Evolving insights into viral hepatitis: Advances, evidence, and expert perspectives from the ESCMID Study Group for Viral Hepatitis (ESGVH) – Part 1: hepatitis A, E, and herpesvirus-associated liver disease

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Abstract

Viral hepatitis remains a global health concern, with growing recognition of the impact of hepatitis A virus (HAV), hepatitis E virus (HEV), and herpesvirus-associated hepatitis, particularly in vulnerable groups. This narrative review from the ESCMID Study Group for Viral Hepatitis (ESGVH) summarizes recent advances and expert perspectives. For HAV, insights into viral evolution, epidemiology, and risk groups underline the preventable nature of severe disease. HEV is increasingly recognized as both a hepatotropic and a systemic pathogen, with expanding knowledge on natural and vaccine-induced immunity. Herpesvirus-associated hepatitis, while rare, poses significant challenges, especially in patients with immunosuppression or during pregnancy, where early suspicion and empirical antiviral therapy can be lifesaving. Collectively, these evolving insights highlight the importance of strengthened diagnostics, targeted prevention, and tailored management strategies to mitigate the burden of these underappreciated but clinically significant causes of viral hepatitis.

Keywords **Viral hepatitis, HAV, HEV, hepatitis A, hepatitis E, herpesvirus, liver.**

Introduction

Viral hepatitis still represents an important global health concern, encompassing a diverse spectrum of pathogens with varied transmission routes, clinical outcomes, and public health implications. While hepatitis B and C have traditionally dominated the scientific and clinical agenda due to their chronicity and burden of liver disease, other hepatotropic viruses – including hepatitis A virus (HAV) and hepatitis E virus (HEV) – as well as hepatotropic herpesviruses, remain of significant relevance.

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These infections are increasingly recognized for causing acute and potentially severe disease, triggering outbreaks in both low- and high-income settings, and complicating the clinical course in vulnerable patients such as those with immunosuppression or underlying liver disease.[1-3]

Interesting work has highlighted the evolutionary history of HAV, its epidemiological distribution and impact, and has allowed a better understanding of patient profiles at risk of severe disease. Parallel advances have expanded knowledge on hepatitis E, with a growing body of evidence on both natural and vaccine-induced immunity and their roles in preventing infection and severe outcomes. Beyond its traditional classification as a self-limiting acute viral hepatitis, hepatitis E is increasingly recognized as a systemic disease capable of extrahepatic manifestations, requiring clinicians to think beyond the liver. In addition, herpesvirus-associated hepatitis continues to be an underdiagnosed but clinically significant entity, particularly in immunocompromised individuals, where it can lead to fulminant disease.

In this context, experts from the ESCMID Study Group for Viral Hepatitis (ESGVH) have drafted a two-piece narrative review, providing an updated synthesis of advances, evidence, and expert perspectives into viral hepatitis. This first part of the series focuses on hepatitis A, hepatitis E, and herpesvirus-associated hepatitis, with the aim of informing both clinical decision-making and future research priorities.

Hepatitis A virus

Hepatitis A virus evolution

Of the five major agents of viral hepatitis (hepatitis A, B, C, D, E viruses), the two viruses with fecal-oral transmission, HAV and HEV, are from phylogenetically unrelated RNA viral families, hepatoviruses and hepeviruses, respectively. Both generate similar clinical manifestations and neither causes chronic infection in immunocompetent individuals. Both are common in resource-poor settings, linked with poor hygiene.

HAV, discovered by Feinstone in 1973,[4] is a 27 nanometer plus-stranded RNA virus belonging to the picornavirus family. HAV is a hepatotropic virus and infects only primates. The virion is highly stable physically against temperature, pH and drying. Genetic diversity is limited, with 6 closely related genotypes where genotypes I, II and III have known A and B subvariants. Genotypes IA and IB are most common among human HAV isolates, while genotypes IIA and IIB are less common but still only found in humans. Genotypes IIIA and IIIB are common in humans but also found in simian infections, whereas genotypes IV, V, VI have been only found as rare isolates among non-human primates. Importantly, only one HAV serotype exists, which has facilitated vaccine development leading to the introduction of HAV vaccines around 1990.

