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N E W S L E T T E R

Hepatitis A and Hepatitis E: Clinical and Epidemiological Features, Diagnosis, Treatment, and Prevention

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Abstract

Hepatitis A and E are both ancient diseases but have only been properly recognized as being caused by distinct pathogens in modern times. Despite significantly different genomic structures, both viruses employ remarkably similar strategies to avoid host detection and increase environmental transmission. There are millions of cases of acute viral hepatitis due to hepatitis A virus (HAV) and hepatitis E virus (HEV) each year, resulting in tens of thousands of deaths. The presentations can be clinically indistinguishable, but each virus also has a range of less common but more specific phenotypes. The epidemiology of HAV is complex, and is shifting in countries that are making improvements to public health and sanitation. HEV presents a significant public health challenge in resource-limited settings but has historically been incorrectly regarded as having little clinical relevance in industrialized countries.

Introduction

Descriptions of a clinical syndrome recognizable as hepatitis can be found in Sumerian medical texts from the third millennium before the common era. Approximately 2,500 years later, Hippocrates recorded the features of "epidemic jaundice," including clinical descriptions suggestive of fulminant hepatitis. By the Middle Ages, the idea that jaundice might be transmissible had emerged; in the 8th century, Pope Zacharias had men with jaundice quarantined to control the spread of the disease, although he had no understanding of the exact etiology of the condition.

Large epidemics of jaundice, variously called "catarrhal jaundice," "infectious hepatitis," "epidemic hepatitis," or similar, were mainly associated with military campaigns and were a significant cause of morbidity and mortality among troops in the Napoleonic Wars, the American Civil War, and both World Wars. It was during the Second World War that the first evidence of the viral etiology of epidemic jaundice, and the existence of distinct forms of the condition, emerged. A series of experiments in Germany, the United Kingdom, and the United States throughout the 1940s used filtered materials from infected individuals to infect volunteers, or in some cases prisoners [1]. By the end of the decade, these studies, along with epidemiological studies, had elucidated two subtypes of viral hepatitis, distinguished by the primary route of transmission and period of incubation: orally transmitted "infectious hepatitis," with a short incubation period, and parenterally transmitted "serum jaundice," with a prolonged incubation period. These were later termed hepatitis A and hepatitis B, respectively. It was the former that would be blamed for the large waterborne outbreaks of hepatitis that had plagued humankind since antiquity.

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By the end of the 1970s, however, evidence of another pathogen causing epidemics of hepatitis started to emerge. Work done during the preceding decade at the U.S. National Institutes of Health had already demonstrated that most cases of transfusion-associated hepatitis were due to neither hepatitis A virus (HAV) nor hepatitis B virus (HBV). The cause of these cases of non-A, non-B hepatitis would eventually be identified as hepatitis C virus (HCV). An outbreak of hepatitis in Kashmir, India, in 1978 provided the first evidence of another hepatitis virus. The epidemic was waterborne, and large, with around 52,000 cases and 1,700 deaths [2]. The mode of transmission and clinical presentation were generally in keeping with hepatitis A; one key distinguishing feature was the excess morbidity and mortality seen among pregnant women. Around the same time, another group was examining serum samples from three previous Indian hepatitis outbreaks, including a large epidemic in Delhi in 1955 [3]. In all cases, serological testing of infected individuals found no evidence of infection with HAV. Further outbreaks of non-transfusion-associated non-A, non-B hepatitis were identified in other parts of Asia, North Africa, and the Middle East [3]. However, as no causative agent had been identified, it was impossible to determine if the same pathogen was involved in each outbreak. Still, it was becoming increasingly clear that clinically apparent hepatitis A was actually very rare in developing countries [3].

A few years later, a Russian virologist named Mikhail Balayan was investigating an outbreak of non-A, non-B hepatitis among Soviet troops stationed in Tashkent, the capital of what is now Uzbekistan. Balayan wanted to take clinical samples back to Moscow for further study, but that would have meant refrigerating the samples. As the infrastructure to do this was lacking, Balayan instead ingested a pooled filtrate of samples from his patients [3]. Upon returning to Moscow, he developed a case of acute hepatitis. Electron microscopy of his stool identified viral particles that caused a hepatitis-like illness when experimentally inoculated into cynomolgus monkeys. Crucially, these novel viral particles did not react with anti-HAV IgM. By the start of the 1990s, the genome of the novel non-transfusion-associated non-A, non-B hepatitis virus had been sequenced, and it had been named hepatitis E virus (HEV) [3].

