MINIREVIEW

Hepatitis B Virus: From Diagnosis to Treatment

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Abstract

Hepatitis B infection is still a global concern progressing as acute-chronic hepatitis, severe liver failure, and death. The infection is most widely transmitted from the infected mother to a child, with infected blood and body fluids. Pregnant women, adolescents, and all adults at high risk of chronic infection are recommended to be screened for hepatitis B infection. The initial analysis includes serological tests that allow differentiation of acute and chronic hepatitis. Molecular assays performed provide detection and quantification of viral DNA, genotyping, drug resistance, and precore/core mutation analysis to confirm infection and monitor disease progression in chronic hepatitis B patients. All patients with chronic hepatitis B should be treated with antiviral medications and regularly monitored for efficient treatment. The current treatment is based on nucleos(t)ide analogs and pegylated interferons that save lives by decreasing liver cancer death, liver transplant, slow or reverse the progression of liver disease as well as the virus infectivity.

Key words: hepatitis B virus (HBV), serology, nucleic acid testing, antiviral treatment

Introduction

Although there are effective vaccines and treatment strategies against hepatitis B (HB), it is still a significant health concern worldwide that can present in acute, permanent, severe liver failure and cancer forms resulting in high morbidity and death. Globally, 2 billion people have been infected with HB. There is an estimated more than 292 million people living with chronic hepatitis B (CHB) infection worldwide. The global HB surface antigen (HBsAg) positivity was estimated to be 3.9% in 2016 (HBF 2018a; Razavi-Shearer et al. 2018). Annually, 887,000 deaths occur each year due to HB and related illnesses, which were mainly related to advanced liver fibrosis and cirrhosis (WHO 2019a). The risk and progression of chronic infection are age-dependent and occur mainly in immunocompromised individuals. It is known that the younger an infected person is, the higher the risk of developing CHB infection. Although acute infection is generally cleared in immunocompetent, chronic infection develops in approximately 90% of infants, 30–50% of children aged five years, and 5–10% adults (Jefferies et al. 2018; Terrault et al. 2018; Hyun Kim and Ray Kim 2018; CDC 2020a). CHB infection is classified in five different clinical stages according to the HBsAg positivity (i) hepatitis B e antigen (HBe Ag) positive infection; ii) HBe Ag-positive hepatitis; iii) HBe Ag-negative infection; iv) HBe Ag-negative hepatitis, and v) HBsAg-negative stages that reflect the interaction between HBV replication and the immune system. Occult hepatitis B infection (OBI) is another sub-category that is characterized by a detectable HBV DNA with undetectable HBs antigen or serological markers of the previous viral exposure in the plasma (Malagnino et al. 2018). OBI is associated with severe liver damage and hepatocellular carcinoma (HCC), and poses a risk for individuals, especially in blood transfusional infection, HBV reactivation, chronic liver disease, and HCC (Roman 2018; Wang et al. 2020).

HBV spreads from mother to child, after exposure to infected blood or body fluids or sexual contact. In addition, HBV can survive and remain infective for several weeks on moist surfaces at room temperature (de Almeida et al. 2015; Terrault et al. 2018; Than
et al. 2019). Despite being transmitted vertically from infected mother to a child, having sex with an infected partner, contacting the infected needle sticks or sharp object injuries, HBV is not transmitted through breastfeeding, hugging, kissing, coughing, and sneezing, or sharing food and drink (CDC 2020b).

HBV vaccination is the main and the safest precaution from being exposed to the virus (WHO 2019a). HBV vaccine has been administered since 1982 and leads to a dramatic decline in HBV infections globally (Van Damme 2016; WHO 2017a). The vaccine against HBV is available and can be administered from birth to older ages. ENGERIX-B®, RECOMBIVAX HB®, HEPLISAV-™ are three single-antigen vaccines while PEDIARIX®, TWINRIX® are two combination vaccines that are licensed for use in the United States (CDC 2020c). The recommended schedules for HBV vaccine are as follows: three-dose vaccination at 0, 1–2, and 6–18 months of a monovalent HepB (Heplisav-B) vaccine for infants; three-dose vaccination at 0, 1–2, and 6 months for the unvaccinated person, and alternative two doses of Recombivax HB at 11–15 years; two dose vaccinations of HepB at 18 years, and three-dose vaccination with Twinrix. Twinrix is a combination of HepA and HepB vaccine to be administered at 18 years and older (Dynavax 2018; CDC 2020c).

