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# CLINICAL SIGNIFICANCE OF HEPATITIS AND IT' S TYPES -A REVIEW

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**Abstract**

*Hepatitis is a liver inflammation caused by a pathogenic virus. Viral infections of the liver have had a profound influence on humanity, causing severe morbidity and mortality in people with acute and chronic infections. The prognosis for hepatocellular carcinoma (HCC), a highly aggressive condition, is incredibly bad. It is a serious malignancy that kills about a million people worldwide each year. The discovery of viral agents increased scientific interest in determining the pathogenesis and diagnostic methods for identifying the infected population, which was previously unknown. With fast scientific and technological breakthroughs in recent decades, managing and even curing diseases became possible, with a strong emphasis on preventive care through vaccination. As a result, primary care physicians and gastroenterologists must have a thorough understanding of hepatitis A, B, C, D, and E before providing care to these patients. The review article addresses epidemiology, etiology, clinical presentation, diagnostic techniques, and current medication treatments, with an emphasis on future therapy options and the importance of liver transplants.*

*Each hepatitis virus, Hepatitis A, B, C, D, E, and G, presents a unique scenario to the patient and practitioner alike. Since the discovery of each virus, a wealth of information on epidemiology, virologic properties, and the natural clinical and immunologic history of acute and chronic infections has emerged. Basic insights concerning host immune responses to acute and chronic viral infections, along with virologic data, have resulted in vaccines to prevent Hepatitis A, B, and E, as well as extremely effective antivirals for Hepatitis B and C. These therapeutic breakthroughs are changing the landscape of hepatology, transplant medicine in general, and public and global health. Most importantly, there is a concerted global effort to eradicate chronic viral hepatitis within the decade.*

**Keywords:** *Hepatitis, Organism, Pathogenic, World Wide*

## INTRODUCTION

Hepatitis is a combination of two words: "hepa" denotes liver or something linked to the liver, and "itis" implies inflammation. The liver is a huge organ that is considered one of the vital organs since it is involved in nutrient digestion, blood filtering, and infection defense. Any type of inflammation or damage might impair its function. Chronic alcohol use, pollutants, certain drugs, and medical disorders are all risk factors for hepatitis, which is typically caused by a virus. Hepatitis A, B, and C are some of its most frequent forms and strains (1).

Hepatitis is an inflammation of the liver. The condition can be self-limiting or can progress to fibrosis (scarring), cirrhosis or liver cancer. Hepatitis viruses are the most common cause of hepatitis in the world but other infections, toxic substances (e.g. alcohol, certain drugs), and autoimmune diseases can also cause hepatitis. There are 5 main hepatitis viruses, referred to as types A, B, C, D and E. These 5 types are of greatest concern because of the burden of illness and death they cause and the potential for outbreaks and epidemic spread. In particular, types B and C lead to chronic disease in hundreds of millions of people and,

together, are the most common cause of liver cirrhosis and cancer. (WHO, hepatitis) (2). Scientists have identified 5 unique hepatitis viruses, identified by the letters A, B, C, D, and E. While all cause liver disease, they vary in important ways.

## HEPATITIS A

### *EPIDEMIOLOGY*

Feinstone detected a spherical 27 nanometer particle in feces of hepatitis A patients in 1973 (3). Hepatitis A virus (HAV), a member of the picornavirus family, is an RNA virus that causes 1.4 million cases each year globally (4), with an estimated 7134 deaths in 2016; over half of these cases were recorded in Asia (5). In the United States, the yearly incidence rate was reported to be 2 cases per 100000 individuals in 2006. Recent outbreaks of the disease have seen a 294% increase in infections between 2016-2018 when compared to 2013-2015 (6, 7).

### *CURRENT OUTBREAKS*

In 1988, around 300,000 persons in Shanghai developed symptoms of HAV after consuming raw clams, resulting in one of the greatest outbreaks in contemporary history (8, 9). Several outbreaks tied to certain food products impacting over 300 patients from different states in the United States have been recorded in recent years (2013–2019). The outbreaks were linked to the ingestion of fresh blackberries, frozen strawberries, raw scallops, and pomegranate seeds. A 2017 study done in four states (California, Kentucky, Michigan, and Utah) found indications of a trend toward large-scale community outbreaks involving person-to-person transmission. The majority of these illnesses have been recorded among those who use injectable or non-injection drugs, as well as those who are homeless (10).

On the contrary, 19947 instances of HAV were recorded from 24 European Union nations between January and December 2017, which is four times more than the same period between 2012 and 2015. In 2016, 4475 outbreak-related cases were reported from 22 European Union nations, with the majority of outbreaks involving males having sex with men (11).