In 2015-2016, hepatovirus-like isolates have been found by molecular means in two non-primate mammal species such as harbor seals and Himalayan marmots.[5,6] In a systematic effort to identify further hepatoviruses in small mammals from 5 continents, Drexler et al. investigated almost 16000 biological samples representing 209 species.[7] They used degenerate polymerase chain reaction (PCR) designed to cover conserved sequences in all known HAV genotypes as well as the avian encephalomyelitis virus, the closest known hepatovirus at the time. Of all samples, 0.7% were positive for hepatovirus RNA. Positive findings were seen in 28 mammal species, including bats, rodents, hedgehogs and shrews. Altogether 13 viruses could be sequenced and characterized as novel hepatoviruses. Subsequently, Vieth et al.[8] in a study from Bolivia identified the closest member to primate HAV to date, in alpacas and llamas. The authors named this virus HAV genotype VII. Interestingly, sera from the bat species *Eidolon helvum* neutralized human HAV growth in cell culture and alpaca IgG reacted in human anti-HAV ELISA, indicating shared epitopes between primate HAV

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and at least two non-primate strains. However, to our knowledge no systematic study has to date been conducted in bigger animals.

An interesting recent finding by Lemon's group is that HAV exists in two different infectious forms.[9] One is the expected, naked picornavirus particle excreted via the bile into feces, while the other is a circulating lipid pseudo-cloaked form that infects cells via the blood, being inaccessible to anti-HAV antibodies due to the lipid cloak. The two seem to use different cellular receptors, with the naked virus using GD1a, a cellular sialinated ganglioside while the pseudo-cloaked form uses TIM1 (T cell immunoglobulin mucin receptor 1), ligand of phosphatidyl serine on the lipid cloak.

Clinical and epidemiological impact of hepatitis A

Hepatitis A virus (HAV) infection typically causes a self-limiting illness in immunocompetent persons, but in certain patient populations the clinical course can be severe. Specifically, severity increases with age, and the prevalence of comorbidities. Individuals with chronic liver disease, especially those with underlying hepatitis B or C, are at increased risk of fulminant hepatitis and liver failure following HAV infection.[1,2] Similarly, patients with immunosuppression, such as those with uncontrolled HIV infection, post-transplant recipients, or patients on long-term immunosuppressive or biologic therapy, may present with atypical manifestations, prolonged clinical course, prolonged viral shedding, or increased morbidity.[10] In addition, older adults tend to experience more severe disease with higher case-fatality rates, highlighting age as a key risk factor influencing prognosis.[11]

During pregnancy, acute HAV infection does not typically lead to more severe liver disease, but associations with adverse maternal outcomes have been described, including preterm labor, premature membrane rupture, or placental abruption.[12]

From an epidemiological perspective, HAV transmission remains primarily fecal-oral, and associated with poor hygiene conditions; waterborne and foodborne transmission are also important contributors. Outbreaks often cluster in vulnerable groups. Men who have sex with men, people who use drugs, individuals experiencing homelessness, and patients with comorbidities represent populations with disproportionate burdens of infection. In recent years, large-scale outbreaks of foodborne hepatitis A in Europe and North America have been responsible for a pooled rate of hospitalization of 32%,[13] and have paralleled outbreaks with high severity among risk groups such as men who have sex with men.[14]

A nationwide population study that analyzed data from more than 200,000 hospitalizations associated to hepatitis A that occurred in the USA between 1998 and 2020, identified the following risk factors significantly associated with mortality: age ≥55 years, underlying liver disease (alcoholic cirrhosis, ascites), hepatorenal syndrome, heart failure, pulmonary hypertension, malignancy.[15] Importantly, since hepatitis A is vaccine-preventable, with safe and effective vaccines being available worldwide, these severe and critical cases could have been prevented through vaccination.[16] This underscores the importance of vaccination and surveillance among groups at risk of acquiring the infection or of developing severe forms of disease. Understanding the interplay between host vulnerability, exposure risk, and local epidemiology is critical for guiding prevention strategies, refining vaccination policies, and protecting high-risk patients from avoidable severe outcomes.

Hepatitis E virus

Natural and vaccine-induced protective immunity against HEV

HEV is a worldwide distributed, hepatotropic, enterically transmitted member of the *Hepeviridae* family, subfamily *Orthohepevirinae*. There are at least four *Hepevirus* genera, two of which can be transmitted to humans: *Paslahepevirus* or *Orthohepevirus* A and *Rocahepevirus* or *Orthohepevirus* C.[17] HEV-A genotypes 1 and 2 are exclusively transmitted by interhuman contact, whereas genotypes 3, 4, 7, and 8 are zoonotically transmitted,[18] as well as

HEV-C 1 and 2.[19] Similarly to HAV, HEV is released from hepatocytes as a 'quasi-enveloped' virion wrapped in host plasma membranes, into the bloodstream and biliary system enclosed in small vesicles resembling exosomes.[20] High concentrations of bile salts disrupt vesicles released from hepatocytes into the biliary system, leading to fecal shedding of highly stable "naked" virus optimized for environmental transmission, even though significantly more susceptible than quasi-enveloped virus to neutralizing antibodies. Quasi-enveloped virions represent the only virus particles found in the peripheral blood during acute hepatitis E.

