75803_Auto_Edited.docx

WORD COUNT 6118
TIME SUBMITTED 10-MAY-2022 04:07PM
PAPER ID 85758459

Name of Journal: *World Journal of Meta-Analysis*
Manuscript NO: 75803
Manuscript Type: REVIEW

Viral Hepatitis: A narrative review from A-E

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Abstract

Viral hepatitis continues to be a major health concern leading to hepatic decompensation ranging from acute hepatitis to cirrhosis and hepatocellular carcinoma. The hepatic and extrahepatic manifestations are not only debilitating but also associated with a significant economic burden. Over the last two decades, the field of virology has made significant breakthroughs leading to a better understanding of the pathophysiology of viral hepatitis, which in turn has led to new therapeutic options.

The advent of direct- acting antiviral (DAA) agents changed the landscape of Hepatitis C virus (HCV) therapy, and new drugs are in the pipeline for chronic Hepatitis B virus (HBV) treatment. There has also been a significant emphasis on screening and surveillance programs, widespread availability of vaccines, and linkage of care. Despite these efforts, significant gaps persist in care, and there is a pressing need for increased collaboration and teamwork across the globe to achieve a reduction of disease burden and elimination of HBV and HCV.

INTRODUCTION

24

Hepatitis A

Epidemiology

Hepatitis A Virus (HAV) is a single-stranded RNA virus belonging to the family of Picornaviridae which affects around 1.5 million people annually (1)The HAV is a resilient virus and is able to survive in most environments for months despite freezing temperatures, acidic environments, and exposure to chemical agents, thus making it an ideal agent for infection through exposure to contaminated water and food supplies (2). Since the advent of the HAV vaccine in 1996, there has been a significant decline in HAV incidence rate worldwide (3). Incidence and prevalence depend on socioeconomic status and geography of the population. Seroprevalence rates are inversely proportional to general hygiene and sanitary conditions and socioeconomic status(4,5).

Prevalence of viral hepatitis in pediatric population

The Prevalence in children of HAV varies based on region from where the data is reported with higher exposure rates in Africa and South East Asia compared to Europe and United States(4)Global estimates for HBV prevalence are significantly lower among children, estimated at 1.3% in children under 5 years There is limited data on hepatitis D prevalence in children(5) Estimates show HCV infection in the pediatric population to be approximately 5 million children and adolescents globally. Studies show that the prevalence rates are rising, ranging from 0.05% to 0.36% in the United States and Europe to 1.8% to 5.8% in certain developing countries, including Mexico(6-8) A systematic review of hepatitis E infection in pediatric population projected a worldwide, seroprevalence of 10% with rising prevalence with age(9)

Disease phases

The incubation period of HAV is usually 14–28 days, and patients are contagious for two weeks prior to, and up to 1–2 wk after symptom onset.(6) Most patients recover spontaneously without chronic consequences (10). Clinical presentation is variable where children can be completely asymptomatic, while adults can present with jaundice, changes in stool and urine color. Relapsing hepatitis A is characterized by the

reappearance of clinical features and laboratory abnormalities consistent with acute hepatitis A after initial resolution of symptoms. Relapse can occur during 6 mo after initial illness. The duration of clinical relapse is generally < 3 wk, however biochemical relapse can last as long as 12 mo. A minority of patients can progress and develop acute liver failure and may need a liver transplant (11, 12). Hepatitis A infection resolves completely in the majority (>99%) of the cases(13). HAV infection, unlike some other viruses, does not cause chronic liver disease(14).

Hepatitis A vaccine and future directions

The current recommendations by The Advisory Committee on Immunization Practices (ACIP) are 2 shots of HAV vaccine, 6 mo apart. (15). There has been a decline in HAV infection from 11.7 to 0.4 cases per 100,000 population, a reduction by 96.6% because of aggressive screening and vaccination protocols (16). Despite intense public health measures, sporadic hepatitis A cases continue to occur, highlighting the need for ongoing efforts for screening, surveillance, immunization, and education programs.

Hepatitis B

Epidemiology

Hepatitis B virus is a major global public health problem with worldwide estimates of around 350 million cases of chronic hepatitis B infection (17). According to WHO, the burden of HBV is highest in WHO Western Pacific Region and the WHO African Region, where 116 million and 81 million people, respectively, are chronically infected. Countries with high prevalence include Ghana, Gabon, Somalia, China, Cambodia and Mongolia(18). In the United States, 2.2 million have chronic hepatitis B (CHB) with a higher prevalence (3.45%) among first-generation immigrants (19). Patients with CHB carry a 15–40% lifetime risk of developing serious sequelae of infection with an increased risk of death from complications such as cirrhosis and (20) hepatocellular carcinoma (HCC) (21).

