Review Paper:

Hepatitis B Virus: A Comprehensive Overview of Virology, Transmission and Clinical Management

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Abstract

The Hepatitis B virus (HBV) represents a major public health issue, accountable for both acute and chronic liver infections that may result in serious complications including cirrhosis, hepatocellular carcinoma (HCC) and liver failure. This study provides a comprehensive overview of HBV including its virology, modes of transmission, clinical manifestations, diagnosis, treatment and epidemiology. The primary mode of transmission is through contact with infectious bodily fluids including blood, semen and vaginal secretions. Clinical presentations range from asymptomatic infections to severe acute liver failure and chronic liver disease. Diagnosis involves various serological and molecular tests, with HBsAg being a critical marker for chronic infection. Treatment aims to suppress HBV DNA, achieve HBeAg seroconversion, and, ideally, attain HBsAg seroclearance, although a complete cure is challenging due to the persistence of cccDNA.

The prevalence of HBV exhibits significant variation epidemiologically, with a notably high endemic presence in areas including Southeast Asia and sub-Saharan Africa and lower rates in developed countries. Vaccination remains the most effective preventive measure, significantly reducing HBV incidence and associated complications. Advances in antiviral therapies and a better understanding of HBV biology are essential for improving patient outcomes and managing this pervasive infectious disease.

Keywords: Hepatitis B virus (HBV), Liver infections, Cirrhosis, Hepatocellular carcinoma (HCC), Chronic hepatitis B (CHB).

Introduction

Hepatitis signifies the inflammatory response and swelling occurring in the liver. It may arise from various factors including autoimmune diseases, drinking too much alcohol, certain medications, or exposure to harmful chemicals. It is important to note that viral hepatitis, which is a viral infection, represents the most prevalent cause of hepatitis. Hepatitis may result from various viral strains. The predominant strains of viral-induced hepatitis found in the United States are Hepatitis A, B and C. Hepatitis D and E represent two less prevalent types of viral-induced hepatitis. Hepatitis is categorized into two types: "acute" and "chronic," depending on the length of time the liver experiences inflammation. Less than six months' worth of inflammation is referred to as "acute," while more than six months' worth of inflammation is classified as "chronic"[56].

Fewer than 5% of individuals with acute hepatitis B progress to develop chronic hepatitis; nonetheless, 1-2% of acute infections can result in fulminant liver failure[32]. The hepatitis B virus is the causative agent of this potentially fatal liver condition. Individuals may either have an asymptomatic infection identified through HBV screening or may exhibit acute symptoms associated with the disease. HBV infection can lead to a range of acute and chronic clinical manifestations. During the acute phase, patients may experience icteric hepatitis, or anicteric hepatitis, or, in rare cases, fulminant hepatitis. Individuals suffering from chronic infections are at a heightened risk of developing cirrhosis, hepatocellular carcinoma and chronic hepatitis. Initial symptoms are often nonspecific and may include vomiting, nausea, loss of appetite, jaundice and abdominal discomfort.

Individuals experiencing significant liver impairment may exhibit symptoms such as jaundice, hepatic encephalopathy and gastrointestinal hemorrhaging resulting from esophageal varices, coagulopathy, or secondary infections[80]. The most reliable strategy for preventing chronic HBV infection is to ensure that all infants, including newborns, receive vaccination.

Recently, two adult vaccines with improved immunogenicity have been authorized in both the USA and the EU, with additional options anticipated to be implemented in the forthcoming period. Individuals suffering from advanced or active liver conditions, cirrhosis, or elevated HBV DNA levels should consider treatment[27]. The hepatitis B virus is the primary contributor to viral hepatitis and is a major factor in the progression to end-stage liver disease globally. Furthermore, enhanced therapeutic strategies will be formulated based on a comprehensive understanding of the virus's biology and its interactions with the host[2]. Viral hepatitis is a significant liver disease that impacts a large segment of the worldwide population.

The hepatitis B virus (HBV) is one of several hepatitis viruses that significantly contribute to the incidence of viral hepatitis, alongside the hepatitis A virus (HAV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV). These viruses are all identical in their symptoms and cannot be distinguished clinically. Acute and chronic

hepatitis infections are the two broad categories into which HBV infections fall. Infections caused by HBV can manifest a diverse array of clinical symptoms, ranging from mild or absent indications to those that may be life-threatening. With a 0.5–1% case fatality rate, acute HBV infections usually resolve on their own.

