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Hepatitis: A Comprehensive Overview of Types, Causes, and Treatment Strategies

Avijit Biswal[1] and Maheswata Moharana[2]*

[1]Department of Chemistry, Bhadrak Auto. College, Bhadrak, Odisha, India
[2]School of Basic Sciences and Humanities, Odisha University of Technology and Research, Bhubaneswar, Odisha, India

Abstract

Hepatitis is described as liver inflammation; viral infection is frequently the source of severe inflammation. The disease can recover on its own or develop into cirrhosis, fibrosis or cancer. The leading cause of hepatitis worldwide is hepatitis virus, non-viral hepatitis such as autoimmune disorders, other infections, and toxic chemicals (alcohols, and drugs) can also cause hepatitis. The 5-different types (A, B, C, D, E) of hepatitis virus are of greatest concern because of the burden of diseases and mortality, as well as the possibility of outbreaks and the spread of epidemics. Specifically, types B and C are the most common causes of liver cirrhosis and cancer, and they cause chronic disease in hundreds of millions of people. Ingestion of contaminated food or water is usually the cause of hepatitis A and E whereas, types B, C, and D usually spread through parental contact with bodily fluids that are contaminated. Each type can affect people of any age, along with newborn babies. WHO acknowledges that viral hepatitis is a significant public health concern and a significant opportunity to enhance equity and quality of life on a worldwide scale. Globally, viral hepatitis affects millions of people's quality of life results in around 1.5 million deaths annually. With an emphasis on clinical care, this chapter attempts to provide an overview of different diagnostic treatment strategies. Future treatment options and potential research in hepatitis virus eradication are also described in detail.

***Keywords*:** Hepatitis, liver inflammation, treatment strategies, virus outbreak, autoimmune disorders

**Corresponding author*: moharana.sweta@gmail.com

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1.1 Introduction

The liver is an essential organ that plays an important role in many body processes, such as immunity, digestion, metabolism, and nutrition storage [1]. It is situated in the upper right region of the abdomen and is separated into the left and right hepatic lobules [2]. When the liver is damaged, it can negatively impact the body's regular processes. Hepatitis is commonly known as a liver inflammation [3]. The severity of hepatitis varies from acute self-limiting to severe chronic cases involving cirrhosis, fibrosis (scarring), hepatocellular carcinoma, or liver failure [4]. Being one of the most prevalent and fatal cancers in the world, hepatocellular carcinoma (HCC) is a global public health concern [5]. HCC is responsible for half a million fatalities annually and is represented by 85% to 90% of primary liver cancers, which account for 3.5% and 7.5% of all cancers in women and men, respectively [6]. It is the third leading cause of cancer-related deaths globally and the fifth most prevalent type of cancer [7]. Significant risk factors for HCC include diabetes and an elevated body mass index, which can lead to the development of non-alcoholic steatohepatitis [8]. This is especially concerning given the rising prevalence of childhood and adult obesity throughout the previous 25 years. Other non-viral causes of HCC or hepatitis include exposure to pesticides, alcohol, tobacco, oral contraceptives, aflatoxin, iron overload syndromes [9], and the common practice of chewing betel quid in developing countries [10]. Hepatocellular carcinoma is also caused by Wilson disease [11], alpha-1 antitrypsin deficiency [12], porphyrias [13], autoimmune hepatitis [14], *Schistosoma jabonium* and thorotrast-ray. The likelihood of an HCC incidence is increased by primary biliary cirrhosis, congestive liver disease, and a family history of liver cancer [15]. Viral hepatitis is the most prevalent cause of hepatitis, it can also be brought on by other infections, autoimmune diseases, and the use of toxic chemicals like alcohol and other pharmaceuticals [16]. Viral hepatitis is acknowledged by the World Health Organization (WHO) as both a serious public health concern and a significant chance to raise equity and quality of life on a worldwide scale. Globally, viral hepatitis affects hundreds of millions of people's qualities of life and results in around 1.5 million deaths annually [17]. Different factors causing viral and non-viral hepatocellular carcinoma are depicted in Figure 1.1. People with low immunity or weak health and living in low-income areas pay the highest costs. There are five main viruses; hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV) can all cause viral hepatitis [18]. Different modes of transmission are recognized by these viruses, which are physiologically unrelated

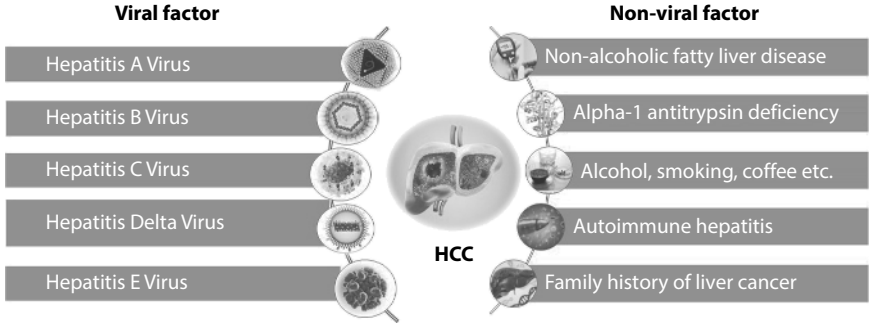

Figure 1.1 Viral and non-viral factors causing hepatocellular carcinoma.

and have distinct infection histories. These viruses, however, are likely to proliferate *via* linked social networks whose populations have similar risk profiles. There is therefore broad agreement that the best way to prevent viral hepatitis is to implement comprehensive policies that are adapted to local circumstances and treat viral hepatitis as a distinct public health concern. Hepatitis with nonviral causes is also becoming recognized as a major cause of liver disease's public health impact.