To reduce the spread of infection, the World Health Organization (WHO) European Region recommends the Universal Hepatitis B vaccination programs for infants born from HBsAg-positive mothers, all infants within the first 24 hours after birth, children up to 18 years old, and adults from the groups of high risk for HBV infection, i.e., people with infected sexual partners, homosexual men, hemodialysis patients, injecting drug users, and healthcare workers (WHO 2019b). In May 2016, the WHO addressed the first Global Health Sector Strategy on viral hepatitis 2016–2021 to end new CHB infections by 90% and reduce the mortality rate by 65% by 2030 (WHO 2016).

One of the most severe forms of hepatitis infections is hepatitis delta, also known as hepatitis D. The infection can develop in people infected with HBV (Gilman et al. 2019). Globally, an estimated of 5% of HBV are also infected with the hepatitis D virus (HDV) (WHO 2020). Individuals with HBsAg positive, the elevated alanine aminotransferase (ALT) level with undetectable HBV DNA should be screened for HDV antibodies and HDV RNA (Gilman et al. 2019). HBV-HDV co-infection is severe, and the risk of liver disease progression, liver cancer, early decompensated cirrhosis, and liver failure is higher (WHO 2020). Although there is no effective vaccine against HDV, vaccination against HBV also plays a significant role in protecting delta infection.

HBV, is a partially double-stranded DNA virus of 3.2 kilobases, and it transforms from pregenomic ribonucleic acid (RNA) to DNA by reverse transcription during its life cycle. The genome consists of an outer lipid envelope and inner nucleocapsid core encoded by four overlapping open reading frames, named C, X, P, and S (McNaughton et al. 2019; Wang et al. 2019). Although it is known as a virus with high replication ability, due to the absence of the proofreading reverse transcriptase enzyme, the naturally occurring mutations may arise in different genome regions. These regions may encode for polymerase, surface antigen, core/precore promoter, and comprise the X genes that significantly influence HBsAg expression and progression of HCC (Shaha et al. 2018; Arikan et al. 2019). Additionally, due to the complete overlapping of pol and S genes, drug resistance and nucleos(t)ide resistance mutations occurring in the pol gene can lead to changes in its product HBsAg (Kırdar et al. 2019).

The mutations in the gene C that encode for precore and core proteins are significantly correlated with liver disease progression in CHB patients (Al-Qahtani et al. 2018). The changes in the amino acid sequences: W28*, G29D, G1896A, G1899A, G1862T in the precore proteins that affect HBeAg, and F24Y, E64D, E77Q, A80I/T/V, L116I, E180A in the core proteins mutations are commonly identified in populations and related to clinical severity (Kim et al. 2016; Wu et al. 2018).

The global genotype distribution of HBV differs in different geographic regions and areas worldwide (Rajoriya et al. 2017). HBV is classified into ten genotypes (A-J), and 40 sub-genotypes till today, according to the phylogenetic analysis (Rajoriya et al. 2017). Genotype A is predominant in Northwest Europe, North America, and Africa; genotypes B and C prevail in East Asia and far East countries, while genotype D is widespread worldwide (Arikan et al. 2016; Kmet Lunacek et al. 2017). Genotype E occurs only in West Africa (Ambachew et al. 2018). Genotype F has been found in Central and South America, and genotype G has been reported in Turkey, France, Canada, Vietnam, Germany, and America. Genotypes H and I have been isolated in Central America, Mexico, Vietnam, and Laos; the recently identified genotype J has only been found in Japan (Mahmood et al. 2016). Fig. 1 illustrates the distribution of HBV genotypes (A-J) worldwide. Additionally, the rate of HBV infection also differs in geographic regions. According to the HBsAg positivity, the prevalence of HBV infection is classified into low (< 2), low-intermediate (2–4.9%), high intermediate (5–7.9%), and high (≥ 8) (Kim et al. 2018). HBsAg is of the main concern, especially for the Western Pacific regions with 6.25 seropositivity. The global prevalence of CHB infection in the Eastern Mediterranean Region, South–East Asia Region, and European Region is estimated at 3.3%, 2.0%, and 1.6% respectively (Fig. 2) (WHO 2019a). HBV genotypes and sub-genotypes have been reported to
Diagnosis and treatment of hepatitis B virus effectively affect disease transmission, progression, and treatment outcome (Kmet Lunacek et al. 2017). Therefore, identifying HBV mutations and genotypes is essential for both disease manifestation and identification of individuals at risk of infection progression.

