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HEPATITIS TYPE B PATHOPHYSIOLOGY AND MANAGEMENT

Nada Fahad M ALSultan [1] , Abdullah Dughailib A Alotaibi [2] , Nader Awad Alanazi [3] , Fatimah Hussain Altarouti [4] , Abdulsalam Jawwad Al Hassan [5] , Abdulrahman salah Almas [6] , Sarah Abdulaziz Nagadi [7] , Manal Mahmood Alsalmi [8] , Basil Abdalruhman Alfarrah [9] , Nameer Mohammed A Alshinqeeti [8] , Razaz Matok Gassas [8]

[1]Prince Sultan Cardiac Center, [2]King Fahad Hospital University, [3]Imam Muhammad Ibn Saud Islamic University, [4]King Khalid University, [5]Poznan University of Medical Science, [6]King Faisal University, [7]King Abdulaziz University, [8]Ibn Sina National College For Medical Studies, [9]Almaarifa University.

Abstract:

Introduction: *Chronic infection with hepatitis B virus (HBV) estimated to affect more than four hundred million people globally, involving around one million in the US. Those who get chronic hepatitis B die, on average, twenty two years earlier in comparison to those without HBV1 due to the serious complications of cirrhosis, hepatocellular carcinoma, and liver failure. The effect of HBV is expected to expand in the face of immigration patterns into the US from highly endemic nations. In spite of the approval of many anti-viral medications, few patients are on treatment. There are several reasons behind this, involving the requirement for lifelong treatment, education and awareness of the disease in largely immigrant, non-English-speaking groups, under screening for the condition in primary care settings, and concerns regarding the requirement for liver biopsies to decide on the need for treatment in many patients. Guidelines for hepatitis B treatment have variable suggestions for the management of some phases of the disease, which can lead to confusion for practitioners.*

Aim of work: *In this review, we will discuss Hepatitis type B Pathophysiology and management*

Methodology: *We did a systematic search Hepatitis type B Pathophysiology and management using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.****Conclusions:*** *Chronic infection with HBV continue to be a critical public health problem. management of hepatitis B is indicated in immune active patients, in those with cirrhosis or fulminant hepatitis B, in prevention of reactivation in HBV carriers who need immunosuppressive or cytotoxic therapies, in pregnant others with high viral load, and in HIV/HBV coinfection. Many of the excellent anti-viral agents that are available require indefinite treatment; so, efforts are being conducted to approaches to improve functional cure rates and permit cessation of therapy. A true virologic cure for HBV is much more elusive, opposite to HCV, because of its highly stable latent form (HBV cccDNA). But, a rich array of viral and host targets is being explored for manipulation. It is probable that a multimodality approach will be important for the achievement of a functional and virologic cure.*

Key words: *Hepatitis type B, Pathophysiology, presentation, management.*

Corresponding author:
Nada Fahad M ALSultan,
Prince Sultan Cardiac Center.

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INTRODUCTION:

Chronic infection with hepatitis B virus (HBV) estimated to affect more than four hundred million people globally, involving around one million in the US. Those who get chronic hepatitis B die, on average, twenty-two years earlier in comparison to those without HBV1 due to the serious complications of cirrhosis, hepatocellular carcinoma, and liver failure. The effect of HBV is expected to expand in the face of immigration patterns into the US from highly endemic nations.

In spite of the approval of many anti-viral medications, few patients are on treatment. [1] There are several reasons behind this, involving the requirement for lifelong treatment, education and awareness of the disease in largely immigrant, non-English-speaking groups, under screening for the condition in primary care settings, and concerns regarding the requirement for liver biopsies to decide on the need for treatment in many patients. Guidelines for hepatitis B treatment have variable suggestions for the management of some phases of the disease, [2] which can lead to confusion for practitioners. [3]

In this review, we will discuss the most recent evidence regarding Hepatitis type B Pathophysiology and management

METHODOLOGY:

We did a systematic search Hepatitis type B Pathophysiology and management using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Hepatitis type B, Pathophysiology, presentation, management

The viral life cycle.