### *PATHOGGENESIS*

HAV is transmitted through the fecal-oral pathway, which includes the ingestion of contaminated food or water as well as person to person contact. Polymerase chain reaction testing is performed on blood donors since transmission by blood transfusion occurs on rare occasions (12). After passing through the mucosa of the small intestine wall, HAV enters the liver via the portal vein. The virus particles then reproduce and are released into the biliary canaliculi, returning to the small intestine via the bile ducts and being expelled in the stool. The HAV enterohepatic cycle continues until the body produces a suitable immune response in the form of antibodies. Human leukocyte antigen-restricted, HAV-specific CD8+ T lymphocytes and natural killer cells have been linked to the damage and death of infected hepatocytes (13-15).

### *SIGNS AND SYMPTOMS*

The typical HAV incubation period is roughly 2-4 weeks. Fever, malaise, and jaundice have been identified as the most common symptoms of HAV infection (16). Other typical symptoms include weakness, exhaustion, nausea, vomiting, abdominal discomfort, arthralgias, myalgias, diarrhea, and anorexia (12). Patients seldom experience a protracted cholestatic period during recovery, and recurrent infections have also been reported (17).

Within six months of the original infection, approximately 10%-15% of patients experience a recurrent course (18). Symptoms during a relapse are usually less severe than those during an initial illness. Notably, type 1 autoimmune hepatitis has been reported in genetically susceptible people in exceedingly rare cases (19). The spectrum of infections can range from asymptomatic patients without jaundice to symptomatic patients with jaundice, cholestasis with extended jaundice, recurring infections, or acute liver

failure (17). Creatinine > 2 mg/dL (the greatest predictor), total bilirubin > 9.6 mg/dL, and albumin < 2.5 g/L have all been linked to greater mortality in individuals with acute liver failure (20).

### *DIAGNOSIS*

Anti-HAV antibodies can be found in serum. The detection of IgM anti-HAV confirms the diagnosis. Antibodies can be found at the outset of symptoms. Serum IgM levels peak during the acute infection and stay high for up to four months on average after symptom onset (21). Immunity is typically assessed using HAV total antibody to identify whether HAV was acquired naturally or by vaccination (22). The presence of IgM antibodies in the absence of clinical symptoms indicates a previous HAV infection with persistent antibodies, an asymptomatic illness, or a false positive test (23).

## HEPATITIS B

Hepatitis B is a viral infection, which can destroy the liver. "Hepatitis" is the term applied to describe the inflammation that it produces in the liver's tissues. It at first seems to be an acute infection that rapidly clears up itself. However, it turns into an illness permanent and never totally goes away in a small percentage of patients (24).

HBV infection is considered to be one of the main public health issues that causes extreme morbidity and mortality in industrialized countries. According to reports, someone dies from HBV infection every 30 to 45 seconds around the world (25). Hepatitis B is common in Pakistan, and thus increases the chance of healthy blood donors being virus carriers without showing symptoms of the disease. According to the WHO screening donors is advisable since most cases neither may nor present any apparent symptoms. The more accurately we know the rate at which hepatitis B virus infects healthy donors, we can estimate the population diseases, increases the rates at which people are treated for the disease, and mitigate the potential problems (26).

### *EPIDEMIOLOGY*

In 2017, HBV caused an estimated 29% of cirrhosis-related fatalities worldwide (27), as well as the bulk of liver cancer deaths. There are ten HBV genotypes (A-J) with 35 sub- genotypes, and their distribution varies globally (28). The diversity in genotype distribution and risk factors is based on common variables in high-risk populations, such as vertical transmission, which has been linked to an increased risk of chronic illness and hepatocellular carcinoma (29). Risk factors for HBV transmission include a history of blood transfusion, intravenous drug or paraphernalia use, contaminated piercing instruments, sexual intercourse with an infected person and organ transplantation from HBV positive donors (30-32).

### *PATHOGENESIS*

The HBV is a double-stranded DNA virus from the Hepadnaviridae family. It was discovered in 1963, dubbed the Australian Antigen after reacting to antibodies from a hemophiliac patient. The virus possesses a specialized trophism for hepatocytes, on which it attaches and integrates during the initial infection (33). Following viral uncoating, the DNA integrates into the host nucleus as a covalently closed circular DNA (cccDNA), which can remain in hepatocytes indefinitely, explaining the possibility of HBV reactivation in chronic inactive disease. Finally, using reverse transcriptase, new viral molecules are synthesized from cccDNA and discharged by exocytosis (33, 34).

