Original Research

Hepatitis B virus infection, structure, genotypes, and epidemiology - A review

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Abstract

There are currently 250 million people infected with the hepatitis B virus (HBV) worldwide, despite the availability of a prophylactic vaccine for many years and the use of efficient and well-tolerated viral suppressive drugs since 1998. In this review, I go through the most recent developments in the structure, and epidemiology and biology of the virus, look at changes in the way the disease is currently being treated, and investigate novel, cutting-edge treatments that are being developed for the treatment of HBV infection. Genotypes and serological subtypes have a strong and statistically significant association, and in some circumstances, serological subtypes can be utilized to distinguish between sub genotypes. geographic distribution of certain genotypes and sub-genotypes varies and plays a crucial role in the clinical manifestation of infection as well as the response to antiviral medication. Thanks to advancements in genetics, the prospect for vaccinations, and tailored management to target the integration of virus with host. HBV persistence occurs due to covalently closed circular DNA can rarely be removed by current pharmacological therapies. Alternative treatment approaches, such as those built on silencing of viral. According to reports, HBV DNA levels can be inhibited and conversion of HBeAg to antibody to HBe Ag can be induced by antiviral medication like nucleotide analog (NUC), which can prevent liver-related death. Additionally, there is a critical need for the creation of global archives of standardized HBV reagents and protocols that can be accessible by all HBV researchers. The plan for HBV cure research presented in this position paper will make a significant contribution to the objective of eradicating HBV infection globally.

Keywords: hepatitis b virus; replication; sub genotypes; chronic hepatitis; HBV vaccine

INTRODUCTION

Hepatitis B virus infection is a well-known threat to global public health[1,2] Early adulthood is the age of infection and sexual and percutaneous transmission are the primary modes of transmission in low incidence (3%) areas like Europe and America and in childhood are the most frequent modes of propagation in areas of moderate prevalence (3–10%). A developing stage of chronic HBV is HBeAg-negative hepatitis, often known as the reactivation phase. Patients with anti-HBe (antibody to antigen) positivity proceed to cirrhosis at an annual rate of 7–25%. But cirrhosis, which can cause liver failure and/or hepatocellular cancer, develops in around 2% of chronic hepatitis B patients each year and causes chronic active hepatitis in about 10% of them (HCC).[3-7] The five stages below generally describe the HBV infection in newborns a natural history. While HBV is actively reproducing in phase 1, the host has no immune response. Inflammation of the liver is essentially nonexistent, and the normal range of blood Alanine transaminase (ALT) level. In adulthood, during second phase blood Alanine transaminase level are elevated. HBeAg is lost, antiHBe develops, the hepatitis B virus DNA in serum is controlled limit, and third phase shows lower inflammation in liver. In phase 4 Hepatitis- e antigen is negative and ALT levels are intermediate, and in phase 5 HBs Ag and HBeAg is negative and ALT is normal[8] (Figure 1). Infection with chronic HBV was expected to affect 316 million people worldwide in 2019 at a prevalence of 4% across all age groups. This rate represents a burden on global populace. A range from 6% to 7% of prevalence and in certain situations, prevalence rates are predicted to be above 25%. Europe and the eastern Mediterranean are low-intermediate zones (3%–6.9%) (Figure 2).[9-11]

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Structure and replication cycle of hepatitis B virus

Three types of HBV can exist: Dane particles, non-pathogenic, such as encased nucleocapsids with immature sub viral particles, and naked nucleocapsids.[12] In the Baltimore Classification, a method used to categories viruses taking into account both replication and transcription, HBV is a Double stranded DNA with intermediate RNA, 42 nm in size, Hepatitis B surface antigen is found in the outside lipoprotein coat, often known as the envelope, of the contagious HB virion (HBsAg). HBV genome and DNA polymerase, is contained within an inner nucleocapsid that is surrounded by HBsAg.[13,14]

A partially double-stranded and circular DNA molecule makes up the HBV genome. 3020–3320 nucleotides make up its entire genome. In 4 substantially overlapping coding areas, known as open reading frames (ORFs), every nucleotide in the genome is active[15] as illustrated in Figures 3 and 4.