Hepatitis B virus (HBV), a hepadnavirus, is considered a partially double-stranded DNA virus, made of a nucleocapsid core (HBcAg), encircled by an outer envelope containing the surface antigen (HBsAg). The viral DNA has 4 main open reading frames:

1. The precore/core gene. It codes for the nucleocapsid protein and the precore protein.
2. The polymerase gene, which codes for the reverse transcriptase/ HBV polymerase.
3. The PreS1/L, PreS2/M, and Surface/S genes, which codes for the three envelope proteins.
4. The X gene, which codes for the regulatory X protein.10

The life cycle of HBV is very complicated. The virus gets into the hepatocyte by binding to a receptor on the cell surface—the sodium taurocholate cotransporting polypeptide, a bile acid transporter. [4] Following uncoating of the viral nucleic acid, the viral genomic DNA is spread to the cell nucleus and the partially double-stranded viral DNA is then transformed into covalently closed circular DNA (cccDNA), a very stable intermediate that serves as a template for transcription of viral mRNAs, involving the pregenomic RNA. The pregenomic RNA has as template for translation of viral proteins, involving the surface antigen, nucleocapsid, and polymerase proteins. Together with the nucleocapsid and polymerase proteins, the HBV pregenomic RNA is encapsidated in the virus core particle. The first step is reverse transcription and first-strand cDNA synthesis, catalyzed by the HBV polymerase— the site of action of oral anti-HBV ucleoside/nucleotide analog (NA) medicaitons. [5]

The next step is second-strand DNA synthesis to produce a partially double-stranded viral DNA genome. The HBV polymerase do not have proofreading activity; thus, mutations of the viral genome are common and lead to the presence of genetically distinct viral types in infected individuals (quasispecies). Nucleocapsids associated with the partially double-stranded HBV DNA could either re-enter the hepatocyte nucleus to replenish the pool of cccDNA or be enveloped for secretion as complete virions via the endoplasmic reticulum. Following the budding into the ER lumen, the envelope proteins are secreted from the cell either as non-infectious subviral particles (HBsAg) or integrated into infectious virions known as Dane particles.

Who should be treated?

Immune-active, HBeAg− chronic hepatitis B. Patients with hepatitis B e antigen-negative chronic hepatitis B must be considered for treatment . For HBeAg− patients with lower HBV DNA levels and borderline normal or minimally elevated ALT levels, liver biopsy should be considered and treatment initiated if there is moderate/severe inflammation or significant fibrosis on biopsy. Many studies have concluded that cases with normal ALT could have substantial liver fibrosis, when ALT concentrations are at the high end of the normal range, HBV DNA concentrations are high, or when they are older than 40 years. [6] Treatment with TDF, ETV, or peg-IFN

are preferred.

Compensated cirrhosis. Management must be considered for cases with cirrhosis and detectable HBV DNA whatever ALT levels are. Patients with compensated cirrhosis are managed very well with NAs due to the risk of hepatic decompensation related to IFN-related flares of hepatitis. In view of the need for long-term therapy, TDF or ETV is preferred.

Decompensated cirrhosis. Management must be properly started with an NA that can produce rapid viral suppression with low risk of drug resistance. At the time of drafting of the last AASLD guidelines in 2009, data that study the safety and efficacy of TDF and ETV in patients with decompensated cirrhosis was very insufficient. Though multiple studies have confirmed safety and efficacy of these medications in this subgroup. [7] So, TDF and ETV are the medications of choice in decompensated cirrhotics with HBV. Management should be organized with a transplant center. IFN/peg-IFN should not be used in patients with decompensated cirrhosis.

In very severe acute HBV with long prothrombin time and increased bilirubin, interferon failed to be efficient, However NAs have been proven to be efficient. A clinical trial of eight 80 patients concluded that early treatment with LAM leads to a greater decrease in HBV DNA levels, better clinical improvement, and mortality improvement but with a lower HBsAg and HBeAg seroconversion rate. [8]

HBV can remain in the human body of all patients with infection, even in those patients with evidence of serological recovery. So, people with a history of HBV infection who receive immunosuppressive therapy are at higher risk for HBV reactivation and a flare of their HBV disease with resultant increased serum aminotransferase levels, fulminant hepatic failure, and possible death. [9]

Who should NOT be treated?

Patients who are in the immunetolerant state in whom HBV DNA levels are high, HBeAg is positive, and ALT levels are normal should not be started on anti-viral agents. Liver biopsy could be considered in patients with fluctuating or minimally elevated ALT levels, especially in those above forty years of age. Management should be started if there is moderate or severe necroinflammation or significant fibrosis on liver biopsy. But it should be known that there could be some benefits to managing patients in the immune-tolerant stage like lowering accumulation of cccDNA and abrogating infection early. Clinical trials are needed in this population to help address this question.

Additionally, patients in the inactive carrier state in whom both HBV DNA levels are very low or undetectable and ALT levels are normal should also not be started on antiviral medications, rather kept monitored on a biannual basis with ALT and HBV DNA levels, as well as with hepatocellular carcinoma screening in high-risk patients.

Eventually, those who are HBeAg− with an intermediate viral load and borderline normal or minimally elevated liver function tests should not be given medicaitons but should be considered for biopsy and managed if there is moderate or severe necroinflammation or significant fibrosis.

Combination therapy.