Very few cases result in acute inflammation or hepatocellular necrosis. In contrast to the acute form, chronic hepatitis B (CHB) occurs less often and generally does not result in significant liver damage. In some individuals, CHB can progress to severe liver fibrosis, cirrhosis and the occurrence of hepatocellular carcinoma (HCC). About a million fatalities worldwide are attributed to cirrhosis, liver cancer, or chronic active hepatitis as a result of HBV[4].

Diagnosis: Comprehending the diagnostic tests at one's disposal is crucial for the effective screening, diagnosis and treatment of individuals infected with Hepatitis B virus. A positive HBsAg test result persisting for over six months signifies the existence of a chronic HBV infection. A functional cure is characterized by seroclearance, which is evaluated using a qualitative HBsAg test. This test specifically indicates the absence of HBsAg, corresponding to levels below 0.05 IU/ml in serum, regardless of whether antibodies (anti-HBs) have developed[14,62,69,78]. Protective immunity is recognized when the level of anti-HBs surpasses 10 IU/ml.

Serological, Molecular and Genomic Testing

Quantitative HBsAg: Throughout the various stages of CHB, there is a notable fluctuation in the levels of HBsAg and the origin of its synthesis. The concentration of HBsAg is elevated during the immune-tolerant phase, while it diminishes in the inactive phase[10,26,62]. In younger individuals who test positive for hepatitis B e antigen (HBeAg), the main origin of HBsAg production primarily stems from the transcription of covalently closed circular DNA (cccDNA). Conversely, in older patients who are negative for HBeAg, the origin of HBsAg is primarily attributed to HBV integrants[62,86]. The level of HBsAg has now been incorporated into the risk assessment scores for hepatocellular carcinoma (HCC) since greater levels may indicate a decreased chance of spontaneous clearance[43,62].

The concentration of HBsAg serves as a significant marker for predicting or assessing a patient's response to peginterferon (PEG-IFN) therapy[9,62]. For instance, in individuals who test positive for HBeAg, an HBsAg level greater than 20,000 IU/ml at week 24 indicates a negative predictive value of 96% for genotype A HBV while it achieves a 100% NPV for genotypes B, C and D. Furthermore, the lack of HBeAg and an HBV DNA level below 2,000 IU/ml six months after treatment are considered as favourable results in the management of HBV infection[62,73]. Notably, although there is a reduction in HBV DNA levels, nucleos(t)ide analogue (NA) therapy leads to a gradual decrease in HBsAg levels This suggests inadequate immunological clearance and persistent transcription of integrated viral genomes which are not influenced by chain terminators[8,62].

HBeAg: The advent of HBV DNA testing has enabled a more precise evaluation of infection and replication by measuring the levels of HBV DNA present in serum. HBeAg's seroconversion marks a significant stage in the immune system's clearance. Nevertheless, certain HBeAg-negative individuals may develop high HBV DNA levels associated with active hepatitis. This condition is frequently described as an HBeAg-negative illness[19,62]. In appropriate circumstances, a significantly elevated HBeAg level may be employed to signify a lack of response, thereby allowing for the early termination of treatment[18,62]. It is not recommended to measure HBeAg levels. The lack of standardization in HBeAg quantification complicates its application in clinical environments[62].

Anti-HBc: Immunoassays designed to measure total anti-HBc, capable of detecting both anti-HBc immunoglobulin G and anti-HBc immunoglobulin M, serve as a means to identify the core antibody associated with the hepatitis B virus. Acute hepatitis B is determined by anti-HBc IgM which is frequently the only indicator still present when HBsAg has stopped being detectable. Patients who undergo acute and intense exacerbations of their chronic hepatitis B often show positive results for anti-HBc[62,85]. In patients undergoing significant immunosuppression and cancer chemotherapy, such as treatment with rituximab, occult HBV infection has the potential to reactivate[62,90]. In individuals with hidden hepatitis B virus infection, the measurable concentration of HBV DNA frequently falls below 200 IU/ml[62].

