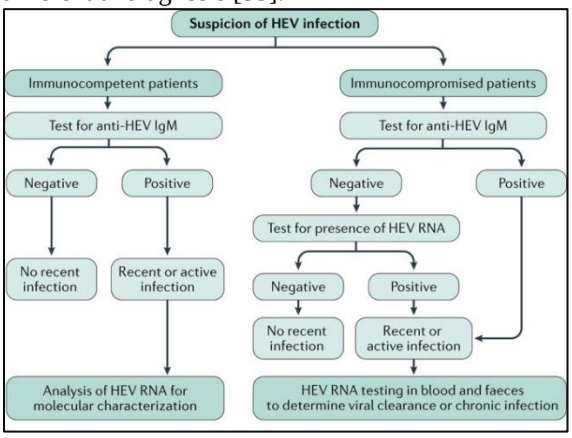

Figure-4: Hepatitis E Diagnosis Flowchart.

Polymerase chain reaction (PCR) testing for HEV RNA in serum or stool offers a definitive method for diagnosis. PCR is particularly valuable in immunocompromised patients, who may not generate sufficient antibody responses. However, in immunocompetent individuals, HEV viremia can be transient, and a negative PCR result does not rule out recent infection. In these cases, serological testing remains an essential diagnostic tool, providing indirect evidence of infection through the detection of specific antibodies [34][35][36]. Chronic HEV infection is defined by the persistent presence of HEV RNA in serum or stool for six months or longer following the initial infection. This condition occurs predominantly in immunosuppressed patients, such as solid organ transplant recipients or individuals receiving immunosuppressive therapy. Chronic infection may progress to fibrosis and cirrhosis if not identified and managed promptly. Accordingly, PCR-based nucleic acid amplification techniques serve as the primary diagnostic modality for chronic HEV, as antibody detection may be unreliable in this population [34]. Guidelines from the 2018 European Association for the Study of the Liver (EASL) recommend a combined diagnostic approach for acute HEV infection, incorporating both serological and nucleic acid amplification testing. For chronic HEV infection, NAT alone is considered sufficient for diagnosis due to its high sensitivity and specificity in detecting ongoing viral replication [14]. This evidence-based approach emphasizes the need for both careful clinical evaluation and laboratory confirmation, integrating serological, molecular, and biochemical data to achieve accurate diagnosis.

In summary, the evaluation of HEV infection requires an understanding of viral kinetics, host immune responses, and the limitations of current diagnostic assays. Serological testing remains central for diagnosing acute infections in immunocompetent patients, while PCR-based detection is essential for confirming infection in immunocompromised individuals and for identifying chronic HEV.

Combining clinical assessment with targeted laboratory investigations ensures accurate diagnosis, timely intervention, and appropriate management of both acute and chronic cases, mitigating potential complications and improving patient outcomes [33][34][36].

Treatment / Management

Acute hepatitis E virus (HEV) infection is typically self-limiting, and management is primarily supportive. Most patients experience spontaneous resolution of symptoms, with biochemical markers of liver injury, such as serum transaminases, normalizing within one to six weeks following the onset of illness. Supportive care focuses on maintaining hydration, nutritional support, and monitoring for complications. Hospitalization may be required for patients with severe symptoms, but in the majority of immunocompetent individuals, no specific antiviral therapy is necessary. In rare instances, acute HEV infection can progress to fulminant hepatic failure, particularly among high-risk groups such as pregnant women, patients with pre-existing chronic liver disease, or those with immunosuppression. In these severe cases, liver transplantation remains the definitive treatment option, as supportive measures alone are insufficient to prevent mortality [36]. The role of antiviral therapy in acute HEV infection remains limited and is not routinely recommended for immunocompetent patients. Ribavirin has demonstrated antiviral activity against HEV, but its use in acute infection is generally reserved for selected cases in immunocompromised individuals or those with severe disease. Importantly, ribavirin is contraindicated in pregnancy due to its teratogenic potential, and its administration requires strict contraceptive counseling for women of childbearing age and men with partners of reproductive potential. Contraceptive measures should continue throughout treatment and for at least six months after completion to prevent drug-induced teratogenicity [36].