### *SIGNS AND SYMPTOMS*

Patients may experience exhaustion, nausea, vomiting, and right upper quadrant pain prior to or during jaundice onset. Notably, less than 1% of cases may result in fulminant hepatitis. During the acute phase, there is a fast increase in HBV viral load in the 10000-100000 ng/mL range, as well as elevations in ALT and AST in the 1000-2000 IU/L range and total bilirubin (35). Chronic HBV can develop in patients who were exposed at an early age (36), have a genetic susceptibility, or did not exhibit symptoms when acute

HBV infection occurred. These people are typically asymptomatic for years, unless there is an HBV exacerbation (37-39).

The prevalence of HBV exacerbations is best described by four stages of disease activity (40). The initial phase known as immune tolerant is characterized by dramatically high HBV titers and positive HBeAg levels with no ALT elevation or liver inflammation, and individuals are asymptomatic. The second phase (immune clearance) is characterized by activation of the immune system, leading to rise of ALT at least five times the upper limit, HBV DNA decrease, and histological evidence of inflammation, perhaps leading to fatigue, jaundice, and right upper quadrant pain.

The third phase (immune control) displays negative HBeAg, indicating seroconversion to positive HBeAb (hepatitis B e antibody) and undetectable to low HBV DNA titers. The fourth phase (immune active) is distinguished by elevated ALT and HBV DNA levels as a result of triggers such as hepatitis D virus (HDV) superinfection or immunosuppression, resulting in symptoms similar to those seen in the immunological clearance phase, as well as the danger of acute liver failure. Importantly, the disease can shift between the third and fourth stages (20).

### *DIAGNOSIS*

Patients with acute HBV have the same serologies as previously stated. However, some patients will be in the "window period," in which the immune system has eliminated the HBsAg but no HBV surface antibody (HBsAb) exists; in this case, the sole positive indication is an elevated IgM HBcAb. Finally, once the infection has been cleared, the patient will have both positive IgG HBcAb and HBsAb levels. However, if the patient develops chronic HBV infection, no HBsAb will be discovered and HBsAg will persist, even if IgG HBcAb exists. Additionally, the HBeAg status, HBV DNA, and aminotransferase levels aid in defining the illness phase and tailoring therapy options. Finally, the population that has been immunized but has never been exposed to HBV will only show positive HBsAb (41).

### *CURRENT TREATMENT POSSIBILITIES*

Based on consensus from different societies, treatment with viral suppression medication is advised if patients have extrahepatic symptoms, pregnancy, family history of HCC, hepatitis C virus (HCV)/HDV co-infection, immunosuppressive prophylaxis, compensated/decompensated liver cirrhosis (42).

Current HBV treatments include nucleoside/nucleotide analogs and PEG-interferon. Overall, the PEG-interferon regimen results in more HBsAg seroconversion than other medicines, although its efficacy is limited due to poor patient tolerance (43). Lamivudine, adefovir, telvidudine, entecavir, tenofovir fumarate, and tenofovir alafenamide are some of the nucleoside/nucleotide analogs that are available Due to the high genetic resistance barrier, the first line regimen for treatment consists of entecavir, tenofovir fumarate, or tenofovir alafenamide monotherapy, with the other medications considered as options based on medication availability and limited access to first line agents (44).

## HEPATITIS C

Hepatitis C is a tiny, encapsulated, positive single-stranded RNA virus that was discovered in 1989 as a member of the Flaviridae family. It is the only member of the Hepacivirus genus. It's highly ordered genome is around 9.6 kb in size (45).

### *EPIDEMIOLOGY*

More than 170 million people worldwide are hepatitis C virus infected, giving rise to a massive global health crisis. In Pakistan, approximately 16 million people carry HCV (46). There are seven major genotypes and 67 subgroups. HCV genotype 1 accounts for almost half of all HCV infections, making it the most common genotype in the world. The second most frequent is HCV genotype 3, which accounts for roughly one-third of all HCV infections and is more prevalent in South Asia, Australia, and numerous European nations. Genotype 2 is found in Asia and West Africa, but genotype 4 is prevalent in central and eastern sub-Saharan Africa, North Africa, and the Middle East. Genotypes 2 and 4 account for roughly 9% to

13% of all HCV cases. Genotypes 5, 6, and 7 are confined to South Africa, South- east Asia, and the Democratic Republic of Congo, respectively (47–49).