HAV and HEV can cause diseases that are clinically indistinguishable from each other, and despite being only distantly related, share some remarkable similarities in terms of the pathogenic strategies they employ. However, they are quite distinct in many other respects. This article reviews their similarities and differences, comparing the epidemiologies, clinical manifestations, diagnosis, treatment, and prevention of the two viruses.

Virology

Taxonomy and classification

HAV is a member of the family *Picornaviridae* and was initially placed in the genus *Enterovirus*. However, further study demonstrated that the virus was sufficiently different from other picornaviruses to be classified within its own genus, *Hepatovirus*. HEV was initially considered to be a member of the family *Calciviridae*

but was later reclassified as a member of the genus *Orthohepevirus*, in the family *Hepeviridae*.

HAV is one of nine species of *Hepatovirus* and the only one known to infect humans. There are six genotypes of HAV, three that infect humans and three affecting simians, but only one serotype [4]. The remaining members of the genus infect a range of species, including bats, hedgehogs, shrews, and rodents. Phylogenetic analysis suggests that the genus originated in small mammals and that human HAV has a rodent origin [4], although a zoonotic reservoir no longer exists.

The genus *Orthohepevirus* contains four species (A to D). Human disease is caused by *Orthohepevirus A*, which has eight genotypes. The remaining three species are found in birds (HEV-B), rodents and ferrets (HEV-C), and bats (HEV-D). Two genotypes of *Orthohepevirus A* are obligate human pathogens (HEV1 and HEV2), and two are endemic in a wide range of species and cause zoonotic infections in humans (HEV3 and HEV4). The remaining genotypes are primarily restricted to wild boar (HEV5 and HEV6) and camels (HEV7 and HEV8). However, human HEV7 infection has been reported [5], and HEV5 is capable of infecting primates [6].

Virion structure: quasi-envelopment, the best of both worlds

Both HAV and HEV are non-enveloped icosahedral viruses. The lack of a lipid envelope offers both viruses a significant advantage in terms of their ability to spread in the environment, as demonstrated by the foodborne and waterborne outbreaks, which are synonymous with both hepatitis A and E [3,7]. This is because a stable, naked protein capsid offers the fragile RNA genome significant protection against harsh environmental conditions. In comparison, the transmission of enveloped viruses tends to require at least close contact between individuals, if not the exchange of bodily fluids. This is because the viral envelope contains virus-encoded glycoproteins called peplomers, which mediate interactions with cell surface receptors. Without these peplomers, the virion is unable to gain access to a host cell, so it is vulnerable to anything that would disrupt the lipid bilayer, such as drying, solvents, or detergents. Within a host, however, enveloped viruses have several advantages over naked virions. The envelope facilitates crossing the plasma membrane, allowing new virions to leave the cell without the need for cell lysis, and also protects the virus from the immune response by hiding antigens from neutralizing antibodies [8].

There is a significant body of evidence that suggests that although both HAV and HEV are non-enveloped viruses, they can also enjoy at least some of the benefits of enveloped viruses. HAV and HEV virions, which are shed in the stool, are naked protein capsids, ideally suited to their role of reaching new hosts across both time and distance in a potentially hostile environment [8]. However, HAV and HEV, which are isolated from the serum of individuals suffering an acute infection, are wrapped in a hijacked layer of host cell membrane, similar to those found on classical enveloped viruses but distinguished by the lack of any virus-encoded proteins at the surface [8]. This allows circulating virions to avoid the immune response, as antigenic proteins are protected from neutralizing antibodies [8]. However, the lack of peplomers

raises questions as to how these quasi-enveloped virions achieve entrance into host cells [8].

Epidemiology and Transmission

The World Health Organization estimates that there are 1.4 million cases of hepatitis A globally each year, resulting in approximately 7,000 deaths [9]. In comparison, there are an estimated 20 million HEV infections each year, leading to 3.3 million symptomatic cases and around 44,000 deaths [10]. These figures are concerned only with parts of the world where HEV is endemic and, as such, are likely to represent a gross underestimate of the actual global disease burden [11].