Chronic HEV infection, which occurs predominantly in immunosuppressed patients such as solid organ transplant recipients, presents a more complex therapeutic challenge. Ribavirin monotherapy has shown good sustained virological response in this population, although resistance-associated mutations may reduce efficacy over time. Management strategies for chronic HEV include both antiviral therapy and optimization of immunosuppressive regimens. Adjustment of immunosuppressive therapy can enhance viral clearance. Calcineurin inhibitors, such as tacrolimus, and mammalian target of rapamycin (mTOR) inhibitors may enhance viral replication, whereas mycophenolate mofetil appears to be less permissive to HEV replication. Accordingly, reducing the dose of tacrolimus while increasing mycophenolate mofetil or corticosteroids may support viral clearance, although no standardized protocols exist for this approach [36][37]. Peginterferon, alone or in combination with ribavirin, has been used in selected patients with chronic HEV, particularly when monotherapy is insufficient or contraindicated. In individuals living with HIV, immune reconstitution induced by antiretroviral therapy can facilitate clearance of chronic HEV viremia. When viral clearance does not occur despite immune recovery, ribavirin may be administered as adjunctive therapy to achieve sustained virological response. Throughout treatment, careful monitoring of liver function, viral load, and potential drug toxicities is essential to guide therapy and minimize adverse effects [37].

Overall, the management of HEV emphasizes supportive care in acute infection, tailored antiviral therapy in chronic or severe cases, and careful consideration of host factors, including immune status and pregnancy. Optimizing immunosuppressive regimens in transplant recipients, monitoring for drug resistance, and integrating antiviral therapy when indicated are critical components of effective management. Early recognition, appropriate intervention, and individualized treatment strategies remain central to reducing morbidity and mortality associated with both acute and chronic HEV infection [36][37].

Differential Diagnosis

The differential diagnosis of hepatitis E virus (HEV) infection requires careful consideration of multiple potential causes of acute liver injury, particularly in patients presenting with jaundice and elevated serum alanine aminotransferase (ALT) levels. Viral hepatitis remains the most common category to evaluate. Hepatitis A, hepatitis B, and hepatitis C must be excluded, with HCV being less common in acute presentations. Other viral infections, including Epstein-Barr virus (EBV) and cytomegalovirus (CMV), can produce similar biochemical and clinical profiles, particularly in immunocompromised or severely ill patients. In addition to viral etiologies, drug-induced liver injury and toxic hepatitis should be considered, as hepatotoxic medications or substances can mimic the laboratory and clinical features of HEV infection. Ischemic hepatitis, resulting from hypoperfusion of the liver during shock or cardiac events, represents another potential cause of acute transaminase elevation and should be evaluated in patients with relevant cardiovascular histories or critical illness. In regions where endemic infectious diseases are prevalent, additional etiologies must be considered. Leptospirosis, dengue fever, yellow fever, and malaria can all cause hepatic involvement, sometimes with overlapping symptoms such as jaundice, fever, malaise, and elevated transaminases. Clinical and epidemiological context, including recent travel, exposure history, and vaccination status, are critical in narrowing the differential diagnosis in these settings. In immunosuppressed transplant recipients in developed countries, elevated ALT levels ranging from 100 to 300 IU/L can reflect a broader spectrum

of hepatic injury. Chronic HEV infection should be considered alongside graft rejection, recurrence of primary liver disease, drug-induced liver injury, or graft-versus-host disease. Additional contributing factors may include refractory viral infections such as EBV or CMV, as well as systemic intercurrent infections like sepsis, which can exacerbate hepatic dysfunction. Accurate differentiation among these possibilities is essential to guide appropriate diagnostic testing, optimize management, and prevent progression to chronic liver injury or graft compromise.

