Prevention and Management of Chronic Hepatitis B

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Review Article

ABSTRACT

Chronic hepatitis B virus (HBV) infection affects an estimated 370 million people worldwide. HBV is endemic throughout the world, and insidiously causes liver damage over years and decades without any warning symptoms or signs. Up to 25–35% of infected individuals eventually die due to complications of liver cirrhosis and hepatocellular carcinoma (HCC) induced by HBV. Screening those individuals at risk of acquiring hepatitis B, and universal vaccination for prevention, would help in limiting the spread and public health repercussions of the virus. Although many new antiviral therapies have been developed for the management of hepatitis B, they still do not offer the possibility of cure. Most individuals who begin oral suppressive therapy will be indefinitely treated. Continuous suppression of HBV replication in individuals with advanced liver disease prolongs life, decreases the need for liver transplantation, and potentially reduces the risk for HCC. In this clinical review, we present a practical approach to prevention of HBV, its natural history and life cycle, as well as its management.

Keywords: Antiviral treatment, diagnosis, hepatitis B, prevention

INTRODUCTION

Chronic hepatitis B virus (HBV) infection affects an estimated 370 million people worldwide.[1] [Figure 1].[2] Chronic hepatitis B insidiously causes liver damage over years and decades without any warning symptoms or signs. Up to 25–35% of infected individuals eventually die due to liver failure and hepatocellular carcinoma (HCC) induced by HBV.[3] Screening those individuals at risk of acquiring hepatitis B, and universal vaccination for prevention of acquisition, would help in limiting the spread and public health repercussions of the virus,[4] especially in countries where this virus is more prevalent.[5-8]

Although many new antiviral therapies have been developed for the management of hepatitis B, they still do not offer the possibility of cure. When starting treatment for HBV, it is important to evaluate the potential benefits of therapy in the context of risk, side effects, resistance development and cost, most individuals who begin oral suppressive therapy will be indefinitely treated. Continuous suppression of HBV replication in asymptomatic individuals with advanced liver disease prolongs

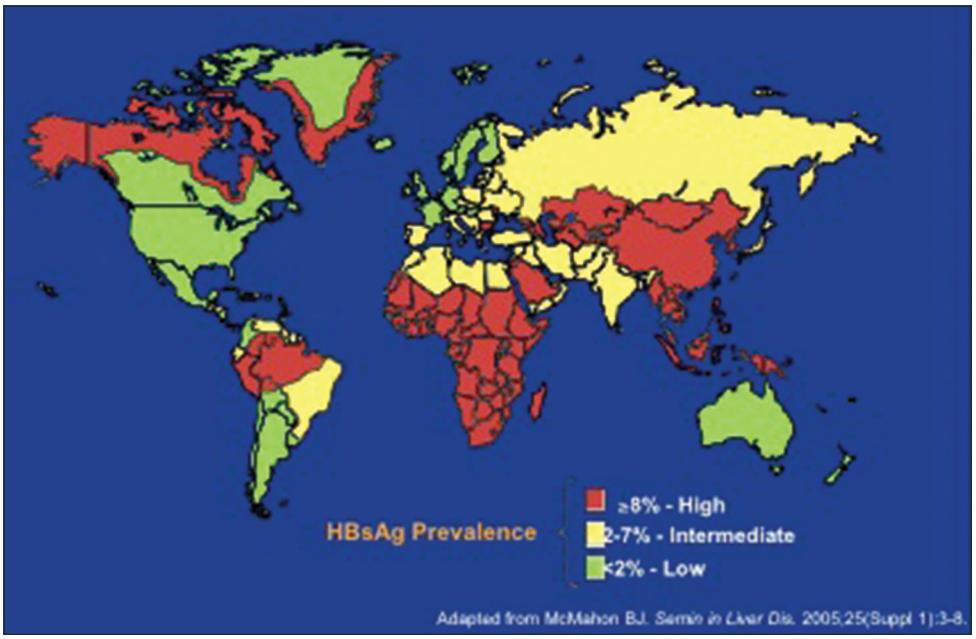

Figure 1: Worldwide prevalence of hepatitis B

life,[9] decreases need for liver transplantation,[10] and potentially reduces the risk for HCC.[11,12]

In this clinical review, we present a practical approach to prevention of and screening for HBV, the natural history of HBV, as well as its management.