Disease transmission and phases

Hepatitis B virus spreads *via* contact of blood or bodily fluids of an infected person, with the route of HBV transmission varying depending on the prevalence and geographic area. Vertical transmission at birth and close household contact among children are among the more common modes in Asia and Sub-Saharan Africa where HBV is endemic(22).In areas with low prevalence, especially developed nations, transmission of HBV among adults usually occurs *via* sexual transmission, percutaneous inoculation through contaminated needles, blood transfusions, or healthcare-associated risk factors such as hemodialysis (22-25). (26, 27). In the United States and Europe, prevalence rates are higher in areas with a larger ratio of immigrant population, who likely contracted HBV in their country of origin (28, 29).

The natural history of HBV depends on the age of the patient at which infection is acquired. For example, in adults, it usually presents as an acute, self-resolving infection where patients who are immunocompetent develop hepatitis B surface antibody (HBsAb) to hepatitis B surface antigen (HBsAg), while only 1-5% progress to developing chronic infection (30). In contrast, the majority of patients infected by vertical transmission or horizontal infection during early childhood are likely to develop CHB, with the risk of developing CHB rising to 90% if the infection was acquired at birth and 16 - 30% if infected during childhood (31, 32).

Chronic hepatitis B can be divided into five phases based on the patient's viral load, elevation in liver enzymes, and hepatitis B serologies (33). In the early "high replicative, low inflammatory" phase, hepatitis B e antigen (HBeAg) is positive, along with very high levels of HBV DNA and a normal serum alanine transaminase (ALT), previously called the "immune tolerant" phase. The next stage's hallmark is immune activation, where HBeAg remains positive along with very high levels of HBV DNA and elevated serum ALT with associated hepatic necroinflammation. Based on the immune activation, the disease may progress to loss of HBeAg and development of hepatitis B e antibody (anti-HBe). In this stage, HBV DNA levels are moderate to high, and liver disease is progressive with risk for subsequent hepatic fibrosis and cirrhosis. In the

"non-replicative" phase (previously known as "inactive carrier"), where HBV DNA is usually very low or undetectable, HBeAg is absent and they have a normal serum ALT. Lastly, "HBsAg loss/occult phase", there is a loss of HBsAg, detectable HBV DNA in the liver, very low but measurable HBV DNA in serum (34).

Extrahepatic manifestations

Both acute and chronic hepatitis B have extrahepatic manifestations. Polyarteritis nodosa is a rare, but serious, systemic complication of chronic HBV affecting the small- and medium-sized vessels (35).HBV associated glomerulonephritis is commonly seen in children and is self-limited. In adults however HBV glomerulonephritis can slowly progress to renal failure(36).The serum-sickness like "arthritis-dermatitis" prodrome is seen in approximately one third of patients acquiring HBV(37).There are several cutaneous disorders associated with HBV infection, typically related to immune complex deposition. These include bullous pemphigoid, lichen planus and Gianotti - Crosti syndrome (papular acro-dermatitis of childhood). Neurological manifestations include Guillain Barre Syndrome , anxiety/depression and psychosis(38).

Definition of cure

Spontaneous seroconversion is the spontaneous loss of HBeAg and development of antibodies to HBeAg (anti-HBe). This state is associated with associated with low HBV-DNA levels and clinical remission of liver disease in many patients (39, 40). Sustained disease remission after HBeAg seroconversion is also associated with a regression of fibrosis upon liver biopsy (41). Overall between 0.5% and 0.8% of chronically infected patients will clear HBsAg per year(42). This clearance of HbsAg is referred to as the recovery phase of hepatitis B.

Resolved chronic hepatitis B is defined as the sustained loss of HBsAg in a person who was previously HBsAg positive, with undetectable HBV-DNA levels and absence of clinical or histological evidence of active viral infection(43).