Prognosis

The prognosis of hepatitis E virus (HEV) infection is generally favorable, as most cases are asymptomatic or self-limiting and resolve without long-term complications. In immunocompetent individuals, acute infection typically follows a mild course, with spontaneous recovery and normalization of liver function within a few weeks. Supportive care is usually sufficient, and the risk of severe outcomes is low in otherwise healthy adults. The overall mortality in this population is estimated to range from 0.5% to 3%, mainly in cases of fulminant hepatic failure [38]. However, certain populations experience significantly worse outcomes. Pregnant women, particularly in the third trimester and when infected with HEV genotypes 1 or 2 in developing regions, face a markedly poor prognosis. Maternal mortality in this group can reach up to 25%, often due to fulminant hepatitis complicated by coagulopathy, disseminated intravascular coagulation, and hepatic encephalopathy. Fetal outcomes are similarly adverse, with more than half of affected infants dying in utero or shortly after birth. The heightened severity in pregnancy is thought to result from hormonal and immunological changes that impair viral clearance and exacerbate hepatic injury [38]. Individuals with preexisting chronic liver disease are also at higher risk. Acute HEV infection can precipitate acute-on-chronic liver failure, dramatically increasing mortality rates, which may approach 70% in this subgroup. In immunocompromised patients, such as organ transplant recipients or those receiving immunosuppressive therapy, persistent HEV replication may result in chronic infection. Chronic HEV can progress to fibrosis and, in rare cases, cirrhosis, highlighting the potential for long-term liver damage if infection is not identified and managed promptly.

Overall, while the majority of HEV infections are self-limiting and carry an excellent prognosis, severe outcomes occur in specific high-risk populations. Pregnant women, individuals with chronic liver disease, and immunocompromised patients require close monitoring, early diagnosis, and appropriate intervention to prevent progression to fulminant hepatitis, chronic liver disease, or death. Understanding these risk factors is essential for guiding clinical management and improving patient outcomes [38].

Complications

Although hepatitis E virus (HEV) infection is predominantly self-limiting, a subset of patients may develop serious complications affecting hepatic and extrahepatic systems. Acute hepatic failure is the most significant complication and is associated with high morbidity and mortality, particularly among high-risk groups such as pregnant women and individuals with preexisting chronic liver disease. Cholestatic jaundice represents another form of hepatic complication, characterized by prolonged hyperbilirubinemia, pruritus, and derangements in liver function tests. While these manifestations are less common, they underscore the potential for HEV to cause clinically significant hepatic injury even in otherwise healthy individuals. In rare cases, persistent viral replication may result in chronic HEV infection, particularly among immunocompromised hosts, which carries the risk of progressive liver disease and eventual cirrhosis [39]. Pregnancy represents a unique and highly vulnerable scenario in HEV infection. Women infected during the third trimester are particularly susceptible to fulminant hepatic failure, with maternal mortality rates reported as high as 25% in developing countries. The pathophysiology behind this heightened severity is likely multifactorial, involving hormonal and immunological changes that modulate viral replication and host immune response. Pregnancy induces immune tolerance to prevent fetal rejection, resulting in a relatively suppressed antiviral response. In the setting of high HEV viral loads, this immunosuppression contributes to uncontrolled viral replication and severe hepatic injury. HEV infection in pregnancy is also associated with adverse fetal outcomes, including intrauterine fetal demise, preterm birth, and vertical transmission of the virus. The highest rates of maternal and fetal mortality are observed during the third trimester, highlighting the importance of early identification and close monitoring of pregnant women with suspected HEV infection.

In patients with preexisting chronic liver disease, HEV infection can precipitate acute-on-chronic liver failure, a syndrome marked by rapid deterioration of liver function and multi-organ involvement. Mortality rates in this subgroup can approach 70%, with predictors of poor outcome including elevated serum bilirubin, prolonged prothrombin time, and concomitant renal dysfunction. Chronic HEV infection in immunocompromised patients, including solid organ transplant recipients, represents another significant complication. Persistent HEV replication, particularly from genotype 3, can lead to chronic hepatitis and progressive liver fibrosis. Any transplant recipient demonstrating viral replication beyond three months should be evaluated for chronic HEV infection. Reinfection is also possible