The primary route of transmission for HAV is fecal-oral, primarily through direct person-to-person contact, but also via contaminated food or water. Men who have sex with men are at increased risk of infection, as are any persons engaging in oral-anal sexual contact regardless of gender or sexual orientation [1]. Parenteral transmission via contaminated blood products has been described [1], and injecting drug users are at high risk [1], with increased prevalence positively correlated with low incomes [1]. Infected individuals shed virus in their stool for around 2 weeks before becoming symptomatic and typically for a few days after but may continue to do so for several weeks. Even with good standards of hygiene and sanitation facilities, the rate of infection in close contacts of cases is high, suggesting very efficient interpersonal transmission.

The rate and pattern of HAV transmission vary widely between different parts of the world, primarily determined by socioeconomic factors. In regions with smaller family sizes, better sanitation facilities, and greater access to clean drinking water, rates of infection are lower. Counterintuitively, lower rates of transmission do not equate to less disease. In resource-poor areas of high endemicity, such as Africa, parts of Asia, and South America, infection with HAV in early childhood is widespread. In most cases, young children are asymptomatic or experience a very mild illness, and HAV infection typically confers lifelong immunity. Conversely, in high-income regions of low endemicity, like North America, Western Europe, Japan, and Australia, exposure in childhood is rarer. As a result, a much smaller proportion of the adult population has anti-HAV antibodies. If HAV is introduced, significant outbreaks can result, particularly in high-risk groups, such as men who have sex with men [12], homeless people, and recreational drug users [13]. These outbreaks primarily affect adolescents and adults, who are more susceptible to becoming seriously ill. Over the past few decades, improvements in hygiene and sanitation in some low- and middle-income countries have reduced HAV transmission and increased the average age at infection [14]. This "epidemiological transition" shifts the epidemiological pattern closer to that seen in industrialized nations, producing a paradoxical increase in both morbidity and mortality associated with hepatitis A [15].

The epidemiology of HAV depends upon the genotype involved and, by extension, the geographical region under examination. As mentioned above, human hepatitis E is predominantly caused by four of the eight genotypes of *Orthohepevirus A*. HEV1 and HEV2 are similar to HAV in that they are endemic in lower-income countries [16], infect only humans, and are spread via the fecal-oral route. However, unlike HAV, infection with HEV does not confer lifelong immunity. This results in both sporadic cases and periodic outbreaks, which occur periodically when anti-HEV IgG seroprevalence in the population drops below a critical threshold for herd immunity [17].

HEV3 and HEV4, in contrast, are zoonoses that infect a wide range of mammalian species; however, pigs constitute the primary viral reservoir [16]. HEV3 causes locally acquired infections in Europe, North America, Australasia, and Japan [18]. HEV4 has historically been restricted to China and Japan [11]. Transmission between pigs occurs via the fecal-oral route, and infection is typically apathogenic in the animals. Consumption of infected meat is the primary vector for human infection, and HEV has been identified in retail pork products at the point of sale [16]. A range of other foods have also been implicated, with viruses isolated from shellfish, fruits, and vegetables [18]; this is likely due to pig slurry contaminating watercourses or being used as fertilizer.

More than two-thirds of zoonotic HEV infections are asymptomatic [19]. Of the remaining cases, only a small fraction are confirmed by serological or molecular testing; historically, most are either misdiagnosed or go unrecognized. In recent years, however, there has been a surge in reported cases. The number of laboratory-confirmed cases in Europe increased by a factor of 10 between 2005 and 2015 [20]. In part, this likely reflects increased awareness of HEV among clinicians, but in at least some countries, there has been an actual increase in incidence [21].

Reports from several different countries have described parenteral HEV transmission via infected blood products [11]. Studies have also demonstrated viremia at the time of donation among healthy blood donors, with a wide variation in the rates of viremia in different countries, from 1:27 in India [22] to 1:74,131 in Australia [23]. The extent of the contribution that transfusion-associated HEV infection makes to the global burden of disease is unclear, but it certainly presents less risk than the primary modes of transmission. However, patients who are at risk of chronic infection or more severe hepatitis are over-represented in the cohort of patients who are most likely to receive blood products. This includes transplant recipients, immunocompromised patients, and pregnant women. In response to this, a growing number of European countries now routinely screen blood donations for HEV [11].