HBV DNA: HBV DNA acts as an indicator for viral replication and is central to antiviral treatment strategies. Present recommendations suggest that antiviral treatment should be commenced for patients exhibiting elevated ALT levels alongside HBV DNA levels ranging from 2,000 to 20,000 IU/ml. This recommendation also extends to individuals with detectable HBV DNA levels who have cirrhosis. It is crucial to conduct HBV DNA testing in patients receiving treatment with nucleos(t)ide analogs (NAs) to assess the effectiveness of the therapy and inform subsequent treatment choices. The probability of acquiring therapeutic resistance escalates if HBV DNA levels are not diminished to undetectable status by the sixth month of treatment with telbivudine and lamivudine, or by the twelfth month of treatment with adefovir, given that both of these drugs possess a low resistance threshold[14,62,69,78]. The effectiveness of peginterferon therapy is also anticipated based on the initial or during-treatment HBV DNA levels[7,62].

HBcrAg: Considering that patients undergoing NA therapy who are HBcrAg positive, exhibit a correlation with pregenomic RNA (pgRNA) levels and intrahepatic HBV DNA, HBcrAg may be an important blood marker for

evaluating the active transcriptional activity of liver cccDNA[22,62]. Higher HBcrAg levels may be linked to a higher risk of liver cancer in individuals receiving NA treatment or not[29,62]. Consequently, HBcrAg may serve as an important indicator of cccDNA presence in the liver, in addition to being an effective instrument for monitoring, assessing treatment efficacy[62].

POC Diagnostics: A recent meta-analysis assessed 49 quick POC assays and summarized the results of 27 research[33,62]. Although the strong specificity ranged from 90% to 100%, the variability in the reliability of individual tests was uneven, ranging from 43.5% to 99.8%. Point-of-care assays for HBsAg could potentially offer greater accuracy, speed and cost-effectiveness compared to laboratory serological screening for HBV in field settings; however, further research is required in this domain[62].

The diagnosis of acute hepatitis B is confirmed clinically through the detection of HBsAg, the observation of associated symptoms and the measurement of increased serum aminotransferase levels. Generally, HBV DNA is identifiable and anti-HBc IgM is present. A diagnosis of chronic infection is established when HBsAg remains detectable for a duration exceeding six months. The detection of both Anti-HBs and IgG anti-HBc indicates a prior infection with HBV[72].

A key feature of occult HBV infection is the continual detection of a minimal quantity of intrahepatic HBV DNA, even in the absence of measurable HBsAg[21,66]. The diagnosis of this serological condition is marked by the absence of HBsAg and anti-HBs antibodies, while isolated anti-HBc is present[72,84]. Given that cccDNA remains within hepatocytes and that HBV DNA can sometimes be found in the liver without being detectable in the serum, the liver is considered the definitive standard for diagnosing occult HBV infection. However, acquiring hepatic HBV DNA in a clinical setting may present difficulties owing to the invasive characteristics of the procedure[66,72].

Tools used to diagnose hepatitis B

- **Biochemical parameters:** It is essential to incorporate serological testing that facilitates the detection of concurrent infections (such as HIV, HDV, or HCV-related chronic hepatitis) to be ruled out.
- **Serological markers:** Essential for determining the CHBVI phase.
- **Abdominal ultrasonography:** To validate or rule out HCC and LC.
- **Transient elastography (TE):** This approach is utilized to evaluate the extent of hepatic fibrosis. At present, it is recognized as the most commonly used non-invasive method. It is essential to highlight that the threshold values for transient elastography (TE) are lower than those associated with hepatitis C and it exhibits several unique characteristics related to CHB.
- **Hepatic biopsy:** The frequency of liver biopsies conducted has notably diminished due to the advent of TEs. A meta-analysis has indicated that the diagnostic precision of transient elastography (TEs) is more proficient in ruling out liver cirrhosis than in verifying its existence[52]. Since ALT levels and accuracy are strongly correlated, a higher ALT will result in a larger dispersion between the biopsy and the TE[59,83].

Treatment: The current objectives of CHB treatment are to achieve HBeAg seroclearance or seroconversion as well as persistent HBV DNA suppression. A significant number of infected individuals have improvements in important clinical outcomes such as cirrhosis, HCC and death rates while using lifetime nucleotide analog (NA) treatments which effectively suppress HBV DNA during treatment and induce HBeAg seroconversion. The FDA sees the best outcome for clinical trials on chronic hepatitis B (CHB) treatment as achieving a lasting clearance of HBsAg without treatment, accompanied by the suppression of HBV DNA, sometimes known as a functional cure, which is uncommon with the existing antiviral medications.