in previously seropositive individuals, particularly when anti-HEV IgG titers are low, emphasizing the need for continuous monitoring in high-risk patients. Extrahepatic complications of HEV are increasingly recognized and may affect multiple organ systems. Neurological involvement is particularly prominent, with HEV genotype 3 frequently associated with inflammatory polyradiculopathy, Guillain-Barré syndrome, peripheral neuropathy, encephalitis, and ataxia. These neurological manifestations may precede or follow hepatic symptoms and can result in significant morbidity if not promptly diagnosed. Renal complications are primarily glomerular in nature, including membranoproliferative and membranous glomerulonephritis, which may present with proteinuria, hematuria, and impaired renal function. Hematologic abnormalities have also been documented, including thrombocytopenia, lymphopenia, and aplastic anemia. Less common associations include acute pancreatitis, inflammatory arthritis, myocarditis, and autoimmune thyroiditis. Collectively, these extrahepatic manifestations demonstrate HEV's systemic potential and underscore the need for a broad diagnostic perspective when evaluating patients with atypical presentations.

Management of HEV complications requires individualized strategies based on patient risk factors, immune status, and severity of disease. Acute liver failure may necessitate intensive supportive care and, in severe cases, liver transplantation. Chronic HEV in immunocompromised patients is typically managed with antiviral therapy, primarily ribavirin, alongside optimization of immunosuppressive regimens to facilitate viral clearance. Early recognition of extrahepatic manifestations is essential to prevent irreversible organ damage. In summary, while HEV infection is often self-limiting, complications can be severe and multisystemic, particularly in pregnant women, patients with chronic liver disease, and immunocompromised individuals, necessitating vigilant monitoring and timely intervention to reduce morbidity and mortality [39].

Consultations

Management of hepatitis E virus (HEV) infection in immunocompromised individuals necessitates a coordinated, interprofessional approach to ensure optimal outcomes. Infectious disease specialists are central to the care team, providing expertise in the selection and monitoring of antiviral therapy, including ribavirin or peginterferon when indicated. They are responsible for interpreting viral load measurements, assessing response to treatment, and guiding modifications in therapy based on efficacy and potential resistance. In parallel, hepatologists evaluate liver function, monitor biochemical markers, and manage complications such as acute-on-chronic liver failure or fulminant hepatitis. Their role is critical in determining the need for intensive supportive care or referral for liver transplantation in severe cases. Transplant specialists contribute by assessing and adjusting immunosuppressive regimens to balance the risk of graft rejection with the need to facilitate viral clearance. In transplant recipients, certain immunosuppressive agents, including calcineurin inhibitors and mTOR inhibitors, may enhance HEV replication, whereas mycophenolate mofetil is considered safer. Close collaboration between hepatologists and transplant teams ensures that immunosuppression is optimized while minimizing the risk of chronic HEV infection or progression to cirrhosis. Immunologists play a complementary role by evaluating host immune competence and identifying factors that may affect antiviral response. Primary care clinicians provide continuity of care, monitoring comorbid conditions, and coordinating follow-up for both acute and chronic HEV infection. This multidisciplinary approach ensures that treatment decisions are individualized, complications are anticipated, and high-risk patients receive timely interventions. By integrating expertise across specialties, the healthcare team can effectively manage viral replication, prevent progression of liver disease, and improve overall prognosis for immunocompromised patients with HEV infection.