In the last 2 years, evidence has emerged of a new zoonotic source of HEV infection. As mentioned above, HEV-C affects rodents. Genotype 1 of HEV-C (HEV-C1) circulates in rats in Europe, Asia, and North America. A recent large prospective study in Hong Kong identified both acute and chronic HEV-C1 infection in both immunocompetent and immunocompromised patients [24]. Extrahepatic manifestations were also described; one patient developed meningoencephalitis and died, with HEV-C1 RNA found in their cerebrospinal fluid (CSF) [24]. The presence of anti-HEV-A antibodies does not appear to offer any protection, and molecular testing for HEV-A does not detect HEV-C1 due to sequence differences between the species. These findings suggest that HEV-C1

could be prevalent around the world and yet be routinely missed, which would have important clinical implications and would pose a threat to the safety of blood products.

Clinical Picture

Acute infection

Clinical symptoms of hepatitis A typically occur following an incubation period of 14 to 28 days but can present as much as 50 days after exposure (Table 1) [1]. The clinical presentation ranges from asymptomatic to fulminant hepatitis [25]. The disease course is typically more severe with increasing age; very young children often have no symptoms at all. The typical presentation involves two phases: a prodromal phase that lasts for 3 to 10 days and is characterized by malaise and myalgia, followed by an icteric phase [25]. The icteric phase involves a mixed hepatic and cholestatic jaundice associated with anorexia, nausea, and fatigue. This stage lasts between 1 and 3 weeks. Acute liver failure occurs in approximately 0.3% of cases, although it is highly age dependent; in children and adults less than 40 years of age, the case fatality rate is between 0.1% and 0.3%, while in adults over 49 years of age, it is 1.8% [26]. Co-existing chronic infection with HBV or HCV increases the chance of acute liver failure due to infection with HAV [26].

A subset of patients with hepatitis A may present atypically [27]. Up to 5% can develop cholestatic hepatitis, which includes a prolonged period of jaundice lasting 12 weeks or more [28]. The typical clinical course in these patients involves significant jaundice, pruritis, fever, weight loss, diarrhea, and malaise [27,28]. Liver function tests (LFTs) show a cholestatic picture, with marked elevation of bilirubin and alkaline phosphatase and a mild to moderate rise in alanine aminotransferase (ALT). Generally, patients with cholestatic hepatitis require only supportive treatment and go on to make a full recovery.

A further 10% of patients experience a relapse of hepatitis A in the 6 months following the primary infection [27,29]. Following an apparent initial recovery, there is a biochemical relapse that may or may not be accompanied by clinical deterioration. ALT levels can exceed 1,000 IU/dl, and patients generally remain anti-HAV IgM seropositive through the course of the illness [29]. There are detectable levels of virus in the stool during relapses, so affected patients should be considered infectious. When symptoms recur, they are typically milder than the initial illness and of short duration, usually less than 3 weeks [29]; however, it can take as long as a year for full biochemical resolution. It is not known what causes some patients to relapse, and no risk factors have been identified [29]. Multiple relapses can occur, but most patients go on to make a full recovery.

Most patients who develop clinically apparent hepatitis E experience an acute, self-limiting illness lasting 4 to 6 weeks [11]. After an incubation period of between 2 and 10 weeks, patients develop features typical of hepatitis—jaundice, fatigue, fever, abdominal pain, nausea, and vomiting. In developing countries where HEV1 and HEV2 are predominant, young adults are the most commonly affected group. Males are more likely to present clinically than women. Overall mortality is between 0.2% and 4% [16] but is significantly higher in vulnerable groups, including children under 3 years of age [30], individuals with pre-existing liver disease [31], and pregnant women (see below).