Loss of HBsAg with acquisition of anti-HBs has been termed functional cure. True cure is defined as elimination of HBsAg and cccDNA (43)

Barriers to cure

Clearance of hepatitis B and host immune response

HBV is a DNA virus with a complex structure and categorized into 10 different genotypes(A-J) based on global distribution, and the severity of the disease, risk of hepatocellular carcinoma, and response to certain treatments (44). The HBV enters the hepatocyte as a consequence of an interaction between the surface antigen and the sodium taurocholate co-transporting polypeptide (NTCP) (45). After entry into the hepatocyte, the closed covalent circular DNA (cccDNA) develops when the relaxed circular DNA (rcDNA) integrates with host cell nucleus, and at the time of HBV replication, pregenomic RNA (pgRNA) can be generated from cccDNA to work as the template for the fully double-stranded DNA (46). Figure 1 shows the lifecycle of HBV virus

A few copies of cccDNA can initiate a full-blown infection after active replication, especially when the host is immunosuppressed (47). Persistent cccDNA has been detected in hepatocytes of patients with resolved HBV infections, and hence the ultimate goal of HBV eradication should aim to clear any remnant cccDNA (42-46). Another very important reason to aim for clearance of cccDNA is the risk of progression to cirrhosis and HCC in patients with low to no HBV DNA in serum, highlighting the important of the role of ccc DNA (48, 49).

HBV virus is unique when compared to other hepatotropic viruses as there is a lack of innate response during HBV infection. (50, 51) Chronic HBV affects the immune system by interfering with the function of T cells and in the synthesis of neutralizing antibodies, which are essential in mounting an appropriate immune response to the virus (52, 53). HBV exposure *in utero* induces a state of trained immunity against HBV (54), and HBV exposed neonates have variable levels of IL-10 and pro-inflammatory

cytokines, and new pharmacotherapeutics exploring this pathway needs further research (54) (55). The goals of therapy have been to control viral replication so that inflammation, development of fibrosis and cirrhosis, and risk of HCC can be reduced, hence lowering the risk of decompensated liver disease and its sequelae and need for a liver transplant.

HBV vaccine and linkage of care

HBV vaccine, although available since 1982, was not widely available secondary to its high cost. In the early 2000's the vaccine coverage increased because of the efforts of the Global Alliance for Vaccines and Immunization (56). There still are major discrepancies in the availability and utilization of the vaccine, especially in regard to universal birth dose administration (57). In 2016, only 19% of countries in the African region and 49% in the Americas and Europe had universal HBV birth dose administration. These percentages are significantly lower compared with 73% administration rate in Southeast Asia and 93% in the western Pacific (58) . WHO recommends B vaccine at birth, preferably within 24 h, followed by 2 or 3 doses of hepatitis B vaccine at least 4 wk apart. Newborns born to mothers whose HBsAg status is unknown should receive hepatitis B vaccine within 12 h of birth(59). Adults who were not vaccinated as children can also receive HBV vaccine with first dose as soon as possible followed by 2 doses at 1 and 6 mo after the first dose.(59) Currently approved vaccines in US include single antigen hepatitis B vaccine and combined hepatitis A ad hepatitis B vaccines. In adults aged 19 through 59 years they can either receive 2 doses 4 wk of single antigen hepatitis B vaccine or a 3 dose series for the combination vaccine.

Multiple factors account for variation in vaccination and linkage of care for HBV across the globe. In China, the major limitation to access and care is secondary to the large

population, high prevalence and the low coverage of diagnosis and treatment programs(60). In resource-rich nations like Australia and New Zealand, despite subsidized screening, specialist management, and treatment for HBV, the barriers include lack of awareness about the implications of HBV infection in general practitioners (GPs), health- care workers, and a lack of consistent clinical guidelines regarding diagnosis and referral to a specialist (61, 62). In the United States, a recent systematic review highlighted the obstacles to care, which include- access to medical care and lack of education and awareness amongst the patients, along with fear of stigma regarding the diagnosis as barriers to testing and care (63). Implementation of effective vaccination policies worldwide, along with strategies to prevent vertical transmission and widely available testing and treatment, would be necessary to attain a reduction in HBV infections worldwide (64).

Current therapies and limitations

Current treatment options for CHB include Interferons and nucleoside analogues but they suppress the viral replication and do not eliminate the virus, and aid in achieving a "functional cure"(65). In HBeAg+ patients, the loss of serum HBeAg and appearance of HBeAb and loss of circulating HBV DNA is the major goal (20). Current therapies lead to HBeAg seroconversion in only 20-30% of treated patients and a mortality reduction by 50% over a ten-year period (20, 66, 67). Table 1 summarizes the current anti-viral therapies for adults and children.

Goal of new therapies

The ultimate target of ongoing research for novel HBV treatments is the eradication of the cccDNA. Currently measurement of cccDNA is not only challenging, requiring a biopsy but also needs sophisticated assays. There is a need for surrogate markers for loss of cccDNA, HBV DNA, HBeAg (68). Table 2 summarizes the newer therapies.