This review describes virological assays, including serological and molecular techniques for diagnosing HB infection and updates on the most effective treatment strategies against the virus for the prevention of liver progression and cirrhosis in chronic HBV carriers.

**Laboratory diagnosis of hepatitis B virus**

Initial assessment of HBV infection begins with patient history, physical examination, evaluation of liver disease activity, and interpretation of different hepatitis markers and/or their combinations such as HBsAg, HB core antigen (HBCAg), HBeAg, HB surface antibody (anti-HBs/HBsAb), HB core antibody (anti-HBc), anti-HBc IgM, HB e antibody (anti-HBe), and focus on the detection of antigens and antibodies (WHO 2017b). The
Hepatitis B Foundation (HBF) recommends screening all adults for HB with the triple serological marker panel that involves HBsAg, anti-HBs, and anti-HBc total (HBF 2018b). To classify the phases of the infection in HBV infected patients, the followings should be performed: i) the assays for HBsAg, HBeAg/anti-HBe, HBV DNA; ii) liver blood tests including aspartate aminotransferase (AST), alanine transaminase (ALT), and iii) transient elastography (Fibroscan) as a noninvasive test or needle liver biopsy as an invasive method for the presence of cirrhosis (EASL 2017).

**HBV serological markers**

Various serological assays can detect virus-specific antigens and antibodies which appear during and after HBV infection. These tests are used to determine whether a patient is susceptible to infection or immune due to passed infection or HBV vaccination (CDC 2020d). Currently, various serological diagnostic assays, including rapid diagnostic tests (RDTs) and laboratory-based immunoassays, such as enzyme immunoassays (EIAs), chemiluminescence immunoassays (CLIAs), electrochemiluminescence immunoassays (ECLs) are used (WHO 2017b). These tests can be performed with serum, plasma and/or capillary/venous whole blood and oral fluid specimens to detect the presence of antigens or antibodies against the virus with high analytical sensitivity, specificity, and accuracy (WHO 2017b). Dried blood spot (DBS) specimen may be an alternative type of specimen in settings where blood taking and RDTs laboratory testing are not available and/or accessible or from a person with poor venous access (WHO 2017b). The laboratory reports are given qualitatively or quantitatively as international units (IU) or signal per cutoff (S/Co) values (Terrault et al. 2018).

**HBsAg.** HBsAg is an envelope protein that is expressed on the surface of the infectious virion called Dane particles. The detection of HBsAg in the serum indicates the current HBV infection. The HBsAg positivity can be considered with a second surface antigen test before further evaluating HBV DNA in the regions with HBsAg prevalence < 0.4 (WHO 2017b). The incubation period for hepatitis is 90 days (60-150 days) after exposure to HBV, and HBsAg appears in the blood for about six weeks (1-10 weeks) after the first exposure to the virus (CDC 2005). During the immunological window period, HBsAg may disappear rapidly without the appearance of HB surface antibodies, and the IgM antibody is the only evidence of the infection during this period (Otero et al. 2018). If HBsAg positivity persists after six months, it implies the progression of a chronic infection. The quantitative immunochemiluminescence analysis is performed to evaluate HBsAg levels of CHB patients and is a useful marker for interferon alfa (IFN-α)-treated CHB patients with HBeAg negative (EASL 2017).

**Anti-HBc.** Detection of anti-HBc antigens confirms exposure to HBV and indicates acute, chronic, or resolved infection but not vaccine-induced immunity (Terrault et al. 2018). The presence of IgM antibodies, together with HBsAg positivity, generally indicates the acute infection that generally persists positive for not more than six months (Jackson et al. 2018). Individuals who are core-antibody positive and HB surface-antibody negative are chronically infected and show a decreased risk of HBV reactivation. There is also no clinical benefit of vaccination for the group of individuals who are positive only for core antibodies due to exposure to HBV or people who are positive for anti-HBc and anti-HBs due to immune control (Cholongitas et al. 2018; Ganczak et al. 2019).

**HBeAg and anti-HBe.** The presence of HBeAg correlated with active viral replication is indicative of the contagiousness of the patient. Whereas, the appearance of anti-HBe indicates the low level of viral replication and is strong evidence for infection resolution (CDC 2005). These tests are often used to determine the CHB infection phase (EASL 2017).

**Anti-HBs or HBsAb.** The presence of anti-HBs indicates the recovery and immunization against HB infection either by HB vaccine or prior infection. People whose first-degree relatives or sex partners are chronic carriers are recommended to be vaccinated if their triple serological screening tests are negative (EASL 2017). The anti-HBs titer should be ≥ 10 mIU/ml in order to be protective (Dini et al. 2017).