1.2 Types of Hepatitis

1.2.1 Viral Hepatitis (Types, Causes, Diagnosis)

Hepatitis A

Due to the fact that viral hepatitis can evolve into a chronic condition that ultimately results in end-stage liver disease and/or the development of hepatocellular carcinoma (HCC), it poses a serious threat to public health [19] and therefore is one of the most common reasons for liver transplantation [20]. Among the 5-different types of viral causes of hepatitis, the hepatitis A virus (HAV), a ribonucleic acid (RNA) picornavirus, is the cause of hepatitis A [21]. Hepatitis A virus (HAV) is a single-stranded, positive-sense RNA virus [22]. It can be found in two forms: the quasi-enveloped form that is detected in an infected person's blood and the naked form that is excreted in their feces [23]. HAV is categorized into six genotypes based on a distinct serotype. Genotypes I–III infect humans, whereas non-human primates have been found to have genotypes IV–VI [24]. Acute viral hepatitis is mostly caused by the virus, which is spread by the fecal–oral pathway. There is no development to chronic hepatitis,

and clinical symptoms range from an asymptomatic infection to acute liver failure, which happens in less than 1% of patients. An estimated 1.4 million hepatitis A cases occur annually worldwide, and 27731 fatalities were reported in 2010 [25]. This illness can spread either sporadically or as an epidemic, and the major ways it can spread are through contaminated food or water or person-to-person contact. World Health Organization (WHO) reported that the percentage of patients with anti-HAV immunoglobulin antibodies is the basis for determining the endemicity levels of the hepatitis A virus (HAV) [26]. This acute illness is characterized by the distinct emergence of any sign or symptom, such as jaundice or elevated serum alanine aminotransferase, in addition to other symptoms including fever, anorexia, and gastrointestinal disorders [27]. Out of the 200 members of *Picornaviridae* family, HAV is a significant class of virus frequently found in developing countries [28]. The human immune system's resistance to the HAV causes hepatic damage. Human leukocyte antigen-restricted HAV-specific CD8+ T lymphocytes and natural killer cells destroy infected cells, causing hepatocellular damage [29]. *Picorna* viruses enter the cytoplasm of their host cells with genomes that are positively polarized [30]. The viral replication takes place in the cytoplasm of hepatocytes [31]. Severe hepatitis is linked to an exaggerated host response and a significant decrease in the amount of HAV RNA in circulation after an acute infection. Since symptoms appear in over 70% of infected individuals, the onset of symptomatic hepatitis is typically correlated with patient age. Within two to three months, 85% of patients show full clinical and biochemical recovery, and almost all patients show full recovery by six months [32].

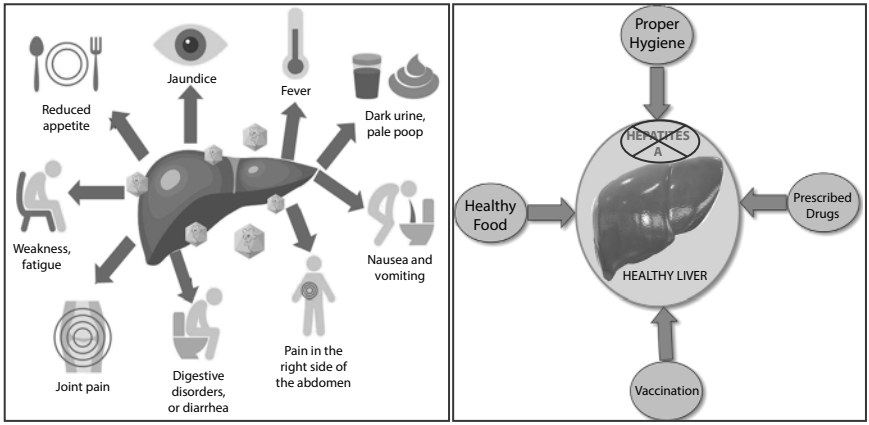

Figure 1.2 Several symptoms and preventive options for hepatitis A virus infection.

The identification of serum immunoglobulin M antibody to HAV, which is recognized for nearly three to six months, establishes the diagnosis. Serum immunoglobulin G antibodies are linked to lifetime protective immunity, show early in the convalescent stage of the illness, and can be detected for decades [33]. Since there are not any particular drugs to treat HAV infection, supportive care is the basis of treatment. Immunoglobulin, vaccination, and attention to hygienic practices – handwashing, avoiding tap water and raw foods in unhygienic places, and properly heating foods-are all part of the prevention of HAV infection [34]. Several symptoms associated with HAV infections and preventive measures are shown in Figure 1.2.