No additional advantage from de novo combination therapy with 2 NAs. Additionally, the combination of peg-IFN and NAs has not gained higher rates of off-treatment serological or virological responses and is not now advised by AASLD. But, a new clinical trial has concluded that a greater proportion of patients treated with TDF plus peg-IFN for 48 weeks had significantly HBsAg loss (less than ten percent) in comparison with those receiving TDF (zero percent) or peg-IFN alone (three percent) or a shorter course of peg-IFN (sixteen weeks) with forty eight weeks of TDF (three percent). [10] Though more studies are needed, consideration could be given to a combination approach to enhance HBsAg loss rates.

Duration of therapy.

In HBeAg+ chronic hepatitis B, management should continue till the patient turn to HBeAg seroconversion and undetectable levels of serum HBV DNA and completed at least 12 months of additional consolidation treatment after appearance of anti-HBe. The best duration of consolidation therapy after HBV seroconversion is not known, however new research reveal better results with longer duration of consolidation. [11]

Lifelong management is suggested for all patients with recurrent hepatitis B after liver transplantation and in all cirrhotics, both compensated and decompensated, many guidelines recommend peg-IFN for fifty weeks in both HBeAg+ and HBeAg− patients. Regardless of the underlying liver disease and the management utilized, patients need to be closely monitored for viral relapse and ALT flares

when medications are stopped, so that treatment can be reinitiated promptly. [12]

Vaccination is also suggested in travelers to regions with high or intermediate endemicity for HBV infection, patients with chronic liver disease, and with HIV infection. [13] Postexposure prophylaxis with the hepatitis B vaccine and/or hepatitis B immune globulin is also suggested for health-care providers who are not immune to HBV virus.

Vaccination in young is suggested as part of the regular schedule of childhood immunizations. 35 years after the availability of a safe and efficient vaccine, universal vaccination of all children is finally available now in 184 of 196 countries worldwide. Global vaccine coverage with all 3 doses of vaccine is estimated at eighty percent.82

How do we cure HBV?.

A functional cure for HBV has a very unique challenges given the stability and latency of cccDNA, along with the fact that replication of HBV DNA is uncoupled from protein (HBsAg) synthesis. Regarding this issue, polymerase inhibitors can bring about DNA suppression without the loss of HBsAg. As HBsAg can subvert the host immune response secretion, a positive functional cure for HBV (HBsAg loss, sAb seroconversion) will probably need a multipronged, multi mechanism approach, involving potential approaches to target both the virus and the host. [14]

Direct virologic methods consist of HBV capsid inhibitors, small interfering RNA targeted to viral mRNA, and cccDNA targeting strategies. The HBV capsid is polyfunctional, as it is critical for HBV genome packaging, reverse transcription, intracellular trafficking, maintenance of cccDNA, and inhibition of host innate immune responses. So, it is an attractive target for HBV therapies. Many capsid inhibitors being evaluated include NVR 3-778, GLS-4, and phenylpropenamide derivatives. [15]

Small interfering RNAs that work against conserved HBV RNA sequences can also break down HBV RNA, proteins, and DNA levels. the HBV small influencing RNA ARC-520 is being assessed in a phase 2 trial. cccDNA targeting strategies include prevention of cccDNA formation (e.g., disubstituted sulfonamide DSS), elimination of cccDNA by inhibition of viral or cellular factors contributing to cccDNA stability/formation (e.g., APOBEC3A, B agonists) or physical elimination of cccDNA, and silencing of cccDNA transcription. [16-17]

Indirect acting host target inhibitors involve entry inhibitors, epigenetic modifiers (sirtuin inhibitors such as sirtinol), morphogenesis inhibitors (glucosidase inhibitors), and secretion inhibitors (Rep 9AC). A new promising target is the inhibition of the sodium taurocholate cotransporting polypeptide receptor. Immunomodulatory methods involve attacking innate and adaptive immune responses. Innate targets include IFN-α, TLR7 agonists, and STING agonists. [18]

CONCLUSIONS:

Chronic infection with HBV continues to be a critical public health problem. management of hepatitis B is indicated in immune active patients, in those with cirrhosis or fulminant hepatitis B, in prevention of reactivation in HBV carriers who need immunosuppressive or cytotoxic therapies, in pregnant others with high viral load, and in HIV/HBV coinfection. Many of the excellent anti-viral agents that are available require indefinite treatment; so, efforts are being conducted to approaches to improve functional cure rates and permit cessation of therapy. A true virologic cure for HBV is much more elusive, opposite to HCV, because of its highly stable latent form (HBV cccDNA). But, a rich array of viral and host targets is being explored for manipulation. It is probable that a multimodality approach will be important for the achievement of a functional and virologic cure.

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