Gene editing- future directions

The major hurdle to eradication of HBV is that effective antiviral therapies target only replicating viruses and do not eradicate latently integrated or nonreplicating episomal viral genomes. Furthermore, HBV infection disseminates extensively beyond the liver and broad range of cell lines, including endothelial cells, neurons, epithelial cells, macrophages, peripheral blood mononuclear cells, and polymorphic nuclear leukocytes are permissive for HBV replication.

Gene editing provides the ability to alter an organism's DNA. Targeted endonucleases are engineered enzymes that can introduce DNA double strand breaks (DSBs) with high specificity into desired target sequences .The major classes of DNA cleaving enzymes include mega nucleases/homing endonucleases (HEs), zinc finger nucleases (ZFNs), Tal-effector nucleases (TALENS), and the RNA-guided engineered nucleases (RGENs) such as CRISPR/Cas9 .(69)

Several features of the HBV virus make it a suitable candidate for eradication with cleavage enzymes. Firstly, HBV has a very small genome (3.2 kb) comprising of four open reading frames (envelope, nucleocapsid, polymerase, and X protein) which are translated into only seven proteins. HBV virus also has Low to intermediate mutability rate and the polymerase mutation rate rages from 1.4×10^{-5}-3.2×10^{-5} mutations/site/year. These factors make it a good target for cleavage enzyme. More recently the CRISPR/Cas9 system has been utilized to target HBV. CRISPR/Cas9 has shown to inhibit HBV replication and target cccDNA. (70, 71) Recently, when Cas9 and guide RNAs were delivered using plasmids In to mouse liver, cccDNA could be cleaved, disrupted and cleared (72). An *in vivo* experiment involving liver-humanized FRG mice chronically infected with HBV and receiving entecavir underwent CRISPR-Cas9 gene editing and showed significantly improved survival of human hepatocytes, showed a trend toward decreasing total liver HBV DNA and cccDNA, and was well tolerated(73). Recent findings of removal of full-length 3,175-bp integrated HBV DNA

fragment using CRISPR-Cas9 demonstrated that CRISP-Cas9 system may emerge as powerful tool capable of promoting a radical or "sterile" HBV cure (74, 75)

Hepatitis C

Epidemiology

Globally, Hepatitis C Virus infection (HCV) prevalence is 1%, and there are about 2.3 million cases in the US(76). The highest prevalence **is** in the Eastern Mediterranean Region and European Regions, followed by South East Asian and Western Pacific region. Countries with high prevalence are Russia, Gabon, Egypt, and Syria(76, 77). HCV is an RNA virus and similar to HBV, it is transmitted *via* contacting blood or body fluids of infected individuals, with most common routes of transmission being intravenous drug use, blood product transfusion, solid organ transplantation, or unintentional cross-contamination in hospitals and other medical facilities (78). Intranasal cocaine use and tattoos administered in unclean parlors are other risk factors (79, 80). Perinatal transmission, though very rare, has been reported in 2–8% of infected mothers (81).

Hepatitis C in pediatric population

A 2018 modelling study estimated the prevalence of HCV in the pediatric population aged 0-18 years was 0·13% (95% uncertainty interval 0·08-0·16), corresponding to 3·26 million (2·07-3·90) children(82). Direct-acting antiviral (DAA) treatment is recommended for all children and adolescents with HCV infection aged ≥3 years. Presence of extrahepatic manifestations like rash, advanced fibrosis, cryoglobuliemia, and glomerulonephritis is an indication for early anti-viral therapy. Table 3 summarizes the treatment options in pediatric population

Extrahepatic **manifestations**

Chronic HCV, which is untreated can cause chronic inflammation, followed by progressive liver fibrosis leading to the development of cirrhosis and HCC (83, 84). Various extrahepatic manifestations are reported in chronic HCV infection like mixed

cryoglobulinemia, vasculitis, glomerulonephritis, and B-cell non-Hodgkin lymphoma, along with increased rates of insulin resistance, diabetes, atherosclerosis, and cognitive impairment (85-87). A meta-analysis of 102 studies looking at prevalence, quality of life, and economic burden of extrahepatic manifestations of HCV showed that the most common extrahepatic manifestations were diabetes (in 15% of patients) and depression (in 25% of patients) (88).

Barriers to elimination

The goal of WHO has been to develop and work on strategies to reduce new infections while treating patients who are infected with HCV (89).