HEV genotypes 3 and 4 can cause chronic infection in immunosuppressed individuals that may respond to reduction of immunosuppression and treatment with ribavirin.

HEV infection induces a robust type I interferon immunity in symptomatic patients.[21] A significant enrichment of type I interferon response pathways was observed in patients with symptomatic hepatitis E. Intracellular viral sensors (IFIH1, DDX58, TLR3, POLR3B, POLR3C) and other molecules involved in type I interferon (IFN) response (IRF7, MYD88, OAS3, GAPDH) played an essential role in preventing symptomatic acute hepatitis E. The importance of type 1 IFN pathway was further emphasized in a model of immunocompromised chronically HEV-infected pigs, in which antiviral responses included downregulation of IFN pathways in the liver, and upregulation of RIG-I and ISGs in the blood and liver.[22]

HEV elicits broad, vigorous and coordinated adaptive immune responses that are facilitated by >85% genetic homology across genotypes.[23] Of note, natural infection induces long-lasting antibody response and sterilizing protective immunity in vivo.[24] Even though ORF2 may be dispensable for viral replication in vivo, it is nonetheless required for protection against HEV re-exposure. The importance of ORF2, the essential component of the viral capsid, is further emphasized by evidence indicating that it contains important immunodominant CD8+ and CD4+ T cell epitope(s). Interestingly, in self-limiting HEV infection, HEV-specific CD8+ T cells were vigorous, contracted after resolution of infection, and led to functional memory responses. In contrast, in chronic infection, HEV-specific CD8+ T-cell responses were reduced, declined over time, and displayed phenotypic exhaustion. Reduction of immunosuppression in these patients improved CD8+ T-cell proliferation and IFN-γ production.[25] As expected, neutralizing antibodies targeting naked HEV were usually found at high titers, while quasi-enveloped HEV particles were less efficiently neutralized. Importantly, HEV-specific CD4+ T cells developed a strong immune response to ORF2-derived capsid whereas ORF3-derived protein, that is contained in quasi-enveloped HEV, was hardly recognized by CD4+ T cells.[26] The data further confirm that viral capsid is also the main target of HEV-specific CD4+ T cells and antibodies in acute-resolving infection, correlating with efficient neutralization of naked HEV.

Dysregulation of T cell-mediated immunity has also been shown to play an important role in the increased risk of pregnant women with HEV to develop fulminant hepatic failure. There was a significant decrease of T cell activation, leukocyte cell-to-cell adhesion and immune response-regulating signaling pathway in women with HEV progressing to acute liver failure.[27] Immune responses were normally activated during HEV infection while being suppressed in acute liver failure during pregnancy, emphasizing the importance of normal adaptive immunity in protection from severe outcome in pregnant women with hepatitis E.

It is well known that HEV infection may lead to several extrahepatic manifestations. Indeed, HEV can ubiquitously generate pathological damage of the kidneys, pancreas, primary intestinal cells and crypts, the male and female reproductive system as well as central and peripheral nervous system.[28] Although very little mechanistic insights have been provided so far, there is circumstantial evidence that immune responses are involved in extrahepatic organ damage either via immune complex formation or via molecular mimicry. HEV is also strongly associated with the development of Guillain-Barré syndrome and, typically, with Parsonage-Turner syndrome or brachial plexus neuritis for

which no abnormally increased innate immunity has been demonstrated.[21]

At least three vaccines, all targeting the capsid protein, have been developed so far, one of which (HEV239 from genotype 1, Hecolin®, Xiamen Innovax Biotech, Xiamen, China) is presently marketed in China[29] but used also outside China to circumscribe outbreaks. The other two experimental vaccines, one expressed in *E. coli* (p179 from genotype 4) and a second expressed in baculovirus (rHEV 56 kDa from genotype 1) are completing trials.

