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HEPATITIS B VIRUS: A CLINICAL REVIEW

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Abstract:

Introduction: *Hepatitis B viral infection is the most common cause of chronic liver disease across the world and is often transmitted through sexual contact, parenteral, or vertical routes. Hepatitis b virus belongs to Hepadnaviridae family where the viral capsid bears viral genome and DNA polymerase that has reverse transcriptase activity. Affected individual present with a range of mild symptoms to symptoms of liver failure, as well as many can be asymptomatic. The disease is classified as acute and chronic based on duration and viral markers.*

Aim of the work: *In this study, our aim was to review the current understanding of Hepatitis B infection, management, and prevention.*

Methodology: *we conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE from January 1994 to March 2017. The following search terms were used: Hepatitis B, acute hepatitis B infection, chronic hepatitis B infection, diagnosis of hepatitis b infection, prevention of hepatitis b infection, and management of hepatitis B infection*

Conclusion: *Hepatitis B virus infection is the most common cause of chronic liver disease across the world which presents with a spectrum of symptoms and complications. An understanding of the symptomology and serologic markers of HBV infection is necessary for a proper diagnosis and management. HBV infection can be prevented with vaccination and awareness of risk behaviors. At risk groups should be vaccinated in order to avoid an infection.*

Keywords: *hepatitis B infection, preventive liver disease, chronic liver disease*

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INTRODUCTION:

Epidemiology

Most chronic liver diseases around the world can be attributed to an infection with HBV, which could be transmitted parenterally, sexually, and through the vertical route. It is estimated that the number of patients infected by HBV around the world have increased to become over 240 million patients, making this huge number of patients at a significantly high risk for developing cirrhosis and liver cancer. Epidemiologists usually divide HBV endemicity into three groups (based on the prevalence of HBV antigens): high HBV antigen prevalence, intermediate HBV antigen prevalence, and low HBV antigen prevalence. In the group of high HBV antigen prevalence, where more than 8% of inhabitants have positive HBV antigens, we can find countries like China, Indonesia, sun-Saharan Africa, and South east Asia. On the other hand, the intermediate HBV antigen prevalence, which means that 2-7% of inhabitants are HBV positive, include areas like Southern Europe, Eastern Europe, South West Asia, and South America. Finally, the low HBV antigen prevalence groups includes countries where less than 2% of inhabitants are HBV positive, like Western Europe and North America countries **[1]**.

Virology

HBV is considered to be a member of the Hepadnaviridae group. It has a diameter of about 35 nm and has an outer envelope and a capsid core. The outer envelope consists of lipid and contains the surface antigen of HBV (HBsAg), and the capsid core is icosahedral and consists of proteins, genome of the virus, and DNA polymerase **[2]**. DNA polymerase has a reverse transcriptase role. The genetic material of the HBV virus consists of DNA that is in circular shape and is partly double-stranded. It has four overlapped open frames for reading **[3]**:

1. The S reading frame, which encodes surface proteins (including the surface antigen HBsAg).
2. The pre-C/C reading frame, which encodes the core antigen (HBcAg), and the e antigen (HBeAg).
3. The P reading frame, which encodes reverse transcriptase along with other polymerases needed for the activity of the virus.
4. The X reading frame, which encodes the transcriptional trans-activator factor (HBxAg).

The covalently closed circular DNA (cccDNA) remains in the nucleus of hepatocytes as a mini-chromosome and is considered to be an HVB transcriptional template. In addition, it is likely that the reverse transcriptase, which is a main part during HBV replication, to have mistakes during this process, making the rates of mutation relatively high, and similar to these rates in RNA viruses and retroviruses **[4]**.

METHODOLOGY:

•Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE, from January 2001 to March 2017. The following search terms were used: Hepatitis B, acute hepatitis B infection, Chronic hepatitis B infection, diagnosis of hepatitis b infection, prevention of hepatitis b infection, management of hepatitis B infection

•Data Extraction

Two reviewers have independently reviewed the studies, abstracted data and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

This study was done after approval of ethical board of King Abdulaziz University.

Acute Hepatitis B

More than 60% of patients who get an HBV infection will develop an asymptomatic subclinical disease that will remain undetected. On the other hand, the remaining proportion of patients who get an HBV infection will develop symptomatic disease that can range from mild hepatitis with only nausea and fatigue, to severe jaundice. In rare cases, patients could develop acute liver cell failure. Clinical picture usually appears within the first six months following exposure to HBV, depending on the exposure levels **[5]**. Symptoms usually start as a prodromal disease that shows mild fatigue, fever, nausea, body aches, and anorexia. Within this phase, liver functions enzymes (ALT and AST) start to elevate in the serum, and serum shows relatively high concentrations of HBV DNA and HBV surface antigen. Few days following the start of the prodromal disease, jaundice starts to appear along with dark urine. This is called the hepatitis B icteric phase and can continue for up to two weeks. Within this phase, concentrations of the viral DNA start to gradually decline. The last phase, also called the convalescence phase, shows resolution of jaundice, but other symptoms (like fever and fatigue) could remain for few months. In the convalescence phase, the virus cannot be detected in the blood, and the surface antigen levels start to disappear **[6]**.