SCREENING FOR HEPATITIS B

Areas of the world with low-prevalence of HBV carriers (0.1–2% of the population) include Canada, the United States, Western Europe, Australia and New Zealand.[13] Areas of the world with the highest prevalence (10–20%) include Southeast Asia, China and sub-Saharan Africa.[14] This large variation in carrier rates can be explained by differences in the routes of transmission and age of infection. In low-prevalence areas, infection is mainly acquired in adulthood through sexual and parenteral exposure, resulting in a low risk of chronicity (5–10%). In areas of higher prevalence, infection also takes place through intra-familial spread in the perinatal period (90%) or in childhood (20%), resulting in a high risk of chronicity.[15,16]

Hepatitis B virus transmission is associated with increasing viral loads and is more infectious than either hepatitis C or HIV, with a transmission rate of up to 30% being reported. HBV exposure can occur in the following situations: Sexual contact (partner infected with HBV, multiple sexual partners, men who have sex with men), parenteral contact (injection drug users, hemodialysis, healthcare workers), household contact (infected parents/siblings, shared personal hygiene items like toothbrushes, razor blades, nail clippers).[17-21] These select populations should be routinely screened by testing for hepatitis B surface antigen (HBsAg), antibody against hepatitis B surface antigen (anti-HBs), and antibody against hepatitis B core antigen (anti-HBc). Anti-HBs antibodies, present as a vestige of exposure to previous HBV infection or induced through vaccination, protect against the establishment of infection by binding and neutralizing the virus before it can infect the liver.[22,23] Those negative for all three markers are at risk for HBV infection and should be vaccinated if they remain at high risk of exposure. Those who are positive for anti-HBs alone were likely vaccinated in the past and are still immune. Those positive for anti-HBc and anti-HBs have already been exposed to HBV in the past and, therefore, do not require vaccination.[24,25]

NATURAL HISTORY

Acute HBV infection is clinically symptomatic in only 30% (icteric hepatitis), whereas the other 70% have subclinical or anicteric hepatitis. The

incubation period lasts between 1 and 4 months, and may be followed by a serum sickness-like syndrome with associated jaundice, right upper quadrant pain, nausea and anorexia.[26] Those with underlying liver disease are more likely to be symptomatic during acute HBV infection.[27] While 95% of immune-competent adults can clear the infection within 6 months of exposure, the other 5% go on to develop life-long chronic infection.[28] Varying degrees of immune control can be achieved through a combination of virus-specific T-cell responses and neutralizing antibodies from virus-specific B-cell responses.[29] Acute HBV infection is treated symptomatically, as pharmacotherapy has not been effective in either decreasing the risk of chronic infection or the 1% risk of fulminant hepatic failure.[30]

There is a dynamic relationship between the HBV and the immune response in chronic HBV infection. To date, four phases have been described: Immune tolerance, immune clearance (hepatitis B e-antigen [HBeAg]-positive hepatitis B), inactive carrier, and reactivation (HBeAg-negative chronic hepatitis B). The various associated serologic, virologic and biochemical parameters are summarized in Table 1.