Complete cure is considered to have been reached when closed covalent circular DNA (cccDNA) is no longer detectable; however, sterilizing cure is sometimes referred to as total HBV eradication[16,39]. Because HBV DNA has become part of the host's genetic material, sterilizing cure is currently thought to be difficult to achieve. A functional cure represents the optimal outcome attainable with existing treatments, associated with significant clinical advantages for patients. It contributes to a decrease in mortality related to liver disease and enhances survival rates by preventing the advancement of liver fibrosis to cirrhosis and hepatocellular carcinoma[16,69].

Two categories of approved medications for the treatment: (i) Interferons 2a and 2b in their standard forms, along with the pegylated variant of 2a. The second treatment is most often utilized since it is more effective, more tolerated and easier to administer (one weekly dose as opposed to three). (ii) Nucleoside analogues such as entecavir [ETV], telbivudine [TBV] and lamivudine [LAM] as well as nucleos(t) ides, such as adefovir dipivoxil [ADV] and the two prodrugs of tenofovir, tenofovir disoproxil fumarate and tenofovir alafenamide. Due to the minimal genetic barrier and potential for resistance mutations to arise, it is currently not recommended to use LAM, ADV, or TBV[83].

In the past twenty years, considerable advancements have been achieved in the management of CHB. Currently, nine medications have received approval for the treatment of CHB, which includes seven nucleos(t)ide analogs (NAs): lentivirus, lamivudine, telbivudine, adefovir, entecavir, tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF) and besifovir dipivoxil along with two types of interferon (IFN): pegylated interferon and standard interferon. The main goals of CHB treatment are to slow the advancement of the disease and improve the survival rates of patients. The modern antiviral treatment focuses on

improving clinical outcomes through both virologic and biochemical responses.

Tests with a detection threshold of 10–20 IU/mL in blood implies that an undetectable level of HBV DNA during nucleos(t)ide analog (NA) therapy is recognized as a virologic response. In the case of interferon (IFN)-based therapy, a viral response is characterized by a serum HBV DNA level below 2000 IU/mL, evaluated both six months after the commencement of treatment and at the conclusion of the treatment regimen. Normalization of serum alanine aminotransferase is referred to as a biochemical response[41,60]. A key objective is to lower the HBV viral load while restoring alanine aminotransferase to normal[41]. Analogs of nucleos(t)ides (NAs) are the most popular choice worldwide. If an HBeAg-positive patient has seroconversion to anti-HBe during treatment, short-term NA treatment is a possibility.

Treatment ought to be maintained for a minimum of one year after HBeAg seroconversion and, preferably, extended for an additional three years to ensure a durable response after the cessation of therapy. Maintaining therapy for a minimum of three years reduces the likelihood of relapses to less than 30% and expedites the eventual elimination of HBsAg[62].

Epidemiology: The prevalence of chronic HBV infection exhibits significant regional disparities. Globally, there are three classifications of endemicity regarding chronic HBV infection: high, moderate and low. The level of endemicity is associated with the age at which individuals become infected. In highly populated emerging regions such as Southeast Asia, China and the Amazon Basin, a minimum of 8% of the population is impacted, with hepatitis B being highly prevalent. In these areas, 70% to 95% of individuals show serological markers indicating either past or current HBV infection. While acute HBV-related diseases are not observed in children due to the predominantly asymptomatic nature of infections, there are notable occurrences of liver cancer and chronic liver disease among adults[1].

Certain regions including parts of South America, Japan, the Middle East and Eastern and Southern Europe, exhibit moderately elevated rates of hepatitis B endemicity. The prevalence of the population showing signs of infection varies between 10% and 60%, with chronic carriers constituting 2% to 7%. While a significant number of HBV infections are found among adults and adolescents, acute cases of the disease are commonly reported in these areas. However, it is the infections occurring in newly born and children that predominantly contribute to the elevated rates of chronic infection[24,79]. In these regions, various transmission patterns coexist, encompassing transmission from newborns, early childhood and adults.

Most developed countries such as Australia, Northern and Western Europe, exhibit reduced levels of HBV prevalence. In these areas, the prevalence of HBV infection ranges from five to seven percent, while the proportion of chronic carriers is notably lower, at only 0.2 to 0.5 percent[24,54]. In these regions, the majority of HBV infections are found among teenagers and young individuals belonging to specific high-risk categories, including individuals who use injectable drugs, men who have sexual relations with men, healthcare workers, patients requiring regular blood transfusions and those undergoing hemodialysis[24]. Indigenous communities exhibit a markedly elevated rate of liver diseases along with a higher occurrence of CHB in various regions[3,55]. The precise reason for the increased prevalence among indigenous populations remains unclear; however, it is likely to be multifaceted.