**Biochemical parameters and fibrosis markers**

The severity of liver fibrosis is assessed using biochemical parameters, including AST and ALT, which are enzymes released from the liver in response to damage and disease. The other biochemical parameters are gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, serum albumin gamma globulin, full blood count, and prothrombin time (PT) (EASL 2017). When biochemical and HBV markers are inconclusive, then invasive and noninvasive methods are used to assess the stage of liver damage (EASL 2017). Since liver biopsy is an invasive, costly, and painful procedure compared to other techniques, various non-invasive methods are preferred to predict the stage of liver fibrosis and the presence of cirrhosis in CHB patients. The WHO recommends AST to platelet ratio index (APRI) calculated according to the formula: APRI = [AST/AST ULN (upper limit of normal)] × 100/platelet count (10^9/l) to estimate the stage
of liver fibrosis (WHO 2017b). TE is another non-invasive method; however, due to its limitations such as high cost, inaccurate results with elevated ALT levels, restriction with liver necro-inflammation, and obesity, the WHO recommends the APRI index as a relatively accurate method for predicting advanced liver fibrosis (EASL 2017; WHO 2017b; Huang et al. 2019). It has been recommended that 40 IU/ml as ULN value should be used in the APRI formula (WHO 2017b). ALT levels should also be measured in CHB patients as it correlates with disease severity. According to the WHO guidelines, the ULN ALT level is below 30 U/l and 19 U/l for men and women, respectively (WHO 2017b).

Molecular assays

The molecular diagnostic techniques are used for HBV DNA quantification, genotyping, detection of drug resistance mutations, and precore/core mutation analysis (Villard et al. 2015). Currently, UltraQual HBV PCR Assay, COBAS AmpliScreen HBV Test, Procleix Ulitro Assay, Procleix Ulitro Plus Assay, and COBAS TaqScreen MPX Test are FDA approved nucleic acids amplification tests (NATs) used for diagnosis of HB infection (FDA 2019).

HBV DNA quantification. HBV DNA quantification. HBV DNA by NAT is used to determine the infectivity of individuals and infectivity of HBsAg positive pregnant women to prevent mother to child transmission risk and reach a decision whether to treat diseases. The HBV DNA measurement with molecular technologies enables early detection of people at risk before HBsAg emerges and rules out OBI (Aghasadelhi et al. 2020). The testing of HBV DNA is also used to monitor the treatment response in CHB patients (WHO 2017b). The viral load of HBV is usually measured either in IU/ml or copies/ml by ultraviolet (UV) spectrophotometry, real-time PCR (rt-PCR), digital PCR, loop-mediated isothermal amplification (LAMP), transcription-mediated amplification (TMA), nucleic acid sequence-based amplification (NASBA), rolling circle amplification (RCA) as well as electrochemical, quartz crystal microbalance, microcantilever, and surface plasmon resonance biosensors (Liu and Yao 2015; WHO 2017b; Al-Sadeq et al. 2019; Sayan et al. 2019; Arikan and Sayan 2020). The HBV DNA level represents the disease progression, long-term results of CHB infection, and the treatment’s achievement to prevent the progression of HCC. The measurement of the level of HBV DNA is recommended to be performed with a more sensitive rt-PCR assay with 10 IU/ml detection limit (EASL 2017).

HBV DNA genotyping, drug resistance, preC/core mutations. To date, ten genotypes of HBV, A to J, and more than 40 sub-genotypes that differ > 8% and 4–8% nucleotide divergence in the genome, respectively, have been identified (Al-Sadeq et al. 2019). Different genotypes and sub-genotypes show different geographical distribution and are correlated with persistence of viral load, risk of developing cirrhosis, HBsAg seroclearance, antiviral therapy response, and prognosis due to the presence of mutations (Paudel and Suvedi 2019; Wang et al. 2019). It has been known that patients infected with HBV genotype A are more likely to develop CHB infection than patients infected with genotype B, associated with the development of antiviral resistance or genotype C, associated with acute hepatitis (EASL 2017; Wang et al. 2019). HBV genotyping is not required for initial diagnosis; however, genome sequencing for evaluation of HBV genotypes and drug resistance mutations are useful parameters for patients at risk of developing HCC in order to monitor an efficient therapy (EASL 2017).