Hepatitis B

Hepatitis B virus (HBV) replicates inside hepatocytes and interacts with multiple cellular proteins [35]. The virus is formed from deoxyribonucleic acid (DNA) and can induce liver diseases and raise the risk of HCC in persons who are infected. It belongs to the *Hepadnaviridae* family, which has ten genotypes (A–J) [36]. After infecting hepatocytes, HBV uses an RNA mediator to start its replication cycle (*via* reverse transcription) and can merge with the host genome to remain in the hepatocyte nucleus [37]. A partially double-stranded and relaxed circular DNA genome (rcDNA) is contained in the nucleocapsid, which is a key component of the viral envelope. The rcDNA is released and transformed into a covalently closed circular DNA (cccDNA) by host factors when the nucleocapsid is carried to the nucleus in the cytoplasm of infected hepatocytes, creating a stable minichromosome [38]. HBV is considered as a silent global public health concern. In particular, chronic HBV infection throughout aging is starting to get attention as a public health concern [39]. Additionally, compared to the general population, inmates are more likely to die avoidably from HBV and other infectious diseases. Additionally, the high rate of HIV infections makes it more difficult to treat infections, increases the replication of HBV, and predisposes individuals to chronicity [40]. Despite immunizations and antiviral therapies, chronic hepatitis B (CHB) viral infections continue to pose a serious threat to global health [41]. Inactive carriers compose more than two-thirds of people with chronic hepatitis B. Due to inadequate innate immunity and HBV-specific immune response activation; they have a low viral replication rate and very little liver necroinflammation [42]. According to natural history of chronic HBV, it is divided into five different phases including varying serological profiles, levels of viral replication, liver inflammation, and liver damage [43]. The first phase is known as the condition of immunological tolerance and is characterized by an asymptomatic illness. It can be identified by low liver damage, high levels of HBV

DNA, Alanine Transaminase (ALT) that remains within the normal range, and HBsAg and HBeAg are positive [44]. Increased ALT and HBV DNA, along with serum HBsAg and HBeAg are the characteristics of the second phase, known as HBeAg-positive chronic hepatitis. Variable phases of fibrosis and moderate to severe liver necroinflammation are detected [45]. HBsAg positive, undetectable or low (< 2,000 IU/mL) HBV DNA, serum antibodies to HBeAg, and a normal ALT level are the features of the third phase, which is known as an HBeAg-negative chronic infection. People have a limited chance of developing cirrhosis and hepatocarcinoma (HCC), but they can develop chronic hepatitis B, which typically happens in people who are HbeAg-negative [46]. The absence of serum HBeAg, detectable anti-HBe, HBsAg positive, persistent or fluctuating moderate to high levels of serum HBV DNA, and fluctuating or chronically elevated ALT measurements are the characteristics of the fourth phase, known as HBeAg-negative chronic hepatitis [47]. The possibility of spontaneous disease remission is low at this phase. Undetectable serum HBsAg and positive antibodies to HBcAg (anti-HBc), with or without detectable antibodies to HBsAg (anti-HBs), are characteristics of the fifth phase, HBsAg-negative infection. Patients typically, though not always, have undetectable serum HBV DNA throughout this phase, and their ALT levels are normal. Over time, there have been major changes in the epidemiology of HBV. For instance. in Africa, the prevalence of HBsAg in children aged 5 ranges from 2.0% to 4.7%, indicating that the incidence rate is still relatively high [48]. Those with chronic hepatitis B, or all HBsAg-positive individuals, are the only people who can be carriers of HBV [49]. Since the risk of having CHB decreases with age, infections during pregnancy and childhood are the primary means of preserving endemicity [50]. In past, the rate of HBsAg seroprevalence in the general population was used to determine the epidemic profiles of various geographic locations. Four epidemic profiles can be established in this manner. Areas classified as highly endemic have an HBsAg prevalence of ≥8%, high intermediate by 5%-7%, low intermediate by 2%-4%, and low endemic by <2% [51]. In many parts of the world, perinatal transmission is the primary means of HBV transmission, and in some areas, like China and South-East Asia, it plays a significant role in preserving the infection reservoir [52]. The main sources of HBV diversity prior to the vaccination period were sexual contact and recreational drug use [53]. Many cases among unvaccinated individuals in settings with intermediate incidence and residual incidence in regions with low endemicity still respond to transmission through sex and drugs. Due to comparable viral transmission mechanisms, HBV is a prevalent infection among individuals with HIV. Those who are coinfected with

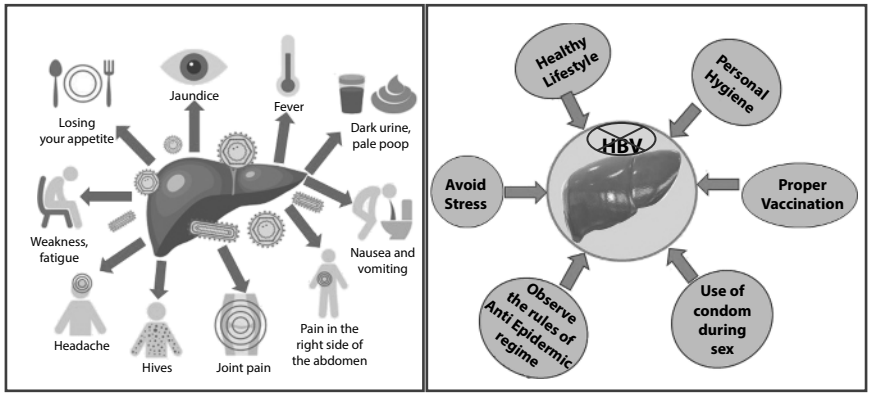

Figure 1.3 Several symptoms and preventive options for hepatitis B virus infection.