Possible contributing factors may include early pregnancies, which correlate with an elevated risk of high maternal viral load in women diagnosed with CHB and characterized by elevated population densities and specific HBV genotypes[12,55], blood-to-blood contact-inducing behaviours like ritual body modification and limited access to prompt vaccination and other essential elements of quality primary health care can be exacerbated by residing in remote locations[55]. After widespread immunization programs were implemented, the prevalence of HBV significantly altered in many Nations, which decreased the incidence of HCC and the HBsAg carrier rate. The occupational risk of HBV exposure was assessed among 595 nurses in northwest Turkey in 2002 and 2003. Among them, 2.7% tested positive for HBsAg and total of 18.7% of individuals had experienced exposure to HBV infection[17].

The prevalence of chronic HBV infection differed according to birthplace, ranging from 21.4% in China to 4.6% among those born elsewhere in Asia[34]. The surface antigen of the hepatitis B virus (HBsAg), which is produced by specific gene, is found in the population in approximately 2–20% of instances. In Asian Nations, the majority of HBV infections take place during pregnancy or early childhood. Conversely, in African and Western countries, horizontal transmission is the primary method of infection[30,31]. In Korea, the hepatitis B vaccine was first made available in 1985. Since 1991, all infants have received the vaccination and women who test positive for HBsAg have received both the active and passive forms of the shot.

The prevalence of HBV infection in metropolitan regions significantly decreased after the vaccine era, with rates dropping to 0.6% in children under the age of ten, 1.6% in teenagers and 3% in those in their early 20s. Acute hepatitis B also grew less common and in the last few years, it was hardly ever seen in those under the age of twenty. However, compared to younger age groups, the incidence of acute hepatitis B among those over 30 is very high which may be because many of them are not vaccinated[37].

In India, the number of individuals infected with the hepatitis B virus is estimated to be roughly 36 million, resulting in an average carrier rate of 4%.

Professional blood donors are at the highest risk for HBV infection in the country, with 14% testing positive for the hepatitis B surface antigen. HBV marker positivity occurs in about 60% of hepatocellular cancer patients. There have been reports of a small number of people having the pre-core mutant virus. It is relatively rare to have both the hepatitis C and hepatitis delta viruses co-infected. Hepatitis B remains a considerable public health concern in India and is expected to continue as such until effective national immunization initiatives and additional preventive strategies are implemented[75].

Pathophysiology: Although HBV possesses a complex life cycle, it primarily functions as a stealth virus by successfully evading the immune system[11,64]. During the initial phase of infection, the HBV virion, or viral particle, binds to a liver cell (hepatocyte) and enters the cytoplasm of the cell[50,64]. Since HBV virion is uncoated, nucleocapsids are able to penetrate the nucleus of the hepatocyte and convert the DNA into a double-stranded form referred to as covalently closed circular DNA[64,82]. Within the framework of long-term health conditions, cccDNA exhibits remarkable stability and can persist within the host nucleus for an extended duration, often lasting several months[28,64]. The method through which the virus reproduces itself does not possess "proofreading capability," allowing for mutations in the virus[23].

Upon entering the bloodstream, the newly formed HBV virions invade additional hepatocytes and initiate the replication cycle again. It is thought that HBV stimulates the immune system to target the hepatocytes in the infected liver, resulting in inflammation and the advancement of fibrosis[61,64]. The HBV incubation period lasts from 30 and 180 days. The age at which a person contracts the virus dictates the course of the illness; 90% of people who have HBV during pregnancy or the early years of life go on to develop chronic hepatitis because their immune systems are unable to eliminate contaminated hepatocytes[42,64]. Only 5–10% of adult infections progress to CHB; 90% of infections are acute[64,70].

People with CHB may very rarely (in 1-2% of instances) lose the HBV surface antigen, which is seen as a conclusive sign of recovery. However, if they experience immunosuppression, the virus may reactivate[49,64]. HBV is an encapsulated virus that does not cause cytopathic effects and belongs to the Hepadnaviridae family. Its genetic material consists of partially double-stranded circular DNA. Severe liver diseases including cirrhosis, HCC, or fulminant hepatitis might result from it. The immunological-related liver damage brought on by active viral replication is primarily responsible for the pathophysiology of HBV-related liver disease[71].