The immune tolerance phase is usually found in younger individuals under the age of 30.[31] The immune system does not recognize or clear the HBV and viral loads are extremely high (often >8 logs IU/mL). Serum alanine transaminase (ALT)/aspartate transaminase (AST) levels remain normal and with the lack of immune damage the liver is normal-appearing on biopsy.[32] HBeAg, a viral protein, is detectable at high titers at this stage. Antiviral therapy may help bring the viral load down to these individuals, but these young people are at low risk of developing complications During this phase of the disease, antiviral therapy is not usually offered unless there are special circumstances (i.e. 3rd trimester of pregnancy).[33]

The immune system starts to recognize the HBV as foreign around age 20–30 years. It is unclear what triggers this transition in the immune system. This phase of immune clearance can be as short as a few months, to as long as years or even decades. The immune system attempts to suppress the virus, with the viral load decreasing to between 10^3 and 10^8 IU/mL (1 thousand to 100 million IU/mL). Hepatocytes harboring HBV and those in the surrounding hepatic parenchyma are damaged in this immune attack, leading to the clinical observation of hepatitis.[34] Patients will have elevated serum ALT/AST levels and evidence of inflammation on liver biopsy. Antiviral therapy at this stage may help prevent significant liver injury, especially if ALT/AST levels are very high or if this phase is prolonged over several years.[35]

Successful immune control of HBV leads to the inactive carrier state. The viral load is suppressed to $<10^3$ IU/mL, HBeAg is negative and there is no further damage to the liver. However, the virus does persist within the hepatocyte and can reactivate if the immune system is weakened later on in life. Reactivation may occur in the setting of immune suppression, such as chemotherapy, use of biological agents for rheumatoid arthritis or Crohn's disease (anti-tumor necrosis factor agents), transplantation, and even high-dose steroid boluses.[36,37] Patients in this phase may already have developed cirrhosis during the preceding viral phases and have normal ALT despite this. Antiviral therapy is not indicated at this stage, given that HBV is not replicating.

The phase of reactivation is known as the HBeAg-negative chronic hepatitis. These individuals have lost HBeAg due to a newly-acquired mutation in HBeAg.[38,39] HBV DNA levels may

Table 1: Interpretation of hepatitis B serology and liver enzymes

Phase	HBsAg	HBeAg	Anti-HBe	ALT pattern	HBV DNA range
Immune tolerant	Positive	Positive	Negative	Normal	$>10^8$ IU/mL
Immune clearance	Positive	Positive	Negative	Normal or elevated	$>2\times10^4$–2×10^5 IU/mL
Inactive disease	Positive	Negative	Positive	Normal	<200 IU/mL
HBeAg-negative chronic hepatitis B	Positive	Negative	Positive	Normal or elevated	Undetectable to $>2\times10^8$ IU/mL
HBsAg negative phase	Negative	Negative	Positive	Normal	Undetectable

Adapted from Sherman, *et al.* Management of chronic hepatitis B: consensus guidelines. Can J Gastroenterol 2007;21:5C-24. HBV=Hepatitis B virus, ALT=Alanine aminotransferase, HBsAg=Hepatitis B surface antigen, HBeAg=Hepatitis B e-antigen

vary between 10^3 and 10^8 IU/mL, with associated increases in ALT/AST and liver injury. Antiviral therapy can suppress HBV in order to prevent continuing damage.[5]

The ultimate complications from hepatitis B include cirrhosis, liver failure, and HCC. Liver failure is much more likely to occur in the setting of advanced liver fibrosis or cirrhosis, although this has become less common in this age of effective antiviral therapy.[40,41] Both cirrhotic and noncirrhotic patients with chronic HBV can develop HCC, which is the third leading cause of cancer death worldwide has a median 5-year survival of 8.9%. Long-term survival is possible if liver masses are detected early when they are small. Therefore, screening ultrasounds are performed every 6 months in those at risk [Table 2].[42] The risk of HCC increases with age and with liver fibrosis.[43] In general, anyone with cirrhosis should be screened for liver cancer. The role of alpha fetoprotein in HCC screening is controversial, given its poor sensitivity and specificity. It can be elevated during active hepatitis and pregnancy (false positive), and low in patients with already diagnosed HCC.[44]

A PRACTICAL APPROACH TO HEPATITIS B

A number of variables need to be considered in the approach to hepatitis B management. Serum ALT/AST elevation can occur due to various causes of liver disease, including HBV, hepatitis C, fatty liver, autoimmune hepatitis, idiosyncratic drug reactions, etc., If HBsAg is positive in this context, the elevated transaminases are most likely due to HBV, especially if the viral load is over 10^3 IU/mL. If the HBV viral load is below this level, the clinician should consider that there is an alternate etiology for the elevated liver enzymes.