In higher-resource settings, locally acquired cases are caused by HEV3 and HEV4. There is significant heterogeneity in the clinical picture of acute infection in these areas; only a small minority of patients present with typical viral hepatitis as described above. Despite this, HEV is the most common cause of viral hepatitis in several European countries, including France, Germany, and the United Kingdom [32]. As with HEV1 and HEV2, genotypes 3 and 4 preferentially affect men, with a male-to-female ratio of around 3:1, although they tend to be older, with a median age of

Table 1. Clinical characteristics of acute hepatitis A and acute hepatitis E

Characteristic	Value	
	HAV	HEV
Incubation period (median no. of days)	30	40
Dose-dependent severity	No	Yes
Mortality (%)	0.1–2.1	0.2–4
Mortality in pregnancy	No difference	Up to 25%
Chronic disease	No	Yes (HEV3, HEV4)
Developed countries	Epidemic, endemic	Sporadic, travel associated (HEV1, HEV2)
		Sporadic, endemic (HEV3, HEV4)
Developing countries	High seropositivity, rare clinical disease	Epidemic, endemic
Age group	Adolescents, young adults	Adolescents, young adults (HEV1, HEV2)
		Older adults (HEV3, HEV4)
Sex	No difference	Males more commonly affected

63 years [33]. It this thought that this is a result of host factors rather than due to variations in exposure. Pre-existing subclinical liver disease has been proposed as a potential risk factor, as both alcohol excess and diabetes, which are associated with hepatic steatosis and fibrosis, are over-represented among patients with acute hepatitis E [34]. Progression to liver failure is generally uncommon; however, a small number of cases have been reported, and a German study identified HEV as the most likely precipitant of acute liver failure in 10% of a cohort of 80 patients. Individuals with pre-existing liver disease are at risk of decompensation or acute-on-chronic liver failure. However, hepatitis E is not as common a cause of decompensation in industrialized countries [35, 36]. This likely represents differences in the pathogenicity of the genotypes, which are found in different regions.

HEV in pregnancy

One of the most important public health challenges related to acute hepatitis E infection, which most commonly occurs in developing countries, is the excess morbidity and mortality seen among pregnant women (Table 1). In these parts of the world, where HEV1 is the predominant genotype, around a quarter of pregnant women with acute hepatitis E die [37]. This highest-risk period is the third trimester, with 33% of women infected during that stage of pregnancy developing fulminant hepatic failure [38]. Other than liver failure, the major causes of HEV-related maternal death are obstetric complications, such as eclampsia or hemorrhage [38]. There is also a significant risk to both the fetus and neonates. Vertical transmission is common [39], and there is a substantial increase in the risk of intrauterine death, stillbirth, pre-term birth, and low birth weight [40]. Fetal mortality is approximately 33%, including those who die as a result of maternal death, and neonatal mortality is around 8% [37].

The mechanisms that underlie the increased disease severity in pregnant women are not well understood. Pathogenic differences between HEV genotypes may play a part, as the rates high of mortality and morbidity are seen with HEV1 and have not been described in the context of HEV3 infection. Both HEV1 and HEV3 are capable of infecting the decidua basalis (i.e., the uterine endometrium at the site of embryo implantation) and the placenta. However, HEV1 replicates with greater efficiency *in vitro* in tissue explants and stromal cells from both tissues and is associated with increased tissue damage [41]. HEV1 also affects the secretion profile of the maternal-fetal interface, increasing the release of pro-inflammatory factors [41]. Both the viral load and serum inflammatory cytokine levels (tumor necrosis factor alpha, transforming growth factor β1, interleukin 6 and interferon gamma [IFN-γ]) are higher in pregnant women than in non-pregnant women infected with HEV1, and levels of the cytokines correlate positively with adverse pregnancy outcomes [41]. Other studies have shown that high levels of HEV RNA are also associated with worse outcomes in pregnancy [41].

Chronic infection

While HAV does not cause chronic infection, persistent infection with HEV has been documented. The majority of the literature on the subject describes solid organ transplant recipients, but chronic infection has been reported in other immunocompromised cohorts, as well, including in HIV-positive patients with $CD4^+$ counts of <200/mm^3, in individuals with hematological malignancies receiving chemotherapy and stem cell transplants, and in rheumatology patients treated with immunosuppressive drugs [11]. In almost all cases, chronic infection involves HEV3 or HEV4, but there has been a single report of chronic HEV7 infection in a patient who had consumed camel meat and milk [5].

Chronic infection is defined as HEV replication persisting for 3 months or more [11]. Around two-thirds of solid organ transplant recipients who are exposed to HEV develop a chronic infection [11]. The risk is increased for those with immunosuppression and for those who are treated with tacrolimus. Most chronic infections are asymptomatic, with only a mild or moderate rise in ALT. Some patients have normal LFTs, and some remain seronegative for anti-HEV antibodies despite active viral replication [11]. Without treatment, the development of fibrosis can occur, with a risk of rapid progression to cirrhosis, decompensation, and death [11].