There is relatively limited laboratory evidence of immunogenicity of the HEV vaccines. In one study, all patients receiving the HEV-239 vaccine displayed seroconversion one month following the first dose and maintained the antibodies throughout the study. HEV-239 was safe and generated a robust hepatitis E IgG response that peaked one month following the second dose. Furthermore, the immune response was durable through at least 6 months after a third dose.[30] In another study of HEV-239, safety was confirmed, and 100% efficacy was documented at 12 months (95% CI: 72.1-100.0%)[29] with 93% efficacy up to 4.5 years (95% CI: 79-98%).[31]

In conclusion, current evidence indicates that naturally acquired immunity to HEV is protective and that immune dysregulation and T-cell exhaustion may lead to acute liver failure or chronic infection, respectively. The virus can elicit autoimmunity and is associated with extrahepatic organ damage. The currently marketed vaccine HEV-239 appears safe and efficacious, inducing long-term protection superimposable to naturally-acquired immunity.

Hepatitis E: a clinical entity beyond the liver

Globally, hepatitis E virus (HEV) infection causes a substantial burden with estimated 1 in 8 individuals ever experiencing HEV infection and 15-110 million individuals with recent or ongoing infection.[32] Over the past 15 years, our understanding of HEV has changed dramatically. Hepatitis E virus represents the leading cause of acute viral hepatitis resulting in nearly 70,000 deaths annually, however, various genotypes of HEV have been identified to produce genotype-specific lesions causing damage beyond the liver.[18,33]

Developing countries of Asia, Africa and Latin America represent endemic areas with epidemic outbreaks related to water, fecally contaminated with the human associated HEV genotype 1 (HEV-1) and genotype 2 (HEV-2).[33] While acute infection with HEV-1 and HEV-2 mostly manifests as an asymptomatic inflammation of the liver or a mild, self-limiting hepatitis with the mortality rate below 1%, a fulminant liver failure may occur in patients with underlying chronic liver disease and in pregnant women.[33,34] The virus crosses the blood-placenta barrier, replicates in placenta and together with hormonal and immunological changes during pregnancy leads to a severe disease with a 25% maternal mortality rate if infection occurs in the third trimester, and a premature delivery in survivors.[34] Additionally, serious liver disease has been described in fetuses and neonates of mothers with HEV infection, with 3000 stillbirths annually registered in developing countries.[33] Interestingly, in Southeast Asia acute pancreatitis episodes have been reported in adult patients infected with HEV-1.[35]

However, the global spread of zoonotic HEV genotype 3 (HEV-3) and genotype 4 (HEV-4) including high-income countries is highly underrecognized and is therefore mistakenly thought to be of minimal clinical relevance, since a large proportion of those autochthonous cases remain un- or misdiagnosed.[18,36] Particularly HEV-3 causes sporadic, usually asymptomatic acute infection with only 5% of patients with infection presenting elevated transaminases; in immunocompromised patients infection can proceed to a chronic infection with a rapid progression to decompensated cirrhosis.[18,37] Over the past years it has been discovered that the tropism of HEV-3 and HEV-4 is not restricted solely to the liver, with viral replication demonstrated in several other tissues, consequently crossing the placental, blood-brain and blood-testis barriers, and ubiquitously affecting several body systems, predominantly central and peripheral nervous system and kidneys, but notably also some others.[3,38,39] This makes hepatitis E a systemic disease with several

extrahepatic manifestations that characterize HEV infection. Although the exact pathophysiological link between HEV infection and extrahepatic manifestations has not yet been established, the direct effects of virus replication causing a cellular damage in affected tissues may be involved together with various indirect, immune-mediated mechanisms.[28]

Clinically, beyond the liver, HEV is most strongly associated with neurological disorders, particularly the development of Guillain-Barré syndrome and, typically, neuralgic amyotrophy (Parsonage-Turner syndrome), as well as meningoencephalitis, mononeuritis multiplex and myositis.[35] Renal disorders, diagnosed in patients with and without immunosuppression, involve membranoproliferative and membranous glomerulonephritis, occasionally with cryoglobulinemia, particularly in patients with chronic HEV infection. Thrombocytopenia is common and can occasionally be severe, while some other hematological disorders possibly related to HEV have been described as single case reports, as were several other extrahepatic disorders such as myocarditis, thyroiditis, Henoch-Schönlein purpura, and myasthenia gravis.[35]

So far, no specific antiviral therapy against HEV has been developed, however ribavirin may be considered in the treatment of cases of severe acute hepatitis E or acute-on-chronic liver failure, as well as in solid organ transplant recipients with no response to decreasing immunosuppression; in liver-transplant recipients with non-response to ribavirin the addition of pegylated interferon alpha is suggested.[35] Sofosbuvir has also been explored, and it displayed modest antiviral efficacy against HEV when used as monotherapy,[40] but in vitro data suggests that it could be considered as add-on to ribavirin as part of rescue treatment.[41]

To conclude, clinical recognition and appropriate diagnosis are essential for the management of HEV infection, particularly beyond the liver. Since the epidemiology affects the clinical presentation, clinicians are urged to identify their major knowledge gaps and include strategies for HEV screening and care in their routine clinical practice.