A positive HBsAg with normal transaminases indicate that the patient is probably immune-tolerant (especially if younger than 30 with a high viral load) or an inactive carrier (viral load $<10^3$). A practical approach to management of Hepatitis B is summarized in Figure 2.

Table 2: Screening for hepatocellular carcinoma in at-risk hepatitis B patients

All patients with cirrhosis
Other HBV-infected individuals
Africans older than 20 years
Asians older than 30-35 years (if infected in childhood)
Asian men older than 40 years
Asian women older than 50 years
Patients with a family history of hepatoma
Patients with active inflammation on liver biopsy
Patients awaiting liver transplantation

Adapted from Sherman, *et al*. Management of chronic hepatitis B: consensus guidelines. Can J Gastroenterol 2007;21:5C-24. HBV=Hepatitis B virus

PREVENTIVE MEASURES

Vaccination for hepatitis B has been available since 1982, which has effectively reduced the incidence of acute viral hepatitis B.[45] There has in turn been a decline in the sequelae of chronic hepatitis B, and a dramatic decrease in hepatitis D infections given its replicative dependence on HBV machinery. Currently, universal immunization of children is being practiced in countries around the world. In the adult population, physicians should identify those patients at high risk (as delineated above), screen and vaccinate them if anti-HBs is negative.

Pregnant women with active HBV replication should commence antiviral therapy during the 3rd trimester in order to prevent vertical transmission. The baby should be administered hepatitis B immunoglobulin and vaccinated at birth to prevent the establishment of infection. Recent evidence points to likely father-to-child transmission of HBV, making the case for universal vaccination.[3]

With respect to patients with established chronic liver disease, both hepatitis A and B vaccination are advised unless they are already immune.[46] The immunogenicity of the 3-dose HBV vaccine is decreased in all chronic liver diseases except for fatty liver and in liver transplant patients.[47] The pneumococcal vaccine is also strongly recommended, given evidence of heightened risk of pneumococcal infection particularly among patients with advanced liver disease, although the efficacy of vaccination is somewhat decreased in this population,[48] The influenza vaccine should be administered to any patient with a high-risk medical condition, including chronic liver disease and postliver transplant.[49-51]