Since the advent of the oral, direct- acting antiviral agents (DAAs) in 2014, there has been a dramatic change in the landscape of HCV therapy (90, 91). DAA therapies are not only well-tolerated and safe but offer cure rates of >95% (92, 93). In comparison to Interferons, treatment with DAA's is short term (94). With the new agents and multiple options, treatment can be tailored based on presence and absence of cirrhosis, decompensated disease, co-infection with HIV and renal function and need for dialysis. Table 4 summarizes the available DAA therapy, their target population, and genotype coverage. DAAs are a promising and have changed the landscape of chronic hepatitis C infection, but there are several barriers to care and cure and below mentioned are a few.

Awareness and screening programs

There remains a general misunderstanding and also lack of awareness regarding HCV in the general population worldwide, as shown in a 2017 WHO Global Hepatitis Report, where of the 71 million people with HCV worldwide, only 20% of them were aware of the infection at the time of confirmation(89). A large population-based study in the USA from 2001 to 2008 showed that fewer than half (49.7%) of those infected with HCV were aware of their status (95). Another National Health and Nutrition Examination Survey (NHANES) study showed that the patients who were unaware of their diagnosis were just as likely to have cirrhosis as those who knew about their infection (96). At a patient

level, fear of the stigma associated with the diagnosis and at the provider level, lack of time, knowledge, and discomfort in asking about high-risk behaviors are barriers to screening, testing, and cure (97). The provider perceptions have changed over the years and now most providers believe that they play an active role in their patient's treatment and their decisions to start treatment are not influenced by high risk behaviors amongst patients (98)

In developing countries, the absence of screening programs and limited resources has resulted in the vast majority of patients being undiagnosed, (99-101) A systematic review and meta-analysis of studies published after 1995 showed that in Africa, only 19% of blood transfusions are screened for HCV due to cost constraints.(102).

The screening strategies have to be tailored according to the population and the country to make these cost-effective (103). As shown in a systematic review of 67 screening programs, in low HCV-prevalence populations, pre-screening can increase efficiency, whereas in high prevalence countries widespread screening programs are cost-effective (104-106).

High risk groups

Intravenous drug users (IVDU) are a well-known high-risk population and the global burden of HCV in injecting drug users is approximately 67% (107). In Europe the prevalence of HCV is estimated to be 50 times higher in individuals who inject drugs compared with the general population. (108). In previous years, this subset of HCV patients was excluded from treatment due to concern of poor adherence, psychiatric co-morbidity and re-infection (109). Current guidelines recommend that people who inject drugs (PWID) should not be excluded from HCV treatment (110) and multiple recent studies have shown that there is no relevant direct influence of IV drugs on the efficacy of anti-HCV therapy among adherent patients.(111-113) and. SIMPLIFY trial demonstrated that HCV treatment should be offered to PWID, irrespective of ongoing drug use and treatment should not be withheld (114). In this high-risk group testing, access to care, prescription of DAA therapy, along with the elimination of stigma

associated with the infection have been proposed as effective strategies for this specific population(115-117).

Prevention of HBV/HCV infection

Both HBV and HCV can be transmitted perinatally, *via* needle stick injury and household contacts. Perinatal transmission for HBV can be prevented by identifying HBV-infected (i.e., hepatitis B surface antigen [HBsAg]-positive) pregnant women and providing hepatitis B immune globulin and hepatitis B vaccine to their infants within 12 h of birth(118). Unfortunately for HCV infection, there are no interventions or prophylactic measures that have been proven to prevent perinatal transmission. Management of needle stick injury for HBV depends on the vaccination status of exposed individual and HBV status of patient. For individuals who suffer needle stick injury and are unvaccinated, vaccination series should be initiated. For vaccinated individuals with documented vaccine response no treatment is required. If the vaccination status is unknown, then its recommended to check anti-Hbs titers and if negative, initiating vaccine series is recommended(119). Recommendations for prevention of HCV after needle stick injury include testing for HCV RNA, HCV antibodies and ALT immediately after event, repeat labs in 2-8 wk and referral to specialist if infection occurs (120). Household contacts should be extensively counselled and education includes measures to avoid sharing razors, toothbrushes *etc.* that predisposes one to contact with body fluids, HCV/HBV positive individuals should refrain from donating blood, organ and tissue(121)