Herpesvirus-associated hepatitis

Herpes simplex virus (HSV) is a well-recognized cause of acute fulminant hepatitis, but the diagnosis is too often made too late for the administration of life-saving antiviral therapy. Pregnant women and patients with immunosuppression are the high risk groups for this condition. A review of HSV hepatitis in pregnancy identified 56 cases; the most common features were an anicteric hepatitis (very elevated transaminases but normal bilirubin), fever and abdominal pain.[42] Only 18% had a vesicular rash, and 13% any symptomatology related to the genital tract; mortality was 39%.[42] HSV hepatitis is a rare diagnosis, but potentially fatal, so empirical therapy with acyclovir should be initiated if there is any suspicion.[43,44] Diagnosis is based on genome amplification. If the clinical differential diagnosis includes sepsis, acute fatty liver of pregnancy, hemophagocytic lymphohistiocytosis or HELPP syndrome, then HSV hepatitis must also be considered. Laboratory findings also include thrombocytopenia, leukopenia and coagulopathies. All patients with immunodeficiency are at risk of HSV hepatitis – a review of 48 cases in solid organ transplant recipients reported 33% as primary, non-donor-derived, 20% as reactivation, and, most notably, 8% as donor-derived.[45] This latter phenomenon has led authors in Spain and Switzerland to recommend pretransplant HSV serology of all donors and recipients, with appropriate antiviral prophylaxis for those who are seronegative.[46,47]

Mild, self-limiting hepatitis is a well-known feature of acute infectious mononucleosis caused by either Epstein-Barr virus or cytomegalovirus (CMV). ALT levels may exceed 500 IU/mL in a minority of such patients.[48] Histopathology shows diffuse lymphocytic sinusoidal infiltrate, with CD8+ve T cells in a string of beads pattern.[49] In comparison with other infectious causes of acute hepatitis, EBV results in a milder transaminitis but a more pronounced rise in alkaline phosphatase.[50] Hepatitis and jaundice are more likely with EBV infection than with CMV (82% versus 69% and 15% versus 9% respectively.[51] There are occasional reports of very severe EBV hepatitis.[52]

Varicella-zoster virus may also cause life-threatening hepatitis, especially in patients with immunosuppression.[53] The typical vesicular rash can precede, occur concomitantly with or develop after the onset of abdominal pain.[54] Patients feel moderately ill for a few days, exhibiting only mild elevation of liver enzymes, but may then develop fulminant hepatic failure with coagulopathy, encephalopathy and multi-organ failure.

Reactivation of human herpesvirus 6 (HHV6) infection has been described as a cause of non-A-E acute liver failure in transplant recipients. Immunochemistry of liver biopsies may show infection of both hepatocytes and the inflammatory cell infiltrate.[54] HHV6A is also reported to be a cause of syncytial giant-cell hepatitis,[55] a rare condition with a characteristic biopsy appearance.

The most important take-home messages in relation to herpesvirus hepatitis are: HSV is a well-recognized but unusual cause of acute liver failure; most cases arise in pregnant or immunosuppressed patients; clinical presentation is non-specific with anicteric hepatitis (100-1000-fold increase in transaminases with a normal or low bilirubin).[56] Diagnosis by PCR of a blood sample is straightforward but only if there is clinical suspicion, especially if there are no visible lesions. There is a high mortality associated with HSV in the absence of acyclovir therapy, which should be given empirically in cases of suspected sepsis in pregnancy.

Conclusions

Hepatitis A, hepatitis E, and herpesvirus-associated hepatitis remain clinically and epidemiologically significant entities, despite differences in transmission patterns, natural history, and disease burden. Advances in understanding the evolution of hepatitis A virus and its clinical patterns underscore the need for vigilance in both outbreak preparedness and vaccination strategies. For hepatitis E, new insights into immunity, as well as recognition of its extrahepatic manifestations, highlight the complexity of this infection and its broader clinical relevance. Herpesvirus-associated hepatitis, though less common, continues to pose diagnostic and therapeutic challenges, particularly in patients with immunosuppression.

Taken together, these evolving insights emphasize the importance of continued surveillance, improved diagnostic capacity, and tailored prevention strategies for the general population as well as at-risk populations. By consolidating current evidence and expert opinion, this review aims to support clinicians and researchers in navigating the landscape of viral hepatitis.

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