both HIV and HBV have higher risks of hepatocellular carcinoma (HCC), liver-related mortality, and all-cause mortality, as well as faster liver disease development than those who are just infected with HBV [54]. Therefore, it is essential that those living with HIV should get the proper therapy and time-to-time HBV screening. In addition, there is a significant chance that cancer patients with HBV infections would have viral reactivation after receiving treatment [55]. However, because the treatments are successful and have high tolerance levels, there have been instances of positive clinical outcomes after transplants from HBV-infected donors. To sum up, antiviral medications help reduce the burden of advanced liver disease caused by HBV, although short-term eradication is still not possible [56]. There are certain symptoms of hepatitis B virus infections including weakness, fatigue, loss of appetite, jaundice, dark urine, joint pain, hives etc. and some basic precautionary measures are depicted in Figure 1.3.

Hepatitis C

Hepatitis C virus, first discovered in 1989. Three scientists-Harvey Alter, Michael Houghton, and Charles Rice, received the 2020 Nobel Prize in Physiology or Medicine in recognition of their work identifying hepatitis C virus (HCV) [57]. Millions of lives were saved by the incredible accomplishment of discovering HCV. It made it possible to create extremely sensitive diagnostic blood tests and to quickly increase the number of antiviral medications that target hepatitis C. Nearly half of the 71 million people who have HCV worldwide are currently unaware of it because of inadequate screening programs [58]. It is an enveloped, single-stranded, positive-sense RNA virus [59]. Its sole

natural host is humans. This virus belongs to the *Hepacivirus* genus and *Flaviviridae* family [60] and encodes a single-standard positive-sense RNA genome which is composed of a single large polypeptide with 3000 amino acid residues [61]. This polypeptide is further proteolytically processed to yield individual viral proteins which are all important for optimal infection by the virus [62]. Hepatotropic and lymphotropic viruses are the cause of the silent systemic diseases known as hepatitis C infection, which has a high chronicity rate [63]. Viral activities, both direct and indirect, cause persistent systemic inflammation, which can be seen by elevated levels of pro-inflammatory cytokines and chemokines. Type 2 diabetes mellitus, and cardiovascular risk are increased by chronic systemic inflammation, which is a known risk factor for insulin resistance [64]. Steatosis, fibrosis, and ultimately cirrhosis are examples of hepatic manifestations [65]. The indications for liver transplantation in this condition are made up of the occurrence of hepatocellular carcinoma (HCC) and the consequences of cirrhosis. HCV can proliferate inside B lymphocytes and stimulate these cells over time due to its lymphotropic characteristics [66]. Purpura or necrotizing acrodermatitis, membranoproliferative glomerulonephritis, peripheral neuropathies, polyarthritis, cryoglobulinemia, and other autoimmune diseases may be caused by this stimulation [67]. Infections with hepatitis C are spread by blood [68]. The predicted global HCV infection rate at the beginning of 2020 was 56.8 million, which was lower than in 2015 [69]. According to US epidemiological data, the frequency of hepatitis C in women of reproductive age is rising; 1%-4% of pregnant women are thought to be infected with HCV, which has a 5% chance of transmission from mother to child [70]. Both pregnant and non-pregnant individuals frequently have it as a persistent infection. HCV can be passed from pregnant women to their unborn child *in utero* or during the postpartum period; infection during pregnancy is linked to a higher risk of unfavorable fetal outcomes, such as low birth weights and restricted fetal growth. HCV/HBV coinfections are frequent in endemic areas, and coinfected individuals are more likely to develop cirrhosis, liver fibrosis, HCC, and other liver disorders. Additionally, it is estimated that 2.4 million people have chronic hepatitis C (CHC) [71]. However, compared to populations without serious mental diseases such major depressive disorder, personality disorder, bipolar disorder, or schizophrenia, patients with these conditions are 3-20 times more likely to have an HCV infection. Furthermore, it is commonly known that inmates are disproportionately more likely than the general population to contract HCV. It was reported that the prevalence of HCV is typically below 2% in high-income nations, although it may exceed 5% in a number of low- to middle-income countries, despite the lack of precise

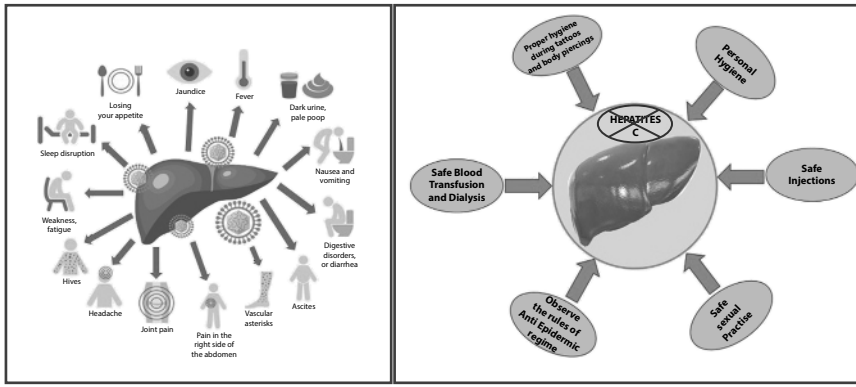

Figure 1.4 Symptoms associated with hepatitis C virus infection and precautionary practices.

statistics on the actual extent of the epidemic [72]. The present estimates of viremic patients in a number of regions, such as India and Central Sub-Saharan Africa, are also subject to a substantial level of uncertainty [73]. The incidence of new infections has, however, altered throughout time in response to varying exposure to important risk factors, such as injectable drug use, blood transfusions, and iatrogenic infections, as suggested by three primary epidemic profiles that may be described by modeling prevalence based on age. Several symptoms are persistently occurring in hepatitis C-infected individuals and there are some practices (Figure 1.4) like personal hygiene, safe injection, safe blood transfusion and dialysis, safe sexual practice, etc. may be helpful for inhibiting HCV infection to some extent.