HBV/HCV coinfection

The worldwide incidence of HBV/HCV coinfection is reported to range from 5-15%(122, 123)(ref). The incidence varies significantly depending on geographic location, with higher incidence in endemic areas (124). HBV/HCV co-infection leads to higher rate of cirrhosis, HCC and decompensated liver disease compared to monoinfection (122, 125). Four serological profiles are seen in co-infection- codominant, HCV

dominant, HBV dominant, and neither replicative and these can evolve over period of time(126). The aim in these scenarios would be to identify and eradicate the dominant virus. Then monitor for reactivation of the other virus. Close monitoring of HBV DNA and HCV RNA is essential before determining viral dominance(127). HBV Monoinfection is treated with a nucleo(s) tide analog (eg lamivudine, entacavir, or tenofovir) and/or PegIFN. Currently DAA are the mainstay of treatment for HCV mono-infection although PegIFN plus ribavirin is effective, but is rarely used(124).

HBV/HCV infection post liver transplantation

HBV recurrence post-liver transplantation is a major cause of allograft dysfunction, cirrhosis of the allograft, and graft failure. Patients can be categorized into high and low risk for recurrent HBV based on pre transplant viral load, HbeAg positivity and history of anti-viral drug resistance(128).Combination of hepatitis B immunoglobulin (HBIG) and a potent nucleos(t)ide analogue is recommended after liver transplantation for the prevention of HBV recurrence in patients with chronic hepatitis B. Recent data suggests that patient with low risk of recurrence can discontinue HBIG but need continued monoprophylaxis with NA (75). HCV recurrence after liver transplant is universal in patients with HCV viremia at time of transplant. The viral levels are shown to rebound and reach pretransplant level with 72 h and DAA therapy should be started within this timeframe to prevent graft reinfection and loss(129)

Hepatitis D

Epidemiology

Hepatitis delta virus (HDV) is a defective virus that encodes its own genome but needs hepatitis B surface antigen and hence HBV for replication, propagation, and transmission (130). The two high-risk groups at risk of infection include intravenous drug users and patients with high risk sexual behaviors (131). In the United States, HDV infection was considered to be a rare infection, but data over the last decade

estimating seroprevalence of HDV has shown higher rates, especially in Asians and immigrants(43).

Transmission

Hepatitis D virus is transmitted parenterally and sexually, while vertical transmission is thought to be rare (132, 133). In low endemicity regions and developed nations, IVDU is the main route of transmission (131).

Clinical presentation

Hepatitis D virus infection is always associated with HBV infection as HBV is integral to the assembly of the HDV virion and release. Two major patterns of infection can occur: co- infection and superinfection.

Co- infection is the simultaneous infection with both viruses that leads to acute hepatitis B and D. Clinically, the presentation is difficult to differentiate from other causes of hepatitis and especially acute HBV(134). Patients who are co-infected can present with symptoms that can be very mild to severe fulminant hepatitis(135). Coinfection is usually self-limited, but it's important to highlight the fact that coinfection can cause severe fulminant hepatitis compared to superinfection(135).

Superinfection occurs when HDV infects an individual with CHB, where the pre-existing HBsAg provides an ideal environment for HDV expression. Patients progress from acute hepatitis to chronic infection in up to 90% of cases, whereas the rest either resolve or progress to fulminant disease (134). Chronic HDV infection, in comparison to HBV mono-infection, is more severe and, up to 70% percent of patients rapidly progress to cirrhosis within 5-10 years(136).

Diagnosis and Management

In patients suspected to have HDV, enzyme-linked immunosorbent assay (ELISA) for anti-HDV is the first-line screening test. During the acute phase of HDV infection, IgM anti-HDV is positive in serum. The presence of IgG anti-HDV antibodies indicates either chronic HDV infection or is a serological marker of past infection with recovery (137). The screening recommendations for HDV differ amongst major societies. European guidelines advise for HDV screening of all HBV-infected patients, whereas in

the United States, screening is limited to patients with high risk factors HCV or HIV and patients with elevated aminotransferases with low or undetectable HBV DNA(43). Screening of all HBsAg-positive patients should be considered given concerns regarding under-estimation of prevalence of HDV (138, 139). This strategy would not only lead to a more accurate determination of the prevalence of HDV infection but also lead to earlier intervention and treatment, reducing the risk of complications (140).