In instances of hepatitis B virus infection, it is acknowledged that the progression of the disease and the clearance of the virus are significantly affected by the adaptive immune response. The removal of hepatitis B virus is believed to rely significantly on T cells, as evidenced by a robust, polyclonal and multispecific T cell response observed in individuals with acute infections who successfully eliminate the virus. In contrast, patients with chronic infections exhibit a comparatively weaker and more narrowly focused T cell response. When interferon alpha/beta (IFNα/β) is produced, numerous interferon-stimulated genes (ISGs) are transcriptionally activated. These ISGs implement various intracellular antiviral strategies that may mitigate pathogenic processes by decreasing the production and dissemination of viruses[11,67].

Hepatocellular carcinoma arises in association with necrosis, inflammation and regeneration in various human liver diseases beyond hepatitis B including alcoholism and hemochromatosis[11,63]. The presence of alpha-1-antitrypsin deficiency alongside primary biliary cirrhosis underscores the critical role of immune-mediated hepatocellular damage in the progression of hepatocellular carcinoma linked to hepatitis B virus (HBV)[11,57]. Consequently, irrespective of the underlying cause or development mechanism, chronic liver cell damage appears to represent a premalignant state that triggers a series of events marked by heightened cellular DNA synthesis and the generation of endogenous mutagens in addition to impaired cellular detoxification and repair processes[11].

Current clinical trial: A variety of innovative therapeutic approaches for managing chronic HBV infection have emerged due to enhanced comprehension of the immune response of the host and HBV lifecycle. These strategies may be categorized into two main types: those that directly target the virus (direct acting antivirals) and those that indirectly affect the virus by modifying a host component or the immune response (immunotherapy)[74]. NA-based antiviral treatments for CHB have established themselves as accepted forms of care. The medications entecavir, telbivudine, lamivudine, adefovir and tenofovir are presently authorized for the treatment of chronic hepatitis B infection. By disrupting the viral replication cycle, the administration of NAs results in a robust and enduring control over virus multiplication.

In as many as 95% of the patients, viral suppression is achieved[13]. The primary disadvantages of NA therapy include the necessity for continuous administration, minimal impact on levels of HBsAg and an elevated hazard of developing drug resistance[94]. Additionally, among patients who are positive for HBeAg, the percentage of antibody development can drop to 20%–25% after a year of treatment[40]. The two main side effects of chronic treatment are myopathy and nephrotoxicity[15].

NAs are synthetic pharmaceuticals that function by competitively inhibiting the reverse transcriptase and DNA-dependent functions of viral polymerase. This action halts the reverse transcription process of pgRNA into the initial strand of viral DNA.

Long-term NA therapy causes HBV to become resistant to the medication being taken. The rates of resistance to older generation NAs such as adefovir, telbivudine and lamivudine are higher. Despite the minimal resistance risk associated with entecavir and tenofovir when used in naive individuals, the danger of cross-resistance makes managing pre-existing antiviral resistance difficult[35,91].

Lamivudine: Because of its inexpensive cost and early approval, lamivudine, a moderately powerful deoxycytidine nucleotide analog, is frequently utilized. It works well against both mutant and wild-type HBV variations by inhibiting viral polymerase/reverse transcriptase[35,95]. In patients diagnosed with chronic hepatitis B, the therapeutic interventions result in HBeAg seroconversions, lower concentrations of HBV DNA and diminished levels of ALT. Furthermore, it is well-tolerated and demonstrates efficacy even in instances of significant viral exacerbations and hepatic failure[65,81]. Unfortunately, resistance mutations, specifically the M204V/I/S mutation, cause the drug's effectiveness to be diminished by changing the reverse transcriptase domain's dNTP-binding pocket[68]. These mutations impact 20% of patients within one year and can affect as many as 70% after a duration of five years[35,51].

Telbivudine: Following administration, thymidine NA telbivudine is efficiently converted into its active triphosphate form through phosphorylation[38]. It is well tolerated, has no side effects that are dose-limiting and shares structural similarities with lamivudine, including resistance profiles[20,35]. In HBeAg-positive individuals the general rate of developing resistance to medication stands at 22%, whereas it is 9% among HBeAg-negative carriers[48]. It demonstrates cross-resistance with lamivudine and poses a significant risk of developing drug resistance, even though it is more effective than both adefovir and lamivudine[35,44].