Hepatitis D

The hepatitis D virus (HDV), which was initially identified in 1977, is a single-stranded circular RNA virus [74]. Since this virus is defective, HDV cannot produce an envelope or capsid; instead, HBV envelopes must be used. Thus, a productive HDV infection in humans requires an HBV infection [75]. Hepatitis D or delta virus is the smallest virus causing disease in humans and represents mortality in worldwide [76]. With the fastest development of cirrhosis, hepatic failure, and HCC, it is the most severe kind of chronic hepatitis. Hepatitis B must first be established for HDV infections to occur in people, and HBsAg and host cellular machinery are necessary for infection replication and spread [77]. Both pregnant and non-pregnant individuals typically get hepatitis D as a chronic infection. HDV speeds up hepatic decompensation, raises the risk of HCC, and

accelerates liver fibrosis in comparison to chronic HBV mono-infections [78]. Therefore, compared to HBV alone, coinfection with both HDV and HBV frequently leads in a more severe illness, with higher chances of cirrhosis, liver failure, and HCC [79]. Worldwide, an estimated 15–20 million persons are afflicted [80]. The diagnosis of HDV infection requires the presence of HBsAg since HDV is dependent on HBV. The presence of serum delta antigen and serum HDV RNA is both beneficial for diagnosis [81]. Acute and chronic HDV infections are both possible. Acute HDV infection can happen as a result of superinfection (HDV infection in an HBsAg-positive person) or HBV coinfection (simultaneous infection with both viruses after the same exposure) [82]. Patients with known risk factors, such as a history of intravenous drug use, high-risk sexual activity, first-degree relative infection, and immigration from HDV-endemic areas, must have a strong suspicion of HDV infection [83].

Hepatitis E

Hepatitis E is caused by a single-stranded, positive-sense RNA virus called HEV. This virus belongs to the family *Hepeviridae*, genus *Orthohepevirus*, which has four main genotypes thought to be closely linked to humans [84]. HEV genotypes 1 and 2 only infect humans, causing acute, self-limiting hepatitis by fecal-oral transmission [85]. Immunocompromised populations are the main target of genotypes 3 and 4, which are found in a wide range of animal species worldwide and can be zoonotically transferred to humans through fecal matter, direct contact, or consumption of tainted meat products. It was reported, in developed countries, HEV may be categorized as a re-emerging virus, and public health would benefit from monitoring incident case numbers, or the quantity of new acute infections [86]. HEV usually affects younger people and goes away on its own, but it can also cause serious sickness, especially in adults and pregnant women, or it can become a chronic infection in patients with impaired immune systems, especially those who have received solid organ transplants. HEV Epidemics are exclusively caused by genotype 1 (but not by any other genotype of Orthohepevirus A) which show a negative correlation with human pregnancy [87]. WHO estimates the annual number of HEV infections at about 20 million, whereas its epidemiology is yet unknown [88]. The disease is linked to reduced morbidity and death as well as a higher prevalence. However, infections in pregnant women can be serious; in endemic places, they are connected with a 30% death rate during the third trimester. HEV is mostly spread through blood transfusions, contact with infected animals and/or raw meat products from these animals, and the fecal-oral pathway (consuming contaminated food or drink) [89]. People that have

close contact with certain animals, such as pigs, wild boars, sheep, goats, rabbits, camels, and rodents, are at a higher risk of receiving HEV since they are natural HEV reservoirs. HEV is now recognized to be endemic even in some industrialized areas, including several parts of Europe, and is thought to have a zoonotic origin. Previously, it was thought to be an acute type of hepatitis responsible for waterborne epidemics in places with inadequate sanitation. From the beginning, it was thought that HEV only caused acute hepatitis. HEV infections are the most frequent cause of acute viral hepatitis worldwide, but they can also result in chronic hepatitis and even extrahepatic symptoms such neurological and renal disorders [90]. Changes in immune state, hormone levels, and viral variables can also impact the disease's severity. Chronic HEV infections can occur in immunocompromised people, including those who have received solid organ transplants, and they can quickly lead to liver cirrhosis, liver fibrosis, and decompensation. Also, there have been cases of bad outcomes for both mothers and fetuses [91]. Additionally, HEV infections caused by genotype-1 or genotype-2 viruses during pregnancy, particularly in the third trimester, can progress to severe sickness and fulminant liver failure; similarly, reports of bad outcomes for both mothers and fetuses have been made.