## *PATHOGENESIS*

HCV, It enters the body by percutaneous needlestick injuries caused by tainted blood (including healthcare or intravenous drug use). It can also enter non-percutaneously by organ transplantation, blood transfusions, sexual intercourse, perinatal transmission, hemodialysis, religious scarification, body piercings, tattoos, and immunoglobulin injection (50). HCV entrance into the bloodstream is facilitated by four host-derived factors: Scavenger receptor class B type I, Occludin, Claudin-I, and CD81 (51). Furthermore, CD81 attaches to the viral particle, possibly via viral envelope protein (E) 2 or other molecules, facilitating its entry into the hepatocyte (52). Although HCV is classified as a non-cytopathic virus, once within the hepatocyte, it replicates and causes cell necrosis by immune-mediated cytolysis (innate and adaptive immunity) and metabolism-mediated inflammation (hepatic steatosis, oxidative stress, and insulin resistance) (51).

Non-structural protein 5A (NS5A) and E2 sections of HCV are also involved in pathogenesis. NS5A deactivates RNA dependent protein kinase (PKR) in hepatocytes, blocking the apoptotic pathway andincreasing anti-inflammatory interleukin production, permitting virus propagation. The E2 protein suppresses PKR, allowing HCV to evade detection. The function of various HCV genotypes in the evolution of liver disease is still debated, however genotype 1b appears to have a more aggressive course, as it has been linked to cirrhosis progression and liver disease decompensation needing transplantation (53).

HCV core proteins cause insulin resistance via direct receptor action or increased release of tumor necrosis factor-alpha, resulting in additional hepatic steatosis, inflammation, and fibrosis. HCV-associated oxidative stress is primarily induced by the HCV-core protein, which promotes glutathione oxidation and a rise in reactive oxygen species (54). NS5A stimulates the formation of reactive oxygen species in the endoplasmic reticulum membrane. NS3 is also suggested to directly cause oxidative stress (55, 56). Finally, HCV promotes steatosis by impairing lipid release from liver cells, increasing free fatty acid synthesis, and inhibiting fatty acid breakdown (51).

Chronic HCV infection can occur in 50%-85% of individuals, with 15%-45% of patients experiencing spontaneous virus clearance (57). The majority of HCV patients exhibit asymptomatic or vague symptoms. Fatigue, sleep problems, nausea, diarrhea, abdominal discomfort, anorexia, myalgia, arthralgia, weakness, depression, anxiety, and weight loss are some of the possible symptoms (58). Patients with cirrhosis may experience jaundice, ascites, and other cirrhosis-related symptoms. Serum aminotransferase levels in chronic HCV patients are rather steady over time. One in every three patients has a normal ALT; only one-fourth have a serum ALT that is more than twice the upper limit of normal; the remaining patients have minor enzyme increases, usually less than twice the upper limit of normal. Rarely, ALT increases greater than ten times the upper limit of normal might occur (59).

On the other hand, it is believed that acute HCV accounts for 15%-20% of all instances of acute hepatitis (60). More than two-thirds of acute HCV infections are typically asymptomatic. Symptomatic patients appear with jaundice, nausea, black urine, and pain in the right upper quadrant, like with other acute hepatitis cases. These symptoms appear 2–26 weeks after exposure and continue 2–12 weeks. Acute liver failure caused by acute HCV infection is highly rare, but patients with chronic HBV (61, 62).

## *DIAGNOSIS*

Third-generation enzyme immunoassays (EIAs) detect antibodies to various HCV antigens, including HCV core, NS3, NS4, and NS5, as early as 8 weeks after exposure, with a sensitivity and specificity of 99% after 2-6 months (63). False negatives can occur in hemodialysis patients and immunocompromised individuals. These are considered indirect tests.

Quantitative HCV RNA tests are a type of direct immunoassay that may identify HCV viremia inpatients with at least 10-15 IU/mL (64). The HCV core antigen immunoassay is an alternative to HCV RNA testing, but it cannot be used to assess response to antiviral therapy due to sensitivity limitations (65). In patients with a low pre-test risk of HCV infection, a negative anti-HCV antibody EIA efficiently rules out

HCV infection. However, in individuals suspected of having acute HCV infection, the HCV RNA virus load must also be determined via polymerase chain reaction (PCR), as antibodies may not appear positive for 2-6 months on average. A positive HCV antibody and HCV RNA confirm HCV infection but do not distinguish between acute and chronic infection. Acute infection can be verified if a patient tested negative in the 6 months preceding infection and did not test positive for both RNA and antibody, or if both RNA and antibody became negative within 6 months. Chronic HCV infection is defined as positive HCV RNA for at least six months.