Extrahepatic manifestations

Extrahepatic manifestations of HAV infection are most commonly reported in patients who experience cholestatic hepatitis or relapsing hepatitis A. Between 10 and 15% of patients develop a rash and/or arthralgia, but a range of rarer complications have also been described. They include vasculitis, cryoglobulinemia, and thrombocytopenia [42,43].

A broad range of extrahepatic manifestations (Table 2) have been reported in the context of both acute and chronic HEV infection, the most important of which are neurological and renal complications. The mechanisms that underlie these manifestations are not currently understood, but both immune-mediated processes and direct viral tropism have been suggested.

Neurological injury is the most frequently reported extrahepatic complication of HEV infection, with around 150 cases involving HEV1 or HEV3 currently described [44]. In all cases, it is the neurological signs and symptoms that dominate the clinical picture. Patients are typically anicteric and have either normal liver enzymes or at most mild to moderately deranged LFTs. A wide variety of neurological illnesses have been reported in association with HEV (Table 2), but the mostly strongly associated conditions are neuralgic amyotrophy (NA), Guillain-Barré syndrome (GBS), and encephalitis/myelitis.

NA is an acute monophasic injury to the brachial plexus that results in pain, weakness, and sensory disturbance in the upper limbs. In a study of Dutch and English patients with NA, 10.6% had evidence of acute HEV infection at the onset of their neurological illness [45]. HEV-associated NA has a characteristic clinical phenotype. The symptoms tend to be more severe, with more extensive bilateral damage to the brachial plexus than is seen in non-HEV-associated cases [46]. An international multi-center study in Europe that prospectively tested 464 patients with acute, non-traumatic neurological injury found evidence of HEV infection in 2.4% of the patients. There were three cases of NA; all three had evidence

of infection, and all three displayed the characteristic clinical phenotype of HEV-associated NA [47].

GBS is an immune-mediated polyradiculopathy involving rapidly progressive muscle weakness, which can lead to respiratory failure. It is considered a post-infective condition, and *Campylobacter jejuni* is the most common precipitant. The causative organism was not identified in over 50% of the cases [48]. The earliest reports of HEV-associated neurological illness involved GBS, following the observation that around a third of Dutch GBS patients had LFT derangement without an apparent cause [44]. Three case-control studies from the Netherlands, Bangladesh, and Japan found evidence of recent HEV infection at significantly higher rates among GBS patients than in control subjects [44].

Twelve cases of HEV-associated encephalitis/myelitis have been reported in Europe, Asia, and the U.S. [44]. Five of them were chronically infected solid organ transplant recipients. Five patients developed ataxia, which appears to be associated with worse outcomes; two of the ataxic patients died, and the remainder had a more significant long-term neurological deficit than those who did not have ataxia. Six patients had HEV RNA in both blood and CSF. In one case, the virus isolated from CSF showed evidence of quasispecies compartmentalization, which may suggest the emergence of directly neurotropic strains [49].

Renal injury has been described in the context of both acute and chronic HEV infection. Renal biopsies of patients with HEV-associated renal impairment show evidence of membranoproliferative glomerulonephritis (MPGN), cryoglobulinemia, and membranous glomerulonephritis [41]. HEV RNA has also been isolated from the cryoprecipitate of an immunocompetent patient who presented with acute HEV infection and MPGN [41]. Once viral clearance is achieved, renal function and proteinuria improve in most patients [41].

Diagnosis

The differential diagnosis of acute hepatitis is extensive. In addition to the five hepatitis viruses, there are several other viral causes, such as cytomegalovirus and Epstein-Barr virus. Non-viral infectious causes include bacterial infections, such leptospirosis, Rocky Mountain spotted fever, and typhoid, or parasitic infection with liver flukes or roundworms. Non-infectious causes include autoimmune hepatitis, systemic lupus erythematosus, drug-induced liver injury—iatrogenic or secondary to deliberate self-harm—and toxins, most commonly alcohol. For several reasons, HEV infection may not be considered a potential diagnosis. As it is still often incorrectly regarded as an "emerging" disease, many clinicians have limited knowledge of the disease. The heterogeneous presentation of HEV infection, especially in developed countries, further compounds the problem.