A correlation between Guillain-Barré syndrome (GBS) and prior HEV infection was found in 2000, but not much is known about HEV-associated GBS. 5% of GBS patients in the Netherlands had an acute HEV infection prior to their diagnosis; in Bangladesh, where HEV is common, this number is higher at 11% [92]. In many healthcare sectors, diagnosis and prevention remain challenging till date. Currently, anti-HEV Ab, HEV RNA, or viral capsid Ag levels in blood or stool are used to diagnosis HEV infections. In both endemic and non-endemic countries, prevention measures are essential for controlling this illness and lowering the overall prevalence of acute and chronic hepatitis E. The characteristics of different types of hepatitis are shown in Table 1.1.

Table 1.1 Characteristics of different types of viral hepatitis.

Virus type	Family	Nucleic acid structure	Epidemics	Infection route	Diagnosis	Vaccine
Hepatitis A	*Picornaviridae*	Positive sense, single-stranded RNA	Yes	Fecal-oral, sexual, parental	Anti-HAV IgM in blood and stool	Yes
Hepatitis B	*Hepadnaviridae*	Circular, double-stranded DNA	No	Blood, sexual, parental	HBs antigen	Yes
Hepatitis C	*Flaviviridae*	Positive sense, single-stranded RNA	No	Blood, sexual, parental	Anti-HCV IgM, IgG	No
Hepatitis D	*Deltaviridae*	Negative-stranded circular RNA	No	Blood, sexual, parental	Anti-HDV IgM	No
Hepatitis E	*Calciviridae*	Positive sense, single-stranded RNA	Yes	Fecal-oral, parental, zoonotic	Anti-HEV IgM	Two vaccines are in trial

1.2.2 Non-Viral Hepatitis (Types, Cause, Diagnosis)

Hepatitis with non-viral causes is becoming recognized as a major cause of liver disease and highly impact the public health. A number of non-viral variables have been responsible to HCC development. Diabetes and an elevated body mass index, which can lead to the development of non-alcoholic steatohepatitis, are important risk factors for HCC. Aflatoxin, alcohol use, tobacco usage, iron overload syndromes, exposure to pesticides, and the chewing of betel quid, a common practice in developing nations, are additional non-viral causes of HCC [93]. Hepatocellular carcinoma is also caused by Wilson disease, α-1 antitrypsin deficiency, porphyrias, autoimmune hepatitis, *Schistosoma japonicum* linked to positive hepatitis B surface antigen, and thorotrast-ray. Some of the factors discussed in this section are given below.

Autoimmune Hepatitis

Autoimmune hepatitis is an uncommon chronic liver disease that primarily affects women but can affect people of all ages [94]. Its etiology is unknown. Chronic hepatic inflammation and necrosis are its defining features, and they usually lead to cirrhosis. The lack of immunologic tolerance against hepatocytes caused by environmental stimuli in genetically

predisposed individuals, potentially through "molecular mimicry," is thought to be the disease's genesis. Initially known as "lupoid hepatitis," it primarily affected young women. However, it is now considered affecting both males and females all age groups. Autoimmunity can be triggered by a variety of factors and causes. It is caused by the existence of underlying genetic predisposition factors, environmental variables, infection, inflammation, and apoptotic bodies [95].

In the general population, autoimmune diseases affect between 3% and 5% of people. They comprise a wide range of disorders that can impact nearly every organ and occasionally several systems. For example, autoimmune thyroiditis and autoimmune hemolytic anemia may be organ-specific [96], whereas systemic lupus erythematosus and vasculitides may affect the entire body. Patients who already have one autoimmune disease are more likely to develop other autoimmune disorders. As liver-restricted autoimmune diseases, autoimmune liver disorders (AILD) are actually organ-specific and frequently coexist with autoimmune diseases of other organs. Wide age range of the patients, the variety of clinical findings, which vary from asymptomatic illness to fulminant hepatic failure, and the varied serologic markers, are all the factors which adversely affect diagnosing autoimmune hepatitis [97]. Typically, this disease is relatively serious and worsens over time if left untreated. The liver cirrhosis that can result from autoimmune hepatitis is usually chronic, meaning it can persist for years. Ultimately, hepatic failure may occur.

Non-Alcoholic Fatty Liver Disease Causing HCC

When there are no additional factors contributing to the accumulation of hepatic fat, such as excessive alcohol usage, hypothyroidism, medication, etc., "hepatic steatosis" in such situation is referred to as non-alcoholic fatty liver disease. This condition is likely a major contributor to cryptogenic cirrhosis and can either lead directly to cirrhosis or to hepatocellular carcinoma (HCC) [98]. The non-alcoholic fatty liver disease (NAFLD) is categorized into two types; non-alcoholic fatty liver where hepatic steatosis is present without any inflammation, the second category is non-alcoholic steatohepatitis which is associated with hepatic inflammation. The latter case is not distinguishable from alcoholic steatohepatitis [99]. The non-alcoholic steatohepatitis (NASH) can also be termed as pseudo-hepatitis, fatty-liver hepatitis, diabetic hepatitis, steatonecrosis, and alcohol-like hepatitis. More than 5% of the hepatocytes exhibit histological steatosis, or fat accumulation in nonalcoholic fatty liver disease, a kind of curable disease [100].