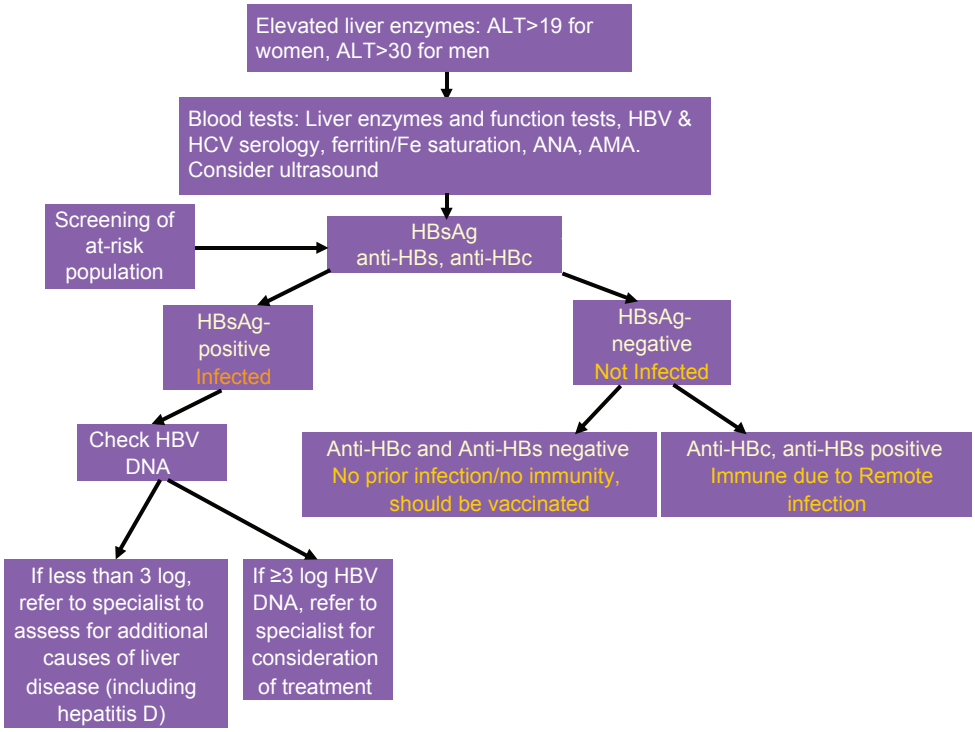

Figure 2: Approach to management of hepatitis B

DECISION TO TREAT

Antiviral therapy is considered for patients in the chronic HBeAg-positive and chronic HBeAg-negative phases (the second and fourth phases of HBV infection), which are characterized by abnormal ALT/AST levels and viral loads persistently over 1×10^3 IU/mL. However, clinical judgment should be used to determine the need for antiviral therapy. For example, a patient in the immune clearance phase may successfully control hepatitis B and transition to the inactive phase within the next few months, thereby not requiring antiviral therapy. However, another patient in the immune clearance phase with very high ALT levels is likely sustaining heavy liver damage, and is a candidate for antiviral therapy.

PHARMACOTHERAPY

Hepatitis B may be treated using two different approaches: Immune modulation and viral suppression.[52] Interferon is the only example of an immune modulator in HBV therapy, as it can induce entry into the inactive carrier phase, thereby effectively controlling HBV. Interferon therapy results in the loss of HBeAg, detection of anti-HBe, sustained low to undetectable HBV viral load and normalization of ALT levels occurs in 20–30% of patients. This successful treatment outcome is associated with decreased risk of fibrosis progression and HCC, as well as increased survival.[53,54] Interferon therapy involves regular injections with many side effects, particularly flu-like symptoms, and therefore not well tolerated. Successful treatment may be associated with an increase in ALT levels. Interferon has been used successfully even in patients with advanced liver fibrosis, but is contra-indicated in decompensated cirrhosis (i.e. those who have ascites, hepatic encephalopathy, variceal bleeding, jaundice).[55] However, interferon is still an option for younger patients given its higher efficacy.[56] Patients may also avoid the need for life-long treatment with potentially teratogenic antivirals during the reproductive age.[57]

Nucleoside or nucleotide analogue antivirals are used in the viral suppression approach to HBV therapy. These medications have daily oral dosing and minimal side effects, which makes them an attractive therapeutic option. Given that these agents are cleared by the kidneys, their dosage must be decreased in the context of a glomerular filtration rate below 50 mL/min. The virus relapses in most patients if therapy is stopped,[58] which

means that it must be continued for years (perhaps even life-long). However, life-long use is rendered difficult by the high cost of medications, issues with compliance and potential teratogenicity for those patients of childbearing age. First-line therapy currently includes tenofovir, telbivudine, entecavir and emcitrabine. Lamivudine is now a second-line medication, given the high risk of resistance over time. In general, drug-resistance mutations for one nucleoside analogue confer cross-resistance or significantly increased risk of resistance to all other nucleoside analogues.[59] These variants can fortunately still be successfully treated with the nucleotide analogues. Given the complex nature of hepatitis B treatment, the decision to start one agent versus another is the best left to an expert in liver diseases.

CONCLUSIONS

The understanding of the natural history and management of chronic HBV has come a long way over the last few decades. Prevention of acquisition through universal vaccination and screening for HBV in individuals at risk are the ideal public health strategies that have been put into place in many countries worldwide. There is a greater role for prevention of hepatic cirrhosis and HCC, given our ability to influence the natural history of HBV through antivirals. The above strategies will hopefully translate into improved clinical outcomes and lessen the economic impact of this chronic infectious disease.

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