Even when HEV infection is considered, there are issues surrounding the availability and reliability of testing. In the U.S., there is no U.S. Food, and Drug Administration-approved assay on the market. Where they are available, there is significant variation in the sensitivity and specificity of tests [50], and the previous "gold standard" test has been shown to substantially underestimate

Table 2. Extrahepatic manifestations of hepatitis E virus infection

Site	Manifestation
Neurological	Neuralgic amyotrophy[a]
	Guillain-Barré syndrome[a]
	Encephalitis/myelitis[a]
	Mononeuritis multiplex
	Myositis
	Bell's palsy, vestibular neuritis, and peripheral neuropathy
Renal	Membranoproliferative and membranous glomerulonephritis
	IgA nephropathy
Hematological	Thrombocytopenia
	Monoclonal gammopathy of unknown significance
	Cryoglobulinemia
	Aplastic anemia
	Hemolytic anemia
Other	Acute pancreatitis
	Arthritis
	Myocarditis
	Autoimmune thyroiditis

[a]Evidence supports a causal role for HEV in this condition.

seroprevalence in comparison to later-generation assays [51]. In chronic HEV infection, as previously described, patients are often seronegative for anti-HEV antibodies, so molecular analysis must be used to detect HEV RNA directly (Fig. 1a). This type of analysis can be less useful in acute infection, as the period of viremia can be very narrow. However, virions are shed in the stool for a longer period.

In contrast, highly sensitive and specific serological assays for anti-HAV IgM have been available for more than 40 years (Fig. 1b) [1]. Specific IgM remains positive for a variable period of time following infection, disappearing from the sera of most patients within 7 months but remaining for up to a year in some individuals [1]. Anti-HAV IgG is seropositive in both current and past infections, as it typically remains present in the serum for life.

Treatment and Prevention

For both hepatitis A and acute hepatitis E, the majority of cases require no specific treatment. The minority of patients who develop fulminant hepatic failure should receive aggressive supportive therapy and be considered for liver transplantation. A small number of patients with severe, acute hepatitis E have been treated with ribavirin, producing a rapid resolution of liver enzyme derangement and viral clearance [11]. It is, however, difficult to draw conclusions from these reports due to the lack of controls and range of different treatment protocols employed.
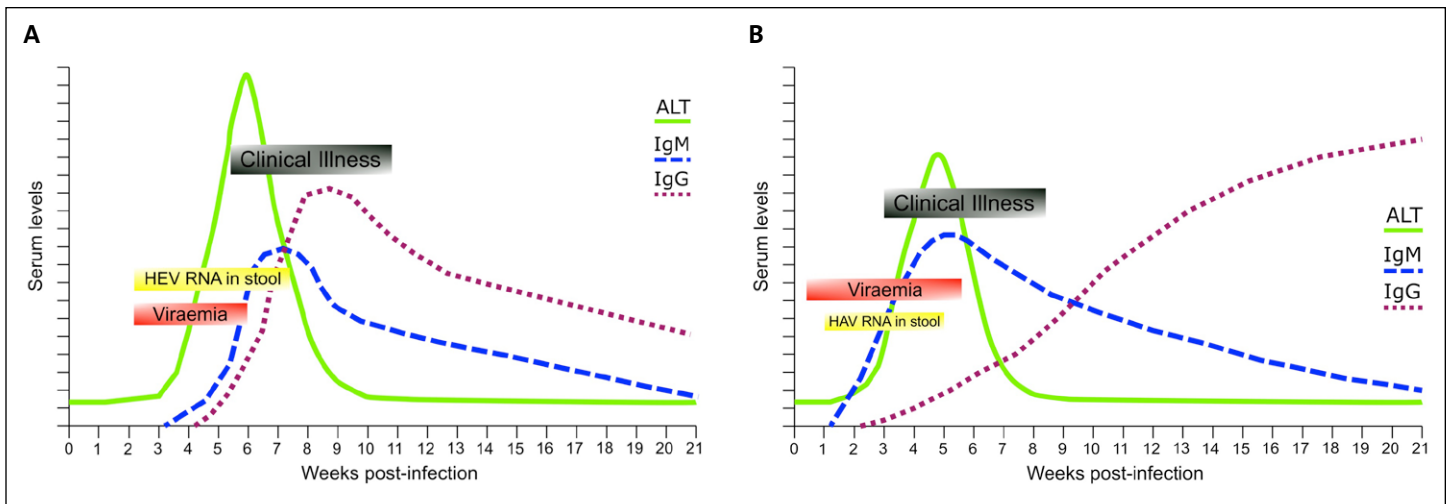
Figure 1. Virus detection and serological and biochemical response to acute HEV infection (a) and acute HAV infection (b).