Worldwide, 6 to 35 percent of people are affected by non-alcoholic fatty liver disease [101]. The prevalence of fibrotic NASH is predicted to rise by

63% from 16.52 million to 27.0 million instances by 2030, while the prevalence of NAFLD is predicted to rise by 21% globally, from 83.1 million in 2015 to 100.9 million. Crucially, the increase in liver-related mortality throughout the same time frame would be around 178% [102]. In India, the epidemiological studies reveal that, the prevalence of NAFLD varies between 9% and 32% of the general population, with a higher prevalence among those who are overweight or obese, have prediabetes, or have type 2 diabetes [103]. Risk factors like insulin resistance (IR), metabolic syndrome (MS), altered gut flora, and chronic inflammation have all been associated to non-alcoholic fatty liver disease (NAFLD). About 3-27 percent of NASH cases with cirrhosis develop into HCC, and 3-15 percent of obese NASH cases proceed to cirrhosis.

The non-invasive criteria for diagnosing HCC were established by the European or American Association of the Study of Liver [104]. This includes either fine needle aspiration cytology or some other criteria such as: arterialization of the liver mass observed on multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) or elevated alpha-fetoprotein greater than 350 ng/ml [105]. Arterial enhancement on two imaging modalities may also be sufficient to make the diagnosis in the absence of elevated alpha-fetoprotein.

Sedentary lifestyles must be avoided in order to stop NAFLD from progressing to NASH and then HCC making an effort to lose weight is beneficial [106]. According to histology and imaging, a 3-7% weight loss has been associated with a decrease in steatosis. Preventing obesity, insulin resistance, and diabetes is essential for lowering the risk of HCC, and it is commonly known that exercise helps burn excess fat. Using anti-diabetic medications, like metformin, to manage diabetes mellitus also stops HCC from developing and spreading [107].

Diet and Lifestyle Leading to HCC

Iron and thiamine intake, among other dietary components, were linked to a substantial exponential increase in the risk of HCC [108]. Those with HCV or HBV were not at increased risk for such dietary compound. Linoleic acid and β-carotene, on the other hand, were associated to a lower incidence of HCC [109]. According to estimates, the average daily intake of nitrate from all sources is 75 milligrams, making it a normal part of the human diet [110]. About 5% of the nitrate consumed by healthy humans is transformed (reduced) to nitrite by bacteria present in saliva. The reduction of nitrate to nitrite in the stomach was done significantly when the pH of the gastric fluid is high (pH>5) which favors the growth of nitrate-reducing bacteria. The nitrates in the stomach can react with the food

proteins o form N-nitroso compounds. The N-nitroso compounds also form when meat containing nitrites or nitrates is cooked at high temperatures. Liver cancer was observed in individuals that had either short-term or long-term exposure to N-nitroso compounds in their diet or drinking water. Moreover, individuals subjected to N-nitroso compounds, however, had internal bleeding, which typically resulted in death [111].

The consumption of alcohol increases the risk of HCC with a primary development of cirrhosis [112]. It was estimated that high alcohol consumption of about >80 g/d ethanol at least 5 years increases the risk of HCC by approximately 5-fold [113]. Numerous studies have reported the link between smoking and the onset of primary liver cancer. It is scientifically conceivable that tobacco use contributes to the development of HCC because numerous of its constituents have the capacity to cause cancer when they are processed in the liver. One of the most addictive drugs is betel quid, which is taken in Asia and by migrant populations in North America, Europe, and Africa [114]. Up to 20% of people worldwide chew betel quid as part of their cultural heritage. Red slaked paste, betel leaves or fruit from *Piper betle*, and the nut of the *Areca catechu* palm (areca nut) make up betel quid. It has been demonstrated that these substances possess genotoxic, mutagenic, and tumorigenic qualities [115].

Drug-Induced HCC

Currently, the most effective TB treatment is a 6-month short-course regimen that includes pyrazinamide (PZA), rifampicin (RMP), and isoniazid (INH) in the intensive phase and RMP and INH in the continuation phase [116]. Almost all patients with TB caused by drug-sensitive organisms can be cured with this regimen, provided they follow it. Unfortunately, though, anti-tuberculosis drugs have a number of side effects, including liver damage brought on by the drugs.

1.2.3 Treatment Strategies of Viral and Non-Viral Hepatitis and Challenges

Since there are currently no particular medications to treat HAV infection, supportive care is the mainstay of treatment. Immunoglobulin, vaccination, and attention to hygienic practices such as handwashing, avoiding tap water and raw foods in contaminated places, and properly heating foods; are all part of the prevention of HAV infection.

Five Nucleos(t)ide Analogues (NA) (telbivudine, entecavir, tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), and two types of Interferon (IFN) (conventional and pegylated) are antiviral

medications used to treat chronic hepatitis B [117]. These medications are not curative and have no demonstrated beneficial effects on the current viral hepatocyte reservoir, despite the fact that they effectively inhibit HBV replication, lower the risk of cirrhosis, and stop the disease from progressing further. According to major hepatology societies the first-line anti-HBV drugs now advised for the treatment of chronic hepatitis B include entecavir, TDF, TAF, and pegylated (Peg) IFN-alpha [118]. In addition to having distinct advantages and disadvantages, NAs and IFNs work in different ways. While IFN may present a greater chance of sustained loss of HBsAg/anti-HBs seroconversion, it also has the advantages of being a treatment with a limited duration, no resistance, and a higher chance of off-treatment sustained virological response when compared to NA [119]. Crucially, appropriate patient selection is necessary for improved clinical efficacy when using Peg-IFN alpha to treat HBV. The likelihood of a better response to treatment is increased by female gender, young age, high transaminase levels, low HBV DNA levels, high liver inflammation rate on biopsy samples (at least METAVIR A2), HBV genotype A or B, and low viral load. Numerous drugs are currently being investigated to help treat HBV infection. Priority must also be given to initiatives aimed at expanding hepatitis B vaccinations.