In rare occasions, less than one percent of infected

patients, fulminant liver cell failure could occur. In this case, patients will show sudden development of severe abdominal pain, fever, jaundice, and vomiting. This will be usually followed by altered mental status, disorientation, and finally, coma. In these occasions, viral load and surface antigen levels decline significantly and are usually negative when the patient develops coma. These patients must be strictly observed and monitored with proper management until they get liver transplantation **[7]**.

Chronic Hepatitis B

The course of chronic disease in HBV has many variations, depending on the patient and other factors. Generally, we can divide this course into 5 phases. However, not all the patients will necessarily develop the all five phases. Moreover, the severity and duration of each phase can differ among patients. All this make the management of patients with chronic hepatitis B infection challenging **[8]**. We will here summarize these five phases:

- **Phase 1: immune tolerant phase**
  This phase is considered to be the initial phase following HVB infection. It is characterized by tolerance of the host's immune system despite the presence of active replication of the virus. Due to the absence of an active immune response, serum liver enzymes levels and hepatocytes are often unchanged. However, HBe antigen, HBV surface antigen, and DNA of the virus are released to the serum during active replication, and are, thus, detected. The only immune response that is usually detected during this phase is thee production of antibodies against the HBV core antigen. However, these antibodies are not effective in neutralizing the infection **[9]**.

- **Phase 2: HBeAg-positive CHB (immune reactive phase)**
  This is the phase when the host starts to express an immune response against the hepatocytes that are infected by the HBV virus. In this phase, liver enzymes levels, ALT specifically, start to elevate in the blood. The elevation in ALT levels increases proportionally with the severity of the response, and damage to hepatocytes. Ultrasound in this phase will show visible active hepatitis, as biopsy will **[9]**. Due to the immune response in this phase, replication of HBV reduces, but still continues. The body starts to clear HBV surface antigen and HBV e antigen, at a rate of 10% and 0.5% annually, respectively **[10]**.
  The immune response in this phase against HBV is usually episodic, and causes sudden significant elevations in the levels of ALT, and anti-HBc antibodies, making it similar to acute infection. During this phase, active hepatitis occurs, which could possibly cause liver cirrhosis, decompensated liver failure, and/or hepatocellular carcinoma **[9]**.
  When the immune system succeeds in clearing HBe antigens, the patient will move to the next phase, which is called 'the low replicative phase'. However, infections could later be reactivated, converting patients to the second phase again **[9; 11]**.

- **Phase 3: low replicative phase**
  In this phase, patients will show minimal replication of the virus, and will have undetectable levels of the virus DNA in their serum. Despite having negative HBe antigens, HBV surface antigens remain positive during this phase. In the past, this phase was used to be called 'Inactive Carrier State'. However, this term is scientifically wrong and misleading, as the virus still carries a risk of reactivation and conversion into an active hepatitis. In fact, it is estimated that up to 10% of patients who reach this phase, will show reactivation of the virus again **[12]**.

- **Phase 4: HBeAg-negative CHB**
  This phase occurs as a result of an infection with an HBV variant that cannot produce the HBe antigen, resulting in a state of being HBeAG negative. This failure of HBe antigens production results from mutations to the core protein of the virus, that affects the production of HBe antigen, but does not affect active replication **[12]**.

- **Phase 5: HBsAg-negative phase**
  This phase represents the clearance of the virus, which becomes undetectable, despite having minimal replication of the HBV virus **[13]**. This phase is correlated with improvements in clinical picture and prognosis, with significant decline in liver complications. However, patients in this phase still have a minimal risk of reactivation of the virus if they develop an immunodeficient state **[14]**.

Prognosis and survival of chronic hepatitis B disease are strongly correlated with the severity of the disease itself. For example, the five-year survival of patients with chronic hepatitis complicated by cirrhosis is about 50% **[15]**. On the other hand, patients with chronic uncomplicated (or

asymptomatic) hepatitis have a significantly better survival. These patients are usually asymptomatic or show minimal symptoms (like fatigue or mild pain), and the only evidence of hepatitis in them are the elevated liver functions and the fibrosed or inflamed hepatocytes on biopsy. In more severe cases, patients could develop symptoms that range from jaundice, to liver cell failure. These patients typically show the stigmata of liver failure which include fetor hepaticus, spider angiomata, splenomegaly, palmar erythema, and gynecomastia. As the disease progresses and becomes more severe, patients will develop ascites, encephalopathy, bleeding, and peripheral edema. In these cases, the elevations of AST and ALT levels are less than acute cases and are not correlated with the severity of the disease. Laboratory investigations show abnormal albumin levels, bilirubin levels, and prothrombin time. Patients who show a significant decline in platelets count generally have the worst prognosis **[16]**.