In chronic infections in immunosuppressed transplant recipients, the first-line treatment is the reduction of immunosuppressive drugs, particularly those that target T cells. Around 33% of patients clear the virus without any other intervention [11]. For the remaining patients, ribavirin may be useful. The optimal duration of treatment is still to be fully determined, but the European Association for the Study of the Liver guidelines suggest an initial 3-month course followed by a further 6-month course for those who fail to clear the virus after the first course [11]. A large retrospective study suggested that around 81% of patients achieve a sustained virologic response following one course of treatment, rising to nearly 90% after a second [52]. Pegylated IFN-α can be considered for liver transplant recipients who cannot tolerate ribavirin or fail to respond but is generally contraindicated in patients who have received other organs as the risk of rejection is increased [11]. In other immunosuppressed cohorts, successful treatment with ribavirin, IFN-α, or a combination of the two has been described [11].

The main methods by which the spread of HAV can be prevented are good hygiene practices, proper sanitation, case investigation and contact tracing during outbreaks, and active and passive immunoprophylaxis. Thorough hand washing and careful food handling practices are of great importance. Postexposure prophylaxis can be considered for close contacts of infected individuals, subject to local guidelines. This can consist of either vaccination or intramuscular immune globulin. The U.S. Centers for Disease Control and Prevention recommends vaccination for healthy people aged 12 months to 40 years; immune globulin for those aged over 40, although vaccination is acceptable; and immune globulin for children under 12 months, immunocompromised individuals, patients with chronic liver disease, and anyone with contraindications for vaccination [53]. Screening for HAV should be offered to at-risk individuals in sexual-health settings, mainly targeting men who have sex with men, intravenous drug users, and patients with HIV, HBV, or HCV disease [54]. Patients who test negative should be offered vaccination [54].

In regions where HEV1 and HEV2 are endemic, the key prevention strategies surround improving sanitation facilities and access to clean, safe drinking water. In resource-rich settings, where zoonotic transmission is the major route of infection, proper preparation of food products is the primary preventive measure. Meat products, in particular pork and game, should be thoroughly cooked [11]. Anyone with risk factors for developing a more severe illness, such as those with pre-existing liver disease or immunosuppressed individuals, should take particular care to avoid uncooked meat. People whose employment brings them into contact with pigs, boar, or deer and their products should take care to minimize direct contact and use appropriate protective equipment. An effective vaccine against HEV, designated HEV-239, has been on the market in China for several years [11]. The vaccine has been designed to offer long-term protection against all genotypes of HEV but has yet to be licensed outside China.

Conclusions

HAV and HEV share many similarities but are distinguishable from each other in many ways. They occupy similar ecological niches and have developed similar characteristics and strategies despite not being closely related. Their status as quasi-enveloped viruses has not been seen in any other virus and likely represents an adaptation to take advantage of the secretory pathways that are accessible from hepatocytes.

Both viruses present public health challenges to both high- and low-income countries. The changing epidemiological patterns that HAV displays in response to socioeconomic progress in developing countries require careful attention. Interventions, such as universal childhood vaccination programs, must be properly implemented and timed correctly. If a vaccination program introduced to a low-endemicity region achieved inadequate coverage, it would likely exacerbate the epidemiological transition it was intended to ameliorate.

Our understanding of HEV, particularly the zoonotic genotypes, remains inadequate, and the COVID-19 pandemic has brought the risks presented by emerging zoonotic infections into sharp focus. There is mounting evidence that HEV is significantly underdiagnosed, particularly in the context of its many extrahepatic manifestations. Further attention is required to elucidate the actual burden of disease presented by HEV and to better understand the risks presented by potential novel zoonoses, such and HEV-C1.

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