Entecavir: Entecavir functions as a guanosine nucleotide analog, operating by competing with deoxyguanosine triphosphate to inhibit the activity of HBV polymerase/reverse transcriptase. Lamivudine-resistant and wild-type HBV variants can be effectively suppressed by it and it has low adverse effects, little resistance and high rates of HBV DNA reduction. It also helps people with decompensated cirrhosis function better with their livers[35,89]. According to clinical trials, entecavir is more effective than lamivudine for patients who are either treatment-naive or lamivudine-refractory. After five years of therapy, patients who have not received prior treatment exhibit a low likelihood of developing resistance to entecavir. However, this probability increases in individuals who have been treated with lamivudine prior, with resistance associated with breakthrough occurring in 50% of such cases[35,77].

Adefovir dipivoxil: Adefovir is an acyclic NA that efficiently prevents HBV, both lamivudine-resistant and wild-type, from replicating[88]. Furthermore, it promotes the activation of NK cells and the production of endogenous IFN. It functions as a DNA chain terminator[35,58]. About 30% of patients acquire resistance to adefovir after five years of treatment; these mutations usually arise in the palm subdomain of the polymerase[5]. Cross-resistance can happen when taken in conjunction with lamivudine in patients who already have lamivudine resistance[35,92].

Tenofovir disoproxil: Tenofovir, a methyl derivative of adefovir, is another acyclic nucleoside analog exhibiting antiviral properties against Hepatitis B virus while exhibiting resistance to lamivudine. The combination of this agent with entecavir, telbivudine, or lamivudine has demonstrated the ability to enhance the suppression of viral replication through an additive effect[25,35].

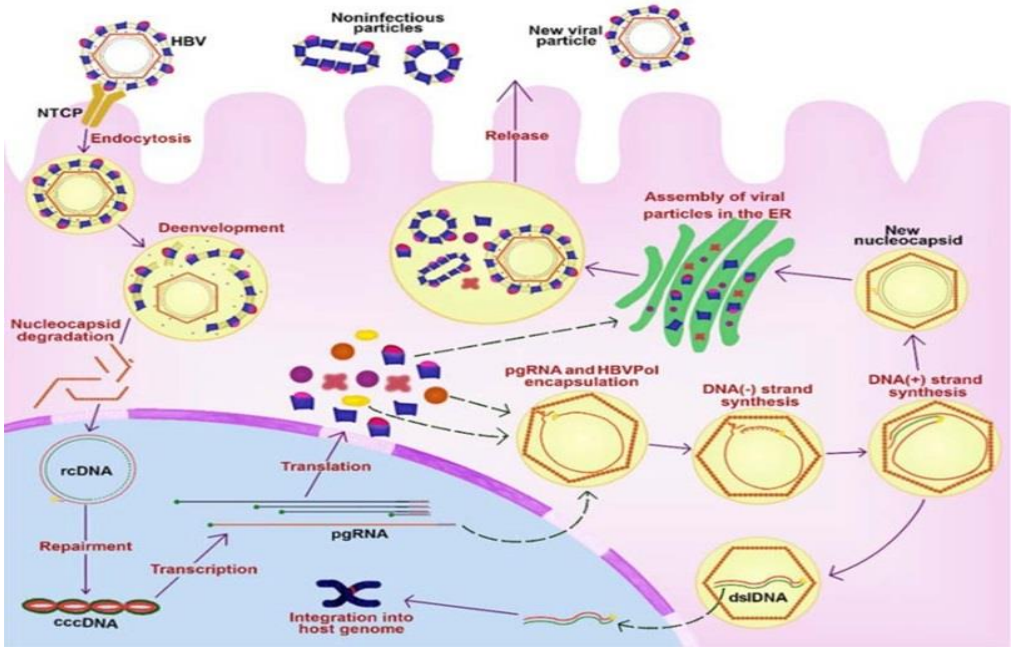

Figure 1: HBV replication cycle

Future Perspectives

Successful management of hepatitis B necessitates a comprehensive understanding and analysis of diagnostic methods; as different treatment approaches address specific manifestations of hepatitis B infection in unique manners. Therefore, to evaluate the effectiveness of a treatment, it is essential to establish a diagnosis utilizing various combinations of hepatitis B infection markers. The integration of markers for HBs and anti-HBs can facilitate the identification of HBsAg seroclearance and the emergence of anti-HBs, which indicates the presence of protective immunity[36,78].