Acute exacerbations of the disease can occur in patients who have chronic hepatitis. These are usually associated with a dramatic increase in ALT levels in the serum. Patients in the 'HBeAg-negative chronic hepatitis' are more likely to develop exacerbation. IgM antibodies against HB core antigens are usually useful markers that help distinguish between an exacerbated chronic hepatitis, and an acute hepatitis. On the other hand, in cases of suspected hepatocellular carcinoma, alpha-fetoprotein marker could be tested **[17]**.

It is estimated that about 33% of patients who have a chronic HBV disease will eventually develop a permeant liver damage like cirrhosis, hepatocellular carcinoma, or end-stage liver cell failure. These outcomes generally depend on the viral load, and characteristics of the host (age, immune status, gender) **[17]**.

Extrahepatic Manifestations of Hepatitis B

It has been reported that up to 10% of patients who get an HBV infection will suffer from systemic manifestations. These manifestations could be polyarteritis nodosa, serum-sickness–like syndrome, Gianotti-Crosti syndrome, and membranous glomerulonephritis. The underlying mechanism behind the development of these disorders in HBV patients is still debatable. Many suggest that the cause is related to immune complexes that cause the injury to different body organs **[18]**.

Serum-sickness–like syndrome usually develops in HBV patients in the stage of acute hepatitis, and before the development of jaundice. This syndrome will manifests as skin rash, polyarteritis, and fever. As soon as jaundice starts to appear, symptoms of serum-sickness–like syndrome will most likely disappear. However, in some patients they can persist throughout the whole acute hepatitis stage. The name of this syndrome comes from the similarity between it and experimental serum sickness, in both the clinical picture and the mechanisms; patients who develop this syndrome show low levels of complements and high levels of immune complexes in their blood **[19]**.

Studies have found that up to half of patients with polyarteritis nodosa are HBV positive, and more likely to have had a recent exposure to HBV. Patients with polyarteritis nodosa will suffer from vascular injury in small, medium, and large vessels. polyarteritis nodosa manifests as anemia, leukocytosis, and fever. Later, the disease will involve different systems in the body leading to the possible development of pericarditis, congestive heart failure, arthritis, hypertension, abdominal pain and bleeding, proteinuria and hematuria, mononeuritis multiplex and central nervous system abnormalities. polyarteritis nodosa is known to have wide variation between different patients. Unfortunately, it has a 5-year mortality rate of 30% when left untreated **[20]**.

Children are more commonly affected by HBV-associated nephropathy than adults. The most common form of HBV-associated nephropathy is Membranous glomerulonephritis. Most of these patients develop renal disease without showing any manifestations of liver disease. About have children with HBV-associated nephropathy will usually recover spontaneously without any intervention. However, when it comes to adults, HBV-associated nephropathy can have a 30% risk of developing into end-stage renal disease that nay require transplant or dialysis **[21]**.

Other syndromes have been suggested to be associated with HBV infection include essential mixed cryoglobulinemia and aplastic anemia. However, this issue is still debatable with no sloid evidence supporting their strong association with the virus **[19]**.

Occult or Latent HBV Infection

This group of the disease describes patients who test positive for the HBV virus DNA, but negative for the HBV surface antigens. These patients will usually test negative for most remaining markers of HBV, with some of them testing positive for antibodies against HBV surface antigen or core antigen **[22]**.

This group of patients can have an underlying

hepatitis. In fact, animal studies have suggested that the long-term presence of the genetic material of the HBV virus can lead to the development hepatocellular injury **[23]**.

Management

Treatment against HBV aims mainly at clearing the serum from the DNA of the virus, to avoid developing cirrhosis, and end-stage liver disease. Secondary objectives of the treatment include clearing the serum from HBV surface antigens and core antigens **[24]**. Usually, treatment should be administrated for a relatively long period to be able to achieve this state of undetectable virus DNA and maintain it, which is called 'sustained virologic response'. It is impossible to achieve total eradication of the virus as the viral DNA persists within the hepatocytes of the host **[25]**.

