



Review Article

Current Challenges in Hepatitis B

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Abstract

Viral hepatitis and its sequelae is one of the important causes of mortality and morbidity world wide. Hepatitis B is a major cause of chronic liver disease and a significant public health issue. Between 350 million to 400 million people world wide chronically infected with HBV. The HBV prevalence in Bangladesh is 2.3 to 9.7 % with an approximate carrier of 10 million. The prevention and treatment of hepatitis B possess a great challenge.

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Introduction

Viral hepatitis is the commonest liver disease in Bangladesh. About 10 million people in Bangladesh have been suffering from hepatitis B. A proportion of them are hepatitis B carrier and another proportion is affected by the long standing consequences of this infection. The treatment of hepatitis B possesses a great challenge. Innumerable authors working to find out cheap, effective, efficient & easily administered drug therapy for chronic hepatitis B.

Hepatitis B Virus

Hepatitis B virus (HBV) belongs to hepadnaviridae family which primarily infects liver cells. The HBV genome is a relaxed circular, partially double stranded DNA of approximately 3,200 base pairs¹. The infectious virion is a 42nm Dane particle composed of an envelop of HBsAg, and a 27 nm diameter nucleocapsid composed of HBcAg and containing the viral genome and a viral encoded DNA polymerase. The replication cycle of HBV begins with the attachment of the

virion to the hepatocyte. Inside the hepatocyte nucleus, synthesis of the plus strand HBV DNA is completed and the viral genome is converted into a covalently closed circular DNA (cccDNA). Based on the inter group divergence of 8% or more in the complete genome nucleotide sequence, HBV has been classified into at least 8 genotypes (A-H). Each genotype has its distinct geographical and ethnic distribution shown in table-I².

Table -I: Genotypes of HBV

Genotype	Geographic distribution
1. A	Northern Europe, Africa, United states
2. B and C	Asia
3. D	Southern Europe, Middle East
4. E	Africa
5. F and H	Central and South America
6. G	Africa
7. A,B,C and D	United States

Genotypes A and D occurs frequently in Africa, Europe and India while genotypes B and C are prevalent in Asia. A study from India indicated that genotype D more often associated with

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HBeAg negative chronic hepatitis B, more severe disease and may predict the occurrence of HCC in young patients³.

Transmission

HBV is 100 times more infective than human immunodeficiency virus (HIV). It is found in blood and body fluids and able to survive in dried blood for longer than 1 week. It can be transmitted by inoculation with contaminated blood or blood products, by sexual contact, by transplantation of organs from infected donors, by sharing contaminated needles, syringes, razors, blades, tooth brush etc. and perinatally from infected mothers. There is no evidence of viral transmission through breast milk⁴. In about one third cases, the underline mode of transmission is not known.

Scenario in Bangladesh

Hepatitis B is a major cause of chronic liver disease and a significant public health issue. Between 350 million to 400 million people world wide chronically infected with HBV⁵. The HBV prevalence in Bangladesh is 2.3 to 9.7 % with an approximate carrier of 10 million⁶. These include healthy adult population 4.4 to 9.7 %, healthy children 3%, school girls 2.3%, a rural community 6.4% and slum communities 3.8%. Perinatal or vertical transmission of HBV in Bangladesh is infrequent due to low HBeAg positivity rate (30.1%) among pregnant females with HBV infection.

Among the high risk population HBV carrier rate that varies widely such as professional blood donors 19.0 to 29.0%, family members of HBsAg carrier 20.6 %, health care workers 8.7%, parenteral drug abusers 6.2 to 12.0%, truck drivers 5.9%, commercial sex workers 9.7%, multiple units of blood recipients 13.8%. HBV is an important cause of liver disease in Bangladesh and is responsible for 19.0 to 35.0% of acute viral hepatitis, 35.7% of acute liver failure, 33.3 to 40.5% of chronic hepatitis and 46.8% of hepatocellular carcinoma⁷.

Incubation period

HBV usually occurs sporadically, has an incubation period varying from 4 weeks to 6 months and is mainly transmitted parenterally, sexually, and from mother to child at birth¹.

Symptoms of acute hepatitis

General symptoms may include lethargy, low grade fever with headache, minor gastrointestinal disturbances and less commonly, myalgias and arthralgias. Jaundice, pale stools and dark urine are also classically, though not universally, present in patients presenting with viral hepatitis. The patients may be asymptomatic. Even those who have a full clinical recovery may continue to experience fatigue, anxiety, failure to regain weight, anorexia, alcohol intolerance and right upper quadrant discomfort. Extra-hepatic manifestations include Gianotti-Crosti syndrome which is characterized by skin eruptions, lymph node enlargement and lymphadenitis which primarily affects young children¹.

Symptoms of chronic hepatitis

Patients with chronic HBV infection may experience an increase in non-specific symptoms (lethargy etc.) as their disease evolves from an asymptomatic carrier phase to an active hepatitis. This may be associated with right upper quadrant discomfort, high liver enzymes and jaundice and, in the most severe forms, present as acute/fulminant liver failure. Extra-hepatic manifestations include glomerulonephritis, polyarteritis nodosa and essential mixed cryoglobulinaemia which are due to immune complex deposition.

Natural history of chronic hepatitis B

Chronic HBV infection is most commonly defined as being present when a person tests positive for HBsAg for an at least six months⁸. The diagnosis of chronic hepatitis although suspected clinically by the continuation of non-specific symptoms, relies on either the persistence of elevated liver enzymes or activity on the liver biopsy in combination with serological markers¹. Three stages of chronic HBV infection were identified at the National Institute of Health Workshop on management of chronic hepatitis B 2000.

- i) The immune tolerant phase
- ii) The chronic hepatitis B phase

- iii) The inactive hepatitis B (or asymptomatic) carrier phase. (Table-II)⁸

Table-II. Definitions of stages of chronic HBV infection (National Institute of Health)

Stage.	HBeAg/Anti HBe	ALT	HBV DNA (copies/ml)	Liver histology
Immune tolerant	HBeAg	Normal	>10 ⁵	Normal or minimal inflammation
chronic hepatitis B	HBeAg or anti HBe	Elevated	>10 ⁵	chronic inflammation
Inactive hepatitis B	Anti HBe	Normal	<10 ⁵	Normal or minimal inflammation

Long-term outcomes of chronic hepatitis B

After acute HBV infection, chronicity develops in 90% of infants infected at birth, 30% of children infected at age 1-5 years and 6% of persons infected after age 5 years. It is estimated that about 15-20% of patients with chronic hepatitis B develop cirrhosis within 5 years⁹, and only 55-85% of those with active HBV related cirrhosis survive for more than 5 years¹⁰. More over, although all patients with chronic HBV infection are at higher risk for HCC when compared with the general population, the risk becomes much higher when cirrhosis develops¹¹. Thus, it is estimated that over 2,50,000 patients world-wide die annually from HBV related liver disease.^{12,13}

Diagnostic markers in HBV infection

(a) Acute HBV infection

- i) Biochemical markers : LFT - Serum bilirubin, Serum alanine aminotransferase (ALT), Serum aspartate aminotransferase (AST), Alkaline phosphatase, Gamma glutamyl transpeptidase (GGTP), Prothrombin time, Serum albumin,
- ii) Radiology - Ultrasonography of upper abdomen.
- iii) Serological markers- HBsAg, IgM anti HBc, HBeAg, Anti HBe, Anti HBs,
- iv) Virological markers - PCR, HBV DNA.
- v) Others - TC,DC,