The current treatment option for chronic HDV infection is pegylated interferon alfa (peg-IFN-α) for 12 mo based on guidelines from the American Association for the Study of Liver Diseases (AASLD), Asian Pacific Association for the Study of the Liver (APASL), and the European Association for the Study of the Liver (EASL) (43, 141, 142). Overall, the response rate to therapy is low with a 1-year course of high-dose standard IFN-α inducing only a 10% to 20% rate of sustained HDV clearance and a 10% rate of HBsAg clearance (143, 144). Studies revealed that 1-year therapy with peg-IFN- α was associated with a response rate that was better than that of standard IFN-α, but rarely exceeded 25% of sustained HDV clearance (145, 146).

Combination therapy involving standard IFN-α with ribavirin(147) or lamivudine (148, 149) has not been more efficacious than IFN-α monotherapy in chronic hepatitis D. Similar results were obtained when peg-IFN-α was used in combination with ribavirin (150)or adefovir (146).

Novel therapeutics

Given the low overall virologic response rate and high rate of relapse, there is an increasing need for therapeutic strategies aimed at improving efficacy of treatment and offering it to patients with advanced disease for whom IFN-α is contraindicated. Currently, three new drugs that interfere with HDV life cycle are being studied in clinical trials, with varying mechanism of actions: hepatocyte entry inhibitors, farnesyltransferase inhibitors, and nucleic acid polymers (NAPs). Table 4

summarizes these novel therapies with the associated adverse effects. Figure 2 highlights the different target approaches for treatment of chronic hepatitis D.

Additional approaches

Small interfering RNAs (siRNA) have shown early promise in this field. In a phase IIa clinical trial that showed that siRNA ARC-520decreased HBsAg levels after one single injection in HBeAg-negative CHB patients in a dose-dependent manner(151). A multi-dose extension study of up to 12 doses, with once a month dosing, demonstrated an additional decline of HBsAg levels, more so in HBeAg-positive than in HBeAg-negative patients(152). The study was stopped secondary to adverse effects of the carrier molecule but demonstrated the effect and highlighted the scope of siRNA as a potential treatment option.

Currently for the management of HDV, new approaches such as DNA vaccines (153), anti-HB immune complexes (154), immunologically active adjuvants such as beta-glucosylceramide are being explored. Targeting the HBV and immune system interaction is another area that has garnered significant interest. Pre-clinical studies have shown that the Toll-like receptors (TLRs) play a key role in sensing pathogen-associated molecule patterns (PAMPs) and activating intracellular antiviral pathways as well as the production of antiviral effectors like interferons (IFNs) and pro-inflammatory cytokines(155). In a study assessing the safety, pharmacokinetics, and pharmacodynamics of oral TLR-7 agonist, GS-9620 was well tolerated and led to the induction of peripheral mRNA expression of interferon-stimulated gene 15 (ISG15) production in CHB patients, however, no effect on HBV DNA was observed (156). Immune checkpoint inhibitors have also been studies in chronic viral hepatitis, and a phase Ib clinical study of nivolumab in CHB patients highlighted its tolerance and was associated with a significant decline in HBsAg levels after a single dose over 24 wk period and in turn reducing HDV related disease progression and complications (157).

Hepatitis E

Epidemiology

HEV is a small, nonenveloped virus and belongs to the Hepeviridae family and is further classified into genotypes 1, 2, 3, 4, and 7(158). Globally, there are about 2.3 billion people infected with HEV and 70,000 deaths attributed to HEV annually(159, 160).

Hepatitis E is mainly transmitted *via* contaminated water and consumption of undercooked pork or wild boar and other foods, while reports of blood transfusion related transmission has been recently recognized (161, 162). Outbreaks of HEV-1 and HEV-2 genotypes have been documented in areas with limited access to water and inadequate sanitary conditions.(163). The prevalence of anti-HEV IgG in Africa ranges from 4.6 to 10.7%, and 34-94% in Asia (164-168). HEV prevalence is probably underestimated as seen in a large German cohort study, as many practitioners do not routinely test for HEV in the presence of acute hepatitis symptoms, in part due to lack of high clinical suspicion but also due to absence of standardized testing, leading to increased morbidity and mortality among susceptible individuals(169).

Laboratory diagnosis of HEV infection is limited due to lack of standardized testing. (170). Diagnosis of acute-HEV is made with positive serum HEV IgM in the right clinical setting. (171). Definitive diagnosis is made with the detection of HEV in serum or stool by polymerase chain reaction (PCR)(172). Paradoxically, in immunocompromised hosts who do not mount an adequate antibody response, PCR testing should be the cornerstone of diagnosis (173, 174). The lack of a U.S. Food and Drug Administration (FDA)-approved diagnostic test, and the variability in the performance characteristics of commercially-available serologic assays makes the utilization and interpretation of the results challenging (175-177).