In past decades, ribavirin and pegylated IFN were the standard of therapy for managing HCV which becomes complicated due to its longer treatment duration as well as considerable side effects [120]. The treatment of HCV infection experienced a dramatic change, especially with the introduction of Direct-Acting Antivirals (DAA), moving away from IFN-based therapies and toward more efficient, palatable alternatives that required shorter treatment periods. DAAs improve patient tolerance to therapy and enable treatment plans to be tailored to each patient's unique characteristics, including HCV genotype, liver fibrosis stage, concomitant diseases, past treatment history, and possible Resistance-Associated-Substitutions [121]. Despite DAAs' clinical success, one drawback is their high cost, which is a crucial factor, particularly in low- and middle-income countries. Boceprevir and telaprevir which are of DAA classes were introduced in 2011 [122], sofosbuvir was approved in 2013 which has high cure rates, reduced side effects, and shorter treatment durations [123]. In 2014, the FDA authorized a combination therapy like ledipasvir/sofosbuvir which simplified the HCV treatment [124]. The pan-genotypic treatment (albasvir/grazoprevir and sofosbuvir/velpatasvir) was introduced in 2016 which effectively treated all HCV genotypes [125].

Peg-IFN alpha is advised by the guidelines to treat chronic HDV infection; however, poor tolerance limits the effectiveness of this treatment. Additionally, people with cirrhosis, active autoimmune diseases, or specific

mental illnesses are often not exposed to it. New treatment approaches that target the HDV life cycle are presently being studied in clinical trials. Drugs like bulevirtide, telafarnibe, and REP3702139 affect HDV cell entry, replication, and viral assembly and release, respectively [126]. Among all, bulevirtide (formerly known as Myrcludex-B) was authorized in 2020 by the European Medicines Agency under the trade name Hepcludex® [127]. For the treatment of an underlying HBV infection, Hepcludex®, which prevents viruses from entering hepatocytes, should be given as monotherapy at a dose of 2 mg once daily by subcutaneous injection or in combination with a nucleoside/nucleotide analogue. This approach of treatment duration is purely unknown. Additionally, Hepcludex® has been evaluated in conjunction with Peg-IFN. There are additional clinical trials under investigation on the combination of Peg-IFN lambda with other drugs for treating HDV.

Since acute HEV infections typically resolve on their own with spontaneous HEV clearance, there is no suggested therapy or treatment. Due to study limitations (such as the lack of a control group), it is challenging to conclude that ribavirin altered the course of the diseases, even though a recent trial indicated that the drug is helpful in treating immunocompetent patients with severe hepatitis E. Although sofosbuvir showed antiviral activity against HEV *in vitro*, its therapeutic effectiveness was not very strong [128]. NITD008, a broad-spectrum chain-terminating adenosine nucleoside analogue that was first created to treat the dengue virus [129], and GPCN114, which binds to the RNA channels of picornavirus polymerases [130], are two examples of novel anti-HEV medications that are being studied. These substances are promising candidates for HEV antiviral therapy. Finally, a potential substitute for traditional medications is T cell treatment [131].

HEV-fighting vaccines have been developed and tested, and one particularly effective vaccine is currently available in China [132]. It's critical to comprehend what makes people susceptible and resistant to recurrent infections and clinical illness. Finding environmental factors that influence lifetime exposures to HEV, such as farming and food processing methods, regional climatic patterns, and water and sanitation practices, may help explain regional variations in the age-specific incidence of the infection and disease severity that cannot be fully explained by genotypic variability. Finding these determinants could also aid in developing risk-based intervention techniques.

1.3 Conclusions and Future Perspective

Despite the fact that viral hepatitis remains an important health concern and a primary cause of death, significant advancements have been made in

this field of research. Although there is currently no effective vaccination to prevent HCV, there are very efficient medications nowadays that are transforming transplant medicine and curing HCV. The rate of cure of hepatitis C is now increasing using the short-term, easy, and safe treatments. It is essential to concentrate on case-finding and linking to care programs in order to eradicate it. Because of the anti-HBV vaccine, the prevalence of hepatitis B and D is declining. Both vaccinations and better sanitation practices will eventually reduce the burden of disease because acute viral hepatitis infections, such as HAV and HEV, are often self-limited and have little to no long-term effects. Future treatments are being encouraged by targeted antiviral drugs against HBV, and the most promising methods for eliminating the virus include immunomodulatory medicines and gene silencing technology. Moreover, the development of nanotechnology for treating HBV is also being investigated. Cationic nanoparticles made up from biodegradable polymers were evaluated for their transfection efficiencies in delivering DNA and siRNA to inhibit hepatitis B surface antigen (HBsAg). Even though there are several challenges, global efforts to eradicate viral hepatitis are still underway and we are optimistic that these challenges will be overcome, resulting in significant advancements.

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