Patient Education

Patient education is a cornerstone in preventing hepatitis E virus (HEV) infection and mitigates its impact, particularly in high-risk populations. Understanding the routes of transmission is essential. HEV is primarily spread through the fecal-oral route via contaminated water, but zoonotic transmission through undercooked pork, deer, or other animal products is also significant, especially in developed countries. Educating patients on safe water consumption and the thorough cooking of meat can substantially reduce infection risk. Patients should be advised to boil, or filter drinking water in endemic regions and avoid raw or undercooked animal products. Hand hygiene, particularly before eating or preparing food, is critical in preventing fecal-oral transmission. High-risk groups, including immunocompromised individuals, solid organ transplant recipients, and patients with chronic liver disease, require targeted education about their increased susceptibility to chronic HEV infection. These patients should be informed that early diagnosis and timely treatment with antiviral therapy, such as ribavirin, can effectively manage chronic infection and prevent progression to cirrhosis. Educating patients on monitoring for persistent symptoms or abnormal liver function tests is essential for timely intervention. In countries where HEV is endemic, patients should be aware that vaccination is currently available only in China, highlighting the importance of preventive measures in regions without licensed vaccines. Travelers to endemic areas should maintain vigilance regarding water quality, food safety, and personal hygiene to minimize exposure risk. Beyond individual precautions, public health education plays a critical role in reducing HEV transmission. Patients should

understand the importance of proper sanitation, clean water supply, and safe food preparation practices. In areas with high HEV prevalence, education regarding the potential risk of HEV transmission through blood transfusions is important. Encouraging awareness of these risks helps patients engage in preventive behaviors and advocate for safer healthcare practices. Public health initiatives that improve water quality, waste management, and sanitation infrastructure further support community-level prevention. Effective patient education integrates personal hygiene practices, awareness of risk factors, and understanding of treatment options, empowering individuals to reduce their risk of infection and improve health outcomes.

Other Issues

Hepatitis E virus (HEV) presents a complex array of clinical and epidemiological considerations that extend beyond its typical self-limited course. HEV is a nonenveloped, single-stranded RNA virus with a diameter of approximately 27 to 34 nm. Its primary mode of transmission is fecal-oral, often via contaminated water supplies, particularly in endemic regions. This characteristic underpins the epidemiology of classic hepatitis E, caused by genotypes 1 and 2. These genotypes are responsible for large waterborne outbreaks in developing countries, frequently affecting young adults and resulting in high attack rates. The disease often remains self-limited in immunocompetent individuals but carries significant risk for severe outcomes in pregnant women, who may develop fulminant hepatitis with high maternal and fetal mortality [40]. In contrast, sporadic or zoonotic hepatitis E, caused by genotypes 3 and 4, is primarily observed in developed countries. Transmission occurs through contact with infected animals or consumption of undercooked meat, particularly pork or game. Sporadic cases typically affect older adults, often men over 40, and usually result in milder clinical manifestations. Despite the generally benign nature of infection, HEV3 and HEV4 can lead to chronic hepatitis in immunocompromised patients, including solid organ transplant recipients, patients on immunosuppressive therapy, or individuals living with HIV. Chronic infection can progress to cirrhosis within two to five years, emphasizing the importance of early detection and management in high-risk populations [15][41][42].

Most HEV infections are asymptomatic or produce nonspecific clinical features that resemble other viral hepatitides, such as malaise, anorexia, nausea, and mild jaundice. Laboratory diagnosis relies on serology and molecular methods. Anti-HEV immunoglobulin M (IgM) testing is commonly employed for acute infection; however, this method is limited by false positives and false negatives. Detection of HEV RNA through polymerase chain reaction (PCR) in serum or stool remains the gold standard, particularly for immunocompromised individuals who may not mount an adequate antibody response. Chronic HEV is confirmed when viral RNA persists in serum or stool for six months or longer, necessitating ongoing monitoring and intervention [15]. Management of HEV infection varies according to the clinical scenario. Acute HEV infection in immunocompetent individuals is managed with supportive care, including adequate hydration, nutritional support, and avoidance of hepatotoxic medications. Severe cases, such as fulminant hepatitis, may require hospitalization or liver transplantation. Chronic HEV infection, most often caused by HEV3 or HEV4, is treated with ribavirin, which demonstrates good virological response. Ribavirin is contraindicated in pregnancy due to its teratogenicity, and appropriate contraceptive counseling is required for individuals of reproductive potential. Adjustments to immunosuppressive therapy, including reducing calcineurin inhibitors or optimizing mycophenolate mofetil, may be necessary to facilitate viral clearance in transplant recipients or other immunocompromised patients. Additional considerations include rare but important transmission routes such as blood transfusion and vertical transmission from mother to fetus. Public health measures targeting safe water, proper sanitation, and food hygiene are essential in preventing outbreaks, particularly in endemic regions. Overall, HEV presents a spectrum of clinical manifestations, transmission patterns, and management challenges that require careful attention to patient risk factors, immune status, and local epidemiology to ensure effective diagnosis, treatment, and prevention [40][42].