Distinct methodologies are required for diagnosing patients in the immune-tolerant and inactive phases due to variations in HBsAg serum levels and their origins. In HBeAg-negative patients, an HBsAg level below 100 IU/mL might suggest ongoing HBsAg clearance, which can only be accurately assessed when considered alongside HBeAg and HBsAg markers[36,45]. Understanding HBV genotypes and both of these indicators may be useful in tracking how antiviral medication is working. Antiviral therapy's effectiveness is known to be influenced by the HBV genotypes of the infected patient[36,47]. By aiding to the determination of the infection stage and subsequent decision-making regarding the sort of therapy to be administered, these indicators may contribute to the achievement of the WHO's objective[36].

The integration of innovative medications may enhance the probability of achieving a successful recovery from Hepatitis B virus infection. The integration of both established and novel anti-HBV treatments has the potential to elevate the rates of HBsAg seroclearance, although the most effective treatment regimens require further validation. Following a 12-week treatment period, a triple-combination therapy based on RNA interference demonstrated a significant reduction in HBsAg levels. Potential therapeutic combinations for exploration include a therapeutic vaccine paired with an antiviral agent such as a CpAM, small interfering RNA and an inhibitor of HBV entry, alongside a direct-acting antiviral[41].

Tenofovir alafenamide, a novel tenofovir prodrug, has shown less exposure to tenofovir and more powerful antiviral activity as compared to tenofovir. These could result in less nephrotoxicity. The presence of nuclear cccDNA, serving as a transcription template for HBV mRNA, plays a role in the continued presence of HBV infection. Nevertheless, the presence of free HBV DNA and its byproducts is directly linked to the advancement of liver disease in individuals who are infected with HBV[76,93].

Despite conflicting opinions, it has been claimed that drugs that up-regulate catalytic polypeptide-like (APOBEC) 3A and 3B and apolipoprotein B mRNA editing enzyme destroy HBV cccDNA noncytolytically[53,76]. Innovative treatment strategies for the management of HBV cccDNA will soon be necessary[76,87]. In the near future, HBV entry inhibitors may also be helpful in managing HBV infection[76]. Nucleocapsid assembly modulators (CAMs) primarily function by causing the nucleocapsid to misassemble. These chemicals cause disruptions to the encapsidation of pgRNA and interfere with the production of capsids.

While HBsAg levels barely decrease, these drugs have been demonstrated to lower serum HBV-DNA and RNA levels. Owing to these restrictions, CAMs' place in upcoming CHB treatments needs to be clarified[6].

Conclusion

In summary, significant advancements have been made in the diagnosis, treatment and management of chronic hepatitis B virus infection. The primary objective of contemporary therapy is to attain a functional cure, defined by sustained HBsAg seroclearance and suppression of HBV DNA without the need for ongoing treatment. This strategy is advantageous from a therapeutic standpoint since it lowers the death rate from liver disease and stops liver fibrosis from progressing to cirrhosis and liver cancer.

It is still difficult to achieve a full sterilizing treatment, which includes getting rid of integrated HBV DNA and closed covalent circular DNA (cccDNA). Nine licensed drugs, including nucleoside analogues (NAs) and interferons, are now part of the treatment regimen for chronic hepatitis B. These medications are designed to impede the advancement of the disease and to enhance the likelihood of survival. A comprehensive grasp of diagnostic methods is essential for effective management since several markers and their combinations are required to track the effectiveness of treatment and the stage of infection.

Novel and established antiviral medication combinations, RNA interference-based therapeutics and immunomodulatory interventions are examples of innovations that hold potential for raising seroclearance rates and enhancing therapeutic results. Future strategies for the treatment of HBV involve targeting various stages of the virus life cycle through the use of cccDNA inhibitors, HBV entry inhibitors and modulators of nucleocapsid assembly. The World Health Organization's objective of eradicating HBV as a threat to public health will probably be achieved with the use of these cutting-edge techniques and a thorough understanding of HBV genotypes and markers. Overall, despite persisting difficulties, there is a hope that new therapy approaches and continuous research will greatly enhance the prognosis.

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