Patients who have either HBeAG positive or negative chronic hepatitis are eligible for treatment. In addition, patients who show signs and symptoms of cirrhosis are also eligible for treatment. On the other hand, patients who are still in the first phase of infection, and patients who do not show signs of liver cell injury are not eligible for treatment. In cases where the physician is not able to accurately determine the phase of the infection, a biopsy of the liver could be useful. Otherwise, both physicians and patients usually tend to avoid getting a biopsy due to its invasive nature. Recent laboratory investigations like transient elastography have also been used to replace the need for biopsy **[24]**.

Seven types of drugs are currently available and used in treatment protocols against chronic hepatitis B infection. These drugs are **[25]**:

1. Nucleos(t)ides analogues (NUCs):
   This group contain five of the drugs used against HBV which are: lamivudine, adefovir, entecavir, tenofovir and telbivudine.
2. Interferons:
   This group contains two of the drugs used against HBV, which are: conventional interferon and pegylated interferon alpha.

Nucleos(t)ides analogues act by inhibiting the replication of the virus by suppressing the polymerase of the virus. On the other hand, interferons act by stimulating the immune response of the host against the virus **[25]**.

Nucleos(t)ides analogues therapy:

Nucleos(t)ides analogues therapy has a relatively safe profile. However, they still carry a risk of viral resistance with long term treatment **[9]**. Clinical trials on lamivudine has concluded that its use in long-term treatment was efficient in reducing the risk of developing cirrhosis and hepatocellular carcinoma. However, no solid evidence is present on the long term effects of other Nucleos(t)ides analogues **[26]**.

The most recent guidelines by EASL recommend initiating monotherapy with tenofovir or entecavir, as these two have been found to achieve the best efficacy in achieving sustained viral resistance. Moreover, they are safer than lamivudine, and have less rates of adverse events **[27]**. When considering patients who are receiving immunosuppressive therapy, the use of lamivudine could be beneficial in preventing the reactivation of the virus **[28]**. Patients who show manifestations of viral resistance against treatment could benefit from the use of adefovir **[28]**. The use if Telbivudine, on the other hand, is not recommended as it has been found to be associated with high rates of viral resistance **[27]**.

Interferon therapy:

Interferons therapy are known to cause no viral resistance, which is considered their main advantage. Other advantages include the shorter treatment duration, and the higher rates of HBV antigens clearance and achievements of sustained viral response **[28]**. In fact, long-term trials have concluded that the use on interferons will lead to significant decline in cirrhosis and hepatocellular carcinoma risk **[26]**.

However, interferons are associated with many side effects that range from mild to severe, making NUCs preferable. Moreover, they can only be administrated through injections, and are not recommended to be use in patients with decompensated liver failure. Patients who are more likely to benefit from interferons therapy are young patients with less hepatitis-related complications **[9; 13]**.

Treatment in children

Regardless of age, treatment must be started immediately when the immune system starts responding against the virus **[10]**. From drugs that are used for HBV treatment, only lamivudine, adefovir, and interferons have been approved to be used in children. No data is present on the use of other drugs in patients younger than 15 years **[10]**.

Pregnancy

Interferons are generally contraindicated in pregnant women. Most recent guidelines suggest the treatment against HBV in pregnant women when they reach the third trimester, aiming at the reduction of vertical

transmission rates **[27]**. Following delivery, infected women have a relatively high rate of developing exacerbation of hepatitis, which makes it necessary to strictly monitor these patients **[29]**.

Treatment of acute HBV:

Acute hepatitis B is usually managed conservatively with symptomatic treatment only. Some studies have suggested that acute hepatitis B complicated by fulminant liver failure could benefit from the use of NUC therapy **[27]**.

Prevention

Vaccination

HBV vaccines are generally administrated three times to achieve sufficient immune response in the patient. the efficacy of the vaccine varies among individuals and is highest in infants and young adults, and lowest in individuals older than 60 years. The presence of liver disease, kidney disease, smoking status, obesity, or immunosuppression, has been found to cause significant decline in the efficacy of the vaccine **[30]**.

Post-exposure prophylaxis

Post-exposure prophylaxis (PEP) is usually achieved using either vaccination alone, or vaccination along with HBV immunoglobulins (passive vaccination) and has been found to effectively prevent the occurrence of an HBV infection. The most important factor in determining the efficacy of Post-exposure prophylaxis is the time of administration, which should start as soon as possible **[30]**

CONCLUSION:

HBV is considered a serious infection that is associated with severe long-term complications that could be as serious as liver cirrhosis and hepatocellular carcinoma. Many advances have been achieved lately in the understanding of chronic HBV infection and its pathophysiology. The best measurement to improve outcomes and decrease the burden of HBV is proper prevention of the disease using vaccination, especially in health care providers who have a higher risk of getting an infection. Antiviral agents have been developing and been found to significantly decrease long-term complications of HBV.

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