## HEPATITIS D

### *EPIDEMIOLOGY*

A recent big meta-analysis by Chen *et al* 2006 containing 182 publications from 61 countries suggested that 62-72 million people worldwide are infected with HDV. Approximately 10.58% of HBsAg carriers were infected with HDV, which is twice as high as previous estimates (66). Western and middle Africa, the Amazon Basin, eastern and Mediterranean Europe, the Middle East, and parts of Asia are the areas with the highest HDV infection prevalence. Notably, a recent epidemiological research of a cohort of HBV-positive intravenous drug users found an alarming increase in HDV seroprevalence, from 29% in 1988-1989 to 50% in 2005-2006 (67). Nonetheless, several of these studies lack HDV RNA validation, making it difficult to estimate HDV prevalence accurately.

### *PATHOGENESIS*

HDV is a single-stranded RNA virus that is deemed dysfunctional since it requires HBV to express and replicate properly. Rizzetto *et al* (68) of Italy discovered a unique antigen-antibody system linked with but immunologically separate from HBV using direct immunofluorescence in 1977. Although there are eight possible HDV genotypes, HDV-1 accounts for the majority of cases in North America, Europe, and the Middle East (69).Like HBV, HDV is spread parenterally through exposure to infected blood or bodily fluids, with a very tiny inoculum required to transmit infection (70).

The clinical spectrum of HDV infection varies from inactive, asymptomatic carriers to severe liver failure (71). Concomitant HBV and HDV infection often results in moderate self-limited illness or, less likely, severe acute hepatitis, with both infections resolving spontaneously (72). In contrast, HDV superinfection in chronic HBV carriers typically leads to a protracted clinical course. Intravenous drug users, and elderly patients in European cohorts. This could be related, to the varied direct cytotoxic effect and immunogenic response of HDV on host hepatocytes (73, 74).

### *CURRENTLY AVAILABLE TREATMENTS*

Current data supports treating chronic HDV infection in patients with detectable viral RNA and biochemical or histological active liver disease, especially if there is substantial fibrosis (44). In contrast, asymptomatic people with normal liver enzymes do not require treatment.

## HEPATITIS E

### *EPIDEMIOLOGY*

The WHO reported an estimated 20 million new hepatitis E virus (HEV) infections per year worldwide, resulting in 3.3 million symptomatic cases of acute hepatitis and over 44000 fatalities in 2015. Although the utility of contemporary antibody assays in seroprevalence studies is controversial, the total seroprevalence of HEV in the United States between 1988 and 1994 was estimated to be 21% (75). Other more recent analyses found a lower but rising overall seroprevalence among US-born persons, from 4.5% in 2013-2014 to 8.1% in 2015-2016, with increasing age, female sex, and Asian ethnicity all being significant predictors of HEV seropositivity (76)

### *PATHOGENESIS*

The HEV is a tiny, single-stranded RNA virus that is thought to be one of the most prevalent yet

underdiagnosed causes of acute viral hepatitis, with the first outbreak occurring in New Delhi in 1955. While it is the only member of the genus Hepevirus in the family Hepeviridaea, a plethora of genotypes have been identified to date, with four of particular clinical significance; genotypes 1 and 2 are limited to humans, whereas genotypes 3 and 4 can infect humans and animals primarily through the fecal-oral route (77, 78).

### *CLINICAL FEATURES*

Most HEV-infected patients are asymptomatic or have a mild, self-limiting HAV-like disease. Typically followed by an incubation period ranging from 2 to 10 weeks. This is largely true for HEV genotypes 1 and 2. However, the zoonotic genotypes HEV 3 and 4 have been progressively identified as causes of chronic hepatitis, virtually exclusively in immunocompromised individuals (79, 80). Less than 5% of acutely infected HEV patients develop acute liver failure, and these individuals are more likely to be pregnant, malnourished, or have a previous liver condition (81, 82).

The standardized antibody assays not being available severely limit a uniform diagnostic approach to HEV infection. Patients who present with a consistent clinical pattern should be tested for anti-HEV IgM antibody assay with a confirmatory HEV RNA viral load if positive.

## CONCLUSION

The recognition of epidemiologic and clinical manifestations of hepatitis A, B, C, D and E is quite helpful in leading through the diagnosis of this. Fortunately, significant medical progresses accomplished over centuries are helpful for efficiently diagnosing such conditions as hepatitis and a highly comprehensive setup establishing its multiorganistic implication in such groups. With the introduction of new therapies, control of the disease is now possible, and cure and eradication of chronic hepatitis B, C, and D are now within the reach.

### Conflict of Interest:

Authors have no conflict of interest.

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