Encoding the vital enzyme for genome replication is the polymerase gene (P gene). In addition to performing the functions of the terminal protein (TP), the enzyme also functions as RNaseH, DNA polymerase, and reverse transcriptase. In addition to encoding HBcAg and HBeAg, the two start codons are in core gene. The viral DNA is encapsulated by HBcAg, a protein. Additionally, it can be found on the surface of hepatocytes, where it triggers a cellular immune response. HBeAg is a sign of active viral replication.[16,17]

Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

Figure 1. The natural history of chronic HBV infection has been schematically divided into five phases

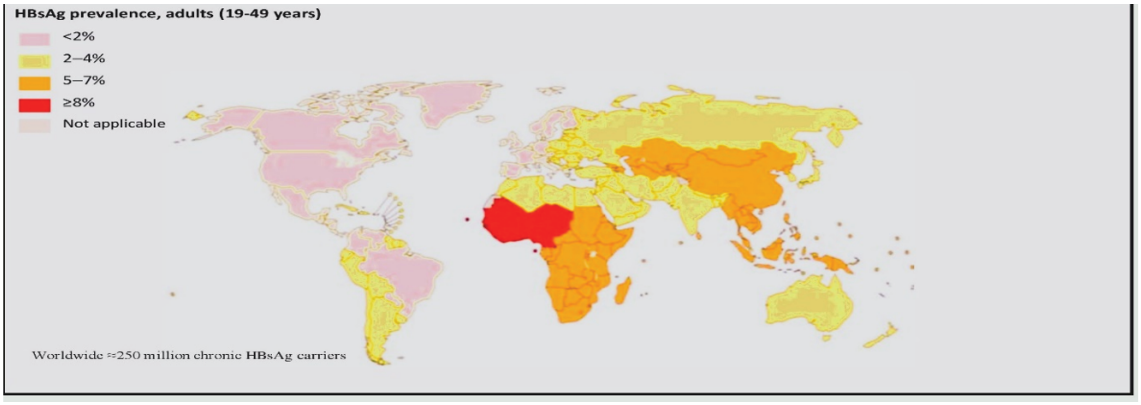

Figure 2. Epidemiology and public health burden

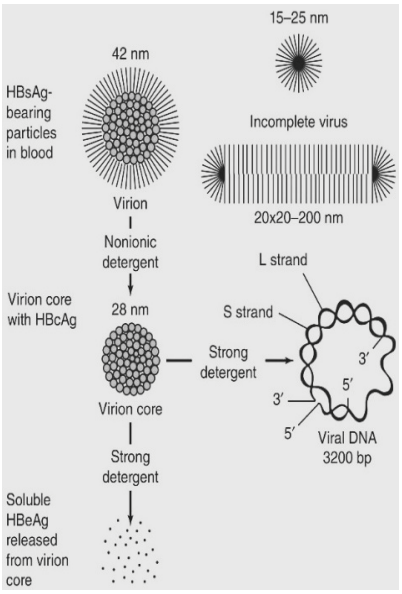

Figure 3. Nonionic detergents have the ability to destabilise the 42-nm spherical Dane particle, releasing the 27-nm core that houses the viral DNA genome that is partially double-stranded. By treating the core particles with a powerful detergent, a soluble antigen known as the hepatitis B e antigen may be released. HBcAg stands for hepatitis B core antigen

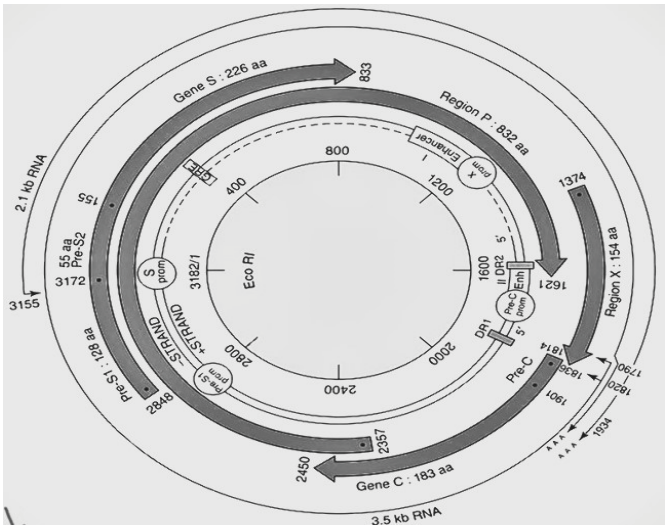

Figure 3. Semi-circular arrows represent the region of coding. They are the X gene, the polymerase gene, the pre-S1, S2, and pre-S3 genes, as well as the polymerase gene, pre-core and core genes, and the pre-S1

Sodium taurocholate cotransporting polypeptide (NTCP) receptor is a recent finding which shows HBV entry and made it possible to create a highly susceptible cell line with high susceptibility to HBV infection. HBV enters hepatocytes, which is accomplished by S1 portion of the envelope of the virus binding to the hepatic receptor Sodium taurocholate cotransporting polypeptide. The replication cycle of HBV begins with the entry. The virion is then brought into the nucleus after being stripped of its coating. The linear DNA genome of the virus is transformed through covalent ligation into closed circular DNA, which is connected to the 5' end of the plus strand via protein.[18] The seven proteins Core, pre-core, polymerase, and outer proteins (L, M & S) are encoded by hepatitis B virus. These proteins are arranged in a carboxy-terminal nested arrangement, the smallest (S), the next large (M), and the largest (L). The reverse transcriptase, RNaseH, and primer enzymes are required for the production of viral DNA, which happens in nucleocapsids found in the cytoplasm of infected hepatocytes. viral nucleocapsid subunit is the core. Core protein and viral reverse transcriptase are both produced by pregenome mRNA. Reverse transcription of pregenomic RNA allows the viral genome to be reproduced. The RNA and the protein are both eliminated during this procedure. The reverse transcriptase causes the synthesis of viral DNA, the enzyme binds to 5 prime end of the template (mRNA) and reverse transcription leads to the synthesis of all copies of cccDNA (Figure 5). It is possible for cccDNA to be toxic to hepatocytes, but an increase in viral envelope proteins prevents its formation.[19-21]

Uncoating: core and viral DNA are released by the HBV membrane into the cytoplasm.

cccDNA formation: The pol. of the virus synthesizes the dsDNA and later causes the formation of cccDNA in nucleus.

Transcription: Host RNA polymerase converts cccDNA into pregenomic and subgenomic

Translation and reverse transcription: core, DNA pol. and reverse transcription, are translated using pregenomic RNA as a template. The pregenomic RNA's packaging signal interacts with the DNA polymerase to form a bond, and the two come together to form the capsid of the virion (core). Through the conversion of pregenomic mRNA to DNA, the HBV genome grows in the core particle.

DNA synthesis: The nucleocapsid, which contains partially dsDNA, is produced following the synthesis of the (-) and (+) strands of DNA.

Assembly: dsDNA consists of Hepatitis B surface antigen and nucleocapsid (virion).

Release: The infected hepatocyte releases the mature infectious agent Dane particle/cccDNA amplification.

Genotypes and Subgenotypes of HBV

Genotype A and its subgenotypes

Genotype A is distinguished by a nucleotide insert at the carboxyl terminus of the core gene.[22]

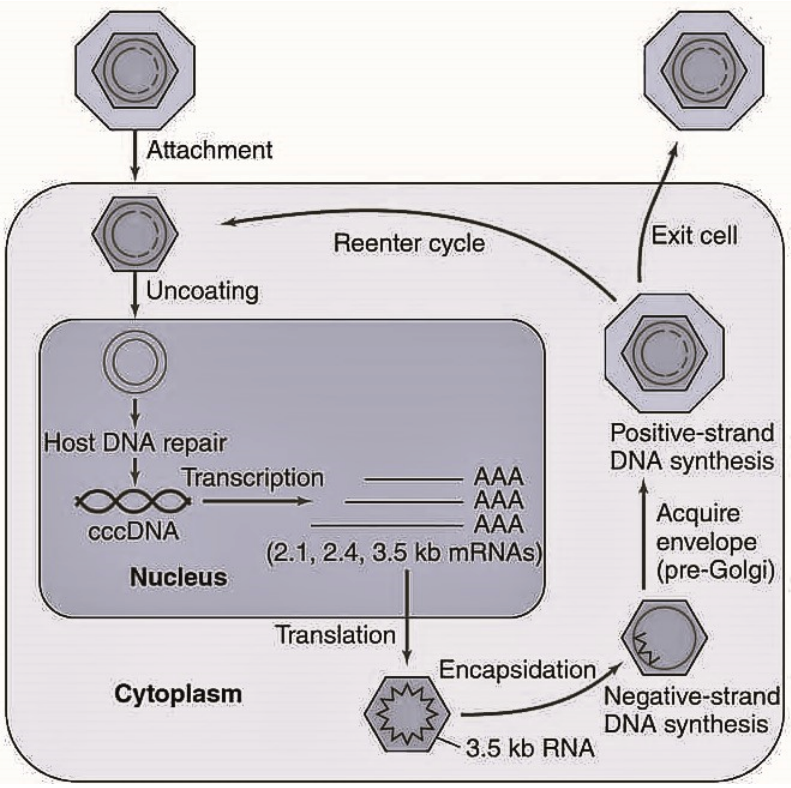

Figure 5. HBV life cycle

Because the latter group of sequences does not match the requirements for a subgenotype classification, genotype A has been classified into A1, A2, and A4 subgenotypes, and quasisubgenotype A3.[23]

Genotype B and its subgenotypes

HBV genotype B is linked to an earlier time of HBeAg seroconversion. The subgenotypes of B have been categorized into: B1, B2, B3, B4, B5, B6 B7, B8, B9, and QS-B3(quasi-subgenotype). Native Americans may have transported subgenotype B1 during their journey from Europe to America and Greenland, as this subgenotype was most likely the ancestor of B5.[24]

Genotype C and its subgenotypes

The earliest HBV genotype is C. It has the most subgenotypes, C1-C16 which reflects the length of time that it has been endemic in humans.[25]

Genotype D and its subgenotypes

There are only 6, not 8, subgenotypes of D, according to a recent systematic and comparative investigation of the subgenotypes.

The genotype D is found globally, its subgenotypes are found in a few regions D1 subgenotype is usually found in Iran, D2 in Russia and Europe, D3 in Alaska and Serbia, D4 in Somalia, and D4,5,6,7,8, and D9 in India, Nigeria and Indonesia.[26]

Genotype E and its subgenotypes

The preS1 region losses its 3 nucleotides that distinguishes E-genotype from A,B,C,D,F,H and I genotypes and it possesses the distinctive serological subtype ayw4. With a low genetic diversity, E- genotype is restricted to Africa and suggests a 300-year-old origin.[27]

Genotype F and its subgenotypes

The four subgenotypes of genotype F isolates, F1 through F4, are all members of the serological subtype adw4. American Indian populations in Central and South America, Alaska, and other parts of the world are all carriers of this gene.[28]

Genotype G and H

HBV genotype G was first detected in an HIV case (homosexual man) from California, however, it was first reported in 2000 as a new genotype when it infects a populace in the united states (Georgia). In 2002 Genotype –H was reported and is mainly found in Mexico and is very rare in Asia. Homosexuals always present a significant risk factor.[28] Both indigenous and mixed-race people in Mexico are predominate of genotype H, indicating that this genotype predates the arrival of Europeans among the Aztecs' descendants and genotype F has the closest ties to it.[29]

Genotype I and its subgenotypes

With a significant bootstrap support for the group, the majority of the sequences had nucleotide divergences of at least 7.5% in comparison to genotype C. Two subgenotypes, I1 and I2, were described, and their corresponding serological subtypes were adw2 and ayw2, respectively.[30] Given the wide geographic distribution, genotype I is clearly indigenous to much of Asia. When the full genome is examined, genotype I is found to be grouped together with genotype A and close to genotype C.[30]

Genotype J

The island (Ryukyu) in Japan reports the new genotype of HBV which was named as H- genotype and it showed a close relationship with human and orangutan genotypes. Non-human HBV isolates from gorillas, chimpanzees, and gibbons cluster along the entire genome.[31]

Hepatitis B virus infection epidemiology and phases

Throughout the world, there are significant regional variations in the hepatitis B virus infection prevalence. In developing nations with sizable populations (China, East Asia and Africa) 6% of the populace was found HBV carriers. Hepatitis B is highly prevalent. 60–75% of the population in these regions demonstrates prior or present serological evidence of HBV infection.[32] Over 250 million persons are Hepatitis B carriers, and an estimated 1.9 billion people globally exhibit symptoms of past or current infection. According to reports, the prevalence of HBsAg is 4 percent nationwide, however it varies by region (figure 4).[33] The Western Pacific has the highest prevalence with 119 million infections, followed by Africa with 87 million, the Eastern Mediterranean with 59 million infections, and Southeast Asia with 59 million infections. There are 13.8 and 5.2 million people in Europe and the Americas, respectively.[34]

Transmission of HBV

Various geographical regions have different predominance modes of HBV transmission. In high-prevalence areas, mother-to-child transfer is a mode of transmission. Comparatively, in regions with intermediate prevalence of Hepatitis B virus, horizontal transmission, particularly in early childhood, is responsible for Chronic Hepatitis B virus infections, whereas in areas with less prevalence, unprotected sexual contact and adult injection drug use are the main sources of transmission. The infection rate of babies born to HBsAg-positive women can reach 95%.[35,36] If vaccines for HBV are not given to newborns.

According to genotypic and phylogenetic research, it is possible for fathers to pass HBV to their children. According to a Taiwanese study, 65% of newborns with HBsAg-negative mothers and HBsAg-positive fathers were infected with HBV.[37] Unprotected babies are assumed to come into close touch with their fathers' contaminated blood and bodily fluids the majority of the time, which is thought to be how these transmissions happen. Although HBV has been discovered in sperm in certain studies, there is no clinical evidence that infected sperm cause HBV infection in the growing baby.[38,39]

Hepatitis B core antibody and HBsAg screening are both advised by the World Health Organization. After serologic testing for HBsAg was implemented, the risk of HBV transmission through blood transfusions was dramatically decreased. By screening for anti-HBc in addition to HBsAg, the danger was substantially diminished. When HBsAg is absent, anti-HBc can be identified during the window phase.[40,41] HBV continues to spread often through sexual contact. In one study that looked

at 2360 instances of acute Hepatitis BVirus infection in the USA, for instance, it was estimated that sexual risk was responsible for the transmission of HBV in about 41% of the cases. At particularly high risk are heterosexual people who have several sex partners, are unvaccinated men who are homosexuals, and those have contact with sex workers.[42-44] Exchanges of syringes and needles among injectable drug users (IDUs) frequently result in percutaneous transmission. A comprehensive study of data from 26 countries estimated that 1.4 million injectable drug users would be HBsAg positive and 7 million would be anti-HBc positive in 2011. In recent years, drug misuse has been identified as the main risk factor for the spread of HBV in the United States.[45] Nosocomial transmission typically takes place via contaminated equipment or an unintentional needle stick from patient to patient or from patient to healthcare professional (HCP). Due in large part to the use of general precautions, initiatives to immunise all HCP against HBV, and the use of postexposure prophylaxis for nonimmune people, the number of HBV infections among HCP has dramatically decreased.[46] The terms immune clearance, tolerance, control, and escape were used in a European attempt to raise awareness of viral hepatitis. Phases 1 and 2 of the four, largely sequential phases of Hepatitis B Ag positive/Negative[47] (figure 5).

Biomarkers of HBV

The essential component of the HBV cccDNA and life cycle of the virus is produced initially from the virus and resides in non-dividing hepatocytes as a stable minichromosome. Hepatitis B e Antigen, Hepatitis B surface Antigen, serum glutamic-pyruvic transaminase, or (SGPT) and DNA of HBV are are currently employed in practice to distinguish between Chronic Hepatitis B (CHB) and disease phases.[48-50] There is an urgent search for novel biomarkers that can track the HBV infection progression of the disease (hepatocellular carcinoma). For the clinical management of CHB various markers are used like HBcrAg measures cccDNA intrahepatic, M2BPGi tracks the liver fibrosis and risk of Hepatocellular Carcinoma, serum HBV RNA and qHBsAg.[51-53]

Serum HBV RNA

The five viral transcripts that are produced by HBV are pregenomic RNA, core RNA, pre-core, X-RNA, Pre S1and S2.[54,55] Since precore, pregenomic RNA are overlength molecules with a size of roughly 3.5 kb, they can only be translated from cccDNA.[56] Viral RNA, which does not easily circulate in serum, is present in particles that resemble viruses. HBV RNA has also been found in complexes of capsids and antibodies as well as in naked capsids. Released HBV RNA- containing viral particles float, just like HBV DNA-containing particles.[57,58] Patients who are HBeAg positive can estimate their treatment response based on their HBV RNA kinetics.[59] From infected hepatocytes the release and mechanism of HBV RNA into the blood is still unclear. In cell cultures of HBV, it has been reported that noncytolytically HBV cultures secrete non-enveloped capsids contain pregenomic RNA, and all types of HBV DNA.[60]

HBcrAg

A marker to track cccDNA and its transcriptional activity and define potentially useful therapeutic endpoints is Hepatitis B core-related antigen. Each HBcrAg component may serve a different purpose and be applied in different patients and genotypes to reflect intrahepatic viral activity, as intrahepatic viral activity varies across genotypes and individual patients, each HBcrAg component can serve a variety of purposes.[61]

The capacity of HBcrAg to distinguish between the various clinical stages of CHB is constrained by the existence of pre-core mutations that affect the amounts of HBeAg.[62-64]

HBsAg

During the various phases of CHB, the big and medium surface proteins that makeup HBsAg differ and have variable behaviours. No differences in HBsAg release or subviral particle formation were found between genotypes when tested in vitro, with the exception of G-genotype, which exhibits faulty release of hepatitis B surface antigen.[65,66]

HBsAg is a classic biomarker of HBV infection. The infected hepatocytes with HBV cause a release of particles (subviral) which helps in evading the immune response of the host. Seroconversion of HBsAg is a goal in treating the disease. The levels of hepatitis B surface antigen ia an important predictor of infection in untreated patients caused by HBV.[67]

Serum biomarkers

The persistence of HBV in chronic hepatitis B is accompanied by dynamic changes in hepatocytes due to inflammation against the disease.[68] The majority of HBV-associated liver illness is immunologically mediated since HBV is not a cytopathogen, and viral detection triggers the host immune response. Dysregulation of the adaptive immune system both generally and specifically to the virus is linked to HBV persistence. Multiple inflammatory processes can be triggered in hepatitis B virus infection without a significant immune response by lymphocytes to cause hepatocellular damage.[69]

Treatment for hepatitis B virus

The protective immune response destroys the hepatocytes infected with HBV. However, the poor or weak response by the immune system leads to chronic infection and if someone is suspected of HBV infection the management of treatment is shown in figure 5.[70] Generally, speaking there is no specific treatment for Chronic hepatitis B infection. However, several medications (oral antiviral) can offer a slow progression of the disease and can minimize liver cirrhosis and long-term survival.[71]

The available studies on the usage of medications for treating chronic hepatitis B in kids and teens, highlight any knowledge gaps and enumerate the main therapy suggestions. (Figure 6)

Ropeginterferon alfa-2b

The antiviral Ropeginterferon alfa-2b 450ug results in early seroconversion of HBeAg. Additionally, it induces an immunological response from cells against HBV-infected hepatocytes, resulting in a decrease in the proportion of cells that contain ccc-DNA.[72]

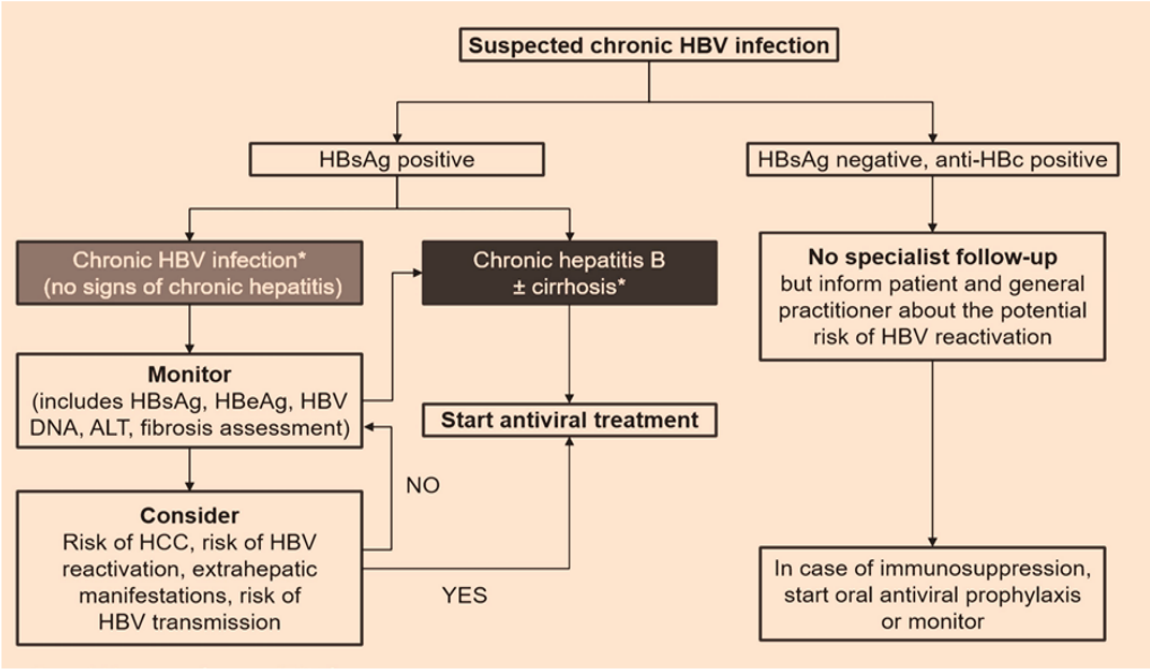

Figure 6. Management of treatment HBV infection

Peginterferon alfa-2b (PEG IFN alfa-2b)

Treatment with PEG-IFN alfa-2b (1.5 µg) for 48 weeks is an effective drug choice for HBV infection. It enhances the seroconversion of HBeAg without additional treatments. however, the US FDA and EMA have not approved it for adolescents with Chronic Hepatitis B.[73]

Lamivudine

A reverse transcriptase inhibitor and nucleoside analogue called lamivudine, is used to treat HBV infection, this synthetic analog (lamivudine) prevents viral replication in human cells.

Lamivudine has been given the all-clear by the EMA and US-FDA to treat Chronic Hepatitis B in children. The suggested dosage is oral, 3 mg/kg each day (100 mg).[74]

Entecavir

A nucleoside analog is called entecavir (analog of deoxyguanosine). It quickly undergoes intracellular phosphorylation. Oral administration of Entecavir causes seroconversion of HBeAg in 20% of patients with positive hepatitis B e antigen.[75] In a randomized, research involving youth and children, the effectiveness and safety of entecavir were examined. Entecavir has been given the all-clear by the US-FDA and EMA to treat CHB in children, adolescents and older.[76]

Tenofovir

DNA polymerase is inhibited by tenofovir, in hepatocytes it inhibits Hepatitis B Virus replication. It has oral route of administration and its well tolerated and safe. Both the EMA and the USFDA have given their approval for the use of tenofovir DF in the treatment of CHB in adolescents and children.[77]

Tenofovir alafenamide (TAF) and Telbivudine

Tenofovir alafenamide 25 mg per day is the suggested dosage for the medication. The FDA and EMA have not approved telbivudine for use in children. After taking TAF orally its converted into tenofovir in hepatocytes and TFV-DF active metabolite is formed which ultimately blocks HBV replication.[78]

Sodium taurocholate cotransporting polypeptide

It has been suggested that the entry of Hepatitis B virus into a host cell is facilitated by the membrane transporter receptor known as sodium taurocholate cotransporting polypeptide.[79] It has been reported that NTCP›s interaction with the HBV large surface protein was prevented by cyclosporine A and its analogues, which also prevented HBV entry.[80]

Future of immunotherapy

The variety of possible immune-based therapeutics will increase as our understanding of important topics connected to immune failure and reconstitution grows, similar to how we are already observing an expansion of medication targets specifically targeted against the virus. Enhancing specificity and lowering toxicity will come from locating the immunological fatigue inflection points that restore T-cell and B-cell immunity[81] with the use of pattern recognition receptor agonists, the therapeutic index of treatments that target innate immunity could be improved by isolating antiviral activity from inflammation. Moving forward with attempts to engineer antiviral immunity has potential in addition to improving immunotherapy methods. Gene therapies targeting the T-cell receptor and chimeric antigen receptor obviate the requirement for restoration.[82] When considering and researching these immunotherapeutic approaches, combination therapy should be taken into

account. The removal of contaminated hepatocytes and robust antiviral effects should result from logically combining antiviral and immunotherapeutic medications based on complimentary mechisms of action, which should increase the cure rate for HBV.

CONCLUSION

We have made significant progress in our comprehension of the Hepatitis B virus infection. However, there are still gaps in our knowledge that currently prevent us from developing medicines that would completely eradicate this debilitating condition. Future research should focus on creating treatments that aim to reduce HBsAg levels, which is the ultimate goal in treating hepatitis B. The therapy options for HBV cccDNA need to be further improved. At-risk populations must be immunised, infected people must be diagnosed and treated, and curative therapy with a set treatment period is required in order to achieve the aim of HBV elimination.

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