Healthcare Team Outcomes

The diagnosis and management of hepatitis E virus (HEV) infection require coordinated efforts across the healthcare team to ensure optimal patient outcomes. HEV poses diagnostic challenges because its clinical presentation is often nonspecific and overlaps with other forms of acute hepatitis. Common symptoms such as malaise, anorexia, nausea, and jaundice are insufficient to distinguish HEV from hepatitis A, B, or C, as well as from drug-induced or ischemic liver injury. Furthermore, standardized laboratory testing is limited, and serological assays for anti-HEV immunoglobulin M (IgM) and IgG may produce false-positive or false-negative results. Polymerase chain reaction (PCR) detection of HEV RNA in serum or stool is considered the gold standard, particularly for immunocompromised patients who may not mount adequate antibody responses. Therefore, a high index of clinical suspicion is essential for timely diagnosis, especially in patients with recent travel to endemic areas or in those who belong to high-risk groups [43][44]. In most immunocompetent individuals, HEV infection is self-limiting and resolves without the need for antiviral therapy, with supportive care being sufficient.

Supportive measures include monitoring liver function, maintaining hydration, and avoiding hepatotoxic medications. However, patients with increased vulnerability—including pregnant women, individuals with preexisting chronic liver disease, and immunocompromised patients—require closer surveillance and a more proactive management strategy. In these groups, HEV infection can result in severe complications such as fulminant hepatic failure, acute-on-chronic liver failure, or progression to chronic infection, which may necessitate antiviral therapy and adjustment of immunosuppressive regimens [45].

Effective healthcare team outcomes depend on interprofessional collaboration. Infectious disease specialists provide guidance on antiviral therapy, monitor viral clearance, and assess the need for ribavirin or other agents in chronic cases. Hepatologists evaluate liver function, manage complications, and determine the need for hospitalization or transplantation in severe cases. Transplant specialists and immunologists contribute by optimizing immunosuppressive therapy to balance viral clearance with graft protection. Primary care clinicians maintain continuity of care, monitor comorbidities, and educate patients about preventive strategies. Prevention remains a critical component of improving healthcare outcomes. Protecting water supplies from contamination with human feces is the most effective measure to reduce HEV incidence in endemic regions. Travelers should avoid untreated water, ice, and foods at risk for contamination, and pregnant women should minimize travel to endemic areas whenever possible. Vaccination with HEV239 is available in China but remains unlicensed in most countries, and evidence regarding pre- or postexposure immunoglobulin prophylaxis is limited. Combining vigilant surveillance, timely diagnosis, interprofessional collaboration, and preventive measures contributes to improved clinical outcomes, minimizes complications, and reduces the burden of HEV infection in both endemic and nonendemic settings [43][45].

Conclusion:

In conclusion, Hepatitis E virus is a pathogen of major global health importance, characterized by distinct genotypes that dictate its epidemiology and clinical impact. While often a self-limiting illness in immunocompetent individuals, HEV poses a severe threat to specific populations, including pregnant women and immunocompromised patients, in whom it can cause fulminant hepatic failure or chronic infection leading to cirrhosis. Accurate diagnosis is paramount and hinges on a nuanced laboratory approach: serology for acute infection in immunocompetent hosts and nucleic acid amplification testing (NAAT) for immunocompromised individuals and for confirming chronicity. There is no specific antiviral treatment for routine acute cases, but ribavirin has proven effective for chronic HEV. Ultimately, managing HEV requires a high index of clinical suspicion, appropriate diagnostic testing, and a coordinated healthcare strategy focused on prevention—particularly through water sanitation in endemic areas and food safety measures globally—to mitigate its significant burden.

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