Clinical presentation

Clinical presentation in HEV is variable, ranging from asymptomatic carriers to fulminant hepatitis. In acute HEV, the incubation period is typically 3–8 wk followed by a short prodrome leading to a symptomatic phase that can last for several days to weeks (mean 4–6 wk)(178). HEV can also infect patients with chronic liver disease and can cause decompensation, and lead to high mortality (179-181). Extrahepatic manifestations of HEV include rash, arthralgias, Guillain-Barre syndrome palsies, and pseudo tumor cerebri(182).

Based on patient's immune response to acute HEV, some may progress to chronic HEV infection, which is defined by persistent elevated aminotransferase levels for at least 3 mo combined with positive serum HEV RNA and consistent histologic findings on liver biopsy (181). Chronic HEV primarily occurs in immunosuppressed patients such as organ transplantation recipients or those with HIV infection, and hemodialysis (183-189).

Infection with HEV, specifically genotype 1, during pregnancy leads to increased risk of adverse outcomes to the fetus such as spontaneous abortion, in utero fetal demise, and premature delivery, while placing the mother at risk of severe hepatitis and complications (190). HEV in pregnancy is associated with eclampsia, hemorrhage, and acute liver failure, and carries a high mortality rate of 15 –25%, especially in the third trimester (181, 191, 192).

Treatment

Acute HEV in immune-competent hosts is self-limiting illness followed by spontaneous clearance and usually does not require treatment (188). The current treatment of choice for patients with chronic HEV infections is monotherapy with the nucleoside analogue ribavirin (193). Three-month ribavirin monotherapy for chronic HEV has been associated with around 78% SVR (194). No established treatment for HEV is available for pregnant women as Ribavirin is contraindicated in pregnancy, hence supportive care is recommended (195, 196). Pegylated interferon, as an alternative to Ribavirin has

shown limited success (197, 198). There is a need for direct acting novel therapies as HEV remains a major public health concern, particularly among immunocompromised patients and pregnant women. The current efforts for these drug developments are focusing either on the inhibition and manipulation of host components or developing direct acting anti-viral therapies that can target viral enzymes without affecting host components (199).

Hepatitis E vaccine and surveillance programs

The need for hepatitis E vaccine was recognized secondary to its worldwide prevalence and severe complications in high risk populations. Early studies of recombinant vaccines in healthy adults have shown promising results, but study populations have unfortunately not included the high-risk groups who are most susceptible to severe and chronic HEV. A Nepalese randomized, double blinded placebo controlled, phase 2, clinical trial of a recombinant HEV vaccine given at 0, 1, and 6 months to a 898 subjects (vs 896 placebo)revealed vaccine efficacy of 88.5 % in intention to treat analysis (200). In a different phase 3 clinical trial, Hecolin (Xiamen Innovax Biotech, China) had112, 604 participants, of which 56,302 in the study arm and 56,302 in the placebo arm, received 3 doses of rHEV and hepatitis B vaccine at 0, 1, and 6 months respectively. The vaccine efficacy of 95.5 %was reported in an intention to treat analysis(201). This vaccine is only approved and commercially available in China(202).

An HEV vaccine that is available worldwide would reduce the incidence of the infection in endemic areas and also confer protection to travelers. (203). Areas and countries with high prevalence should also focus on improved sanitation, access to clean water with a specific focus on high-risk groups, especially pregnant women and patients with chronic medical conditions (166, 204).

CONCLUSION

Overall, with the recent advancements in the arena of molecular virology, the landscape for the management of viral hepatitis has evolved dramatically. We have a better

understanding of the molecular structure of these pathogens and their interplay with our immune system, which has paved the way for novel drugs and therapeutics. While the success of the decade is focused on DAA as the cure for HCV, the burden of chronic HBV and HDV infections continue to persist as research is ongoing for both a cure for HBV and treatment options for HDV. Drugs that hold promise regarding complete eradication of HBV cccDNA from hepatocytes are under investigation and may be pivotal in complete eradication of the infection in the future. Despite the advancement in the field of serologic and PCR testing for HBV, HCV, and HDV, there is a continued need for improvements in screening protocols for these infections. Standardized testing along with options for treatment and vaccination remain areas of interest for HEV. Work continues on implementation of universal vaccination for HAV and HBV, while clinical trials are ongoing for HEV vaccination. There remains a pressing need for increased collaborative efforts to help combat these illnesses, as we continue to learn about the viral hepatitis to fill the gaps in our knowledge.

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