There are many genotyping systems, including reverse hybridization, restriction fragment polymorphism (RFLP), multiplex nested PCR or real-time PCR, oligonucleotide microarray chips, reverse dot blot, restriction fragment mass polymorphism (RFMP), and invader assay (Fletcher et al. 2019). Molecular identification of HBV genotypes could also be done by sequencing the whole HBV genome, followed by phylogenetic analysis. Phylogenetic analysis is performed by constructing a phylogenetic tree with nucleotide sequences of the entire HBV genome to characterize different HBV genotypes and subgenotypes. A web-based program available through the National Center of Biotechnology Information is used that enables us to make the comparison between the newly obtained HBV sequences with the reference sequences available in GenBank. BLAST or FASTA are tools for searching similar sequences available in the EBI web site (http://www.ebi.ac.uk/Tools/homology.html) (Schreiber 2007).

The whole-genome sequences of different HBV strains are aligned, and the phylogenetic tree is constructed using distance methods including neighboring joining (NJ), un-weighted pair-group using arithmetic averages (UPGMA) or character-based techniques including maximum parsimony (MP) and maximum likelihood (ML) (Rozanov et al. 2004; Schreiber 2007). The similarity method is considered the “gold standard” approach for genotyping and sub-genotyping and can be performed on individual genes on the HBV S gene instead of the complete genome. However, the partial sequencing (HBV S gene) allows determining only the HBV genotype, not the HBV sub-genotype (Pourkarim et al. 2014).

Apart from HBV genotyping, HBV drug resistance mutations are also tested by using sequence-based assays. Several sequence-based assays such as line
Recommendations for the treatment of HBV/HIV coinfection, which was updated in 2015, on the use of antiretroviral drugs for treating and preventing HIV infection. Interferon or Peg IFN as antiviral therapy was eliminated from these guidelines because their use is restricted in LMICs due to its high cost and significant adverse effects that need careful monitoring (WHO 2015). In addition, Peg-IFN was found to have only about 20% sustained non-treatment response in terms of viral suppression and low HBsAg loss and seroconversion rates (Lin et al. 2016).

New generation NUCs act by inhibiting HBV DNA replication by normalizing ALT levels. Unfortunately, NUC’s use relies on long-term therapy and induces drug-related mutant infection (Tsuge et al. 2013). NUCs rarely eliminate all of the chronic HBV infection and HBV replication (Jeng et al. 2010). In recent years, NUCs or IFN monotherapy or combination therapy in CHB treatment have been investigated to minimize the therapies (Scaglione and Lok 2012). Since the combination of NUCs and IFN can inhibit more than one step of the HBV lifecycle than mainly targeting the reverse transcriptase step by NUCs monotherapy (Wei et al. 2015). Benefits and limitations of antiviral drugs used against for HBV infection are given in Table I (Abdul Basit et al. 2017).

The chemical name of TAF is L-alanine, [(S)[[(1R)-2-(6-amino-9H-purine-9yl)-1 (methylethoxy)methyl]phenoxyphosphinyl]-1-methyl ethyl ester, (2E)-2-butenedioate (Gilead Sciences 2015). TAF pharmacokinetics are linear and dose-dependent. According to the 28-day phase 1b study, which assessed antiviral activity, safety, and pharmacokinetics in CHB patients, TAF was found to be well-tolerated and safe. However, some side-effects, including headache, nausea, fatigue, cough, and constipation, were also reported. The antiviral effect of TAF over the 4 weeks was demonstrated by changes in serum HBV DNA levels of the treated patient groups in the same study (Agarwal et al. 2015).

Conclusions

The review summarized the serological, molecular diagnosis techniques, and current treatment strategies for HBV infection. The initial diagnosis with the serological assays is used to detect HBsAg and other HBV antigens and antibodies. Next, molecular assays are performed to verify the first step of diagnosis, quantify HBV viral load, and identify HBV genotypes and determine drug resistance mutation. Although molecular assays are frequently preferred due to their high sensitivity, high cost, the need for experienced personnel, and numerous equipment for analysis are the main limitations of molecular analysis. In the future, there is a need for new technologies such as biosensors that provide faster time to result with not only high specific-
ity, sensitivity, and low cost but also low false positive/ negative ratio that can play a significant role in screening, diagnosis, and management of HBV infection. Additional technologies may also help to develop new treatment targets. A combination of the HBV therapies and small-molecule drugs or biologics will be necessary to control the HBV infection effectively.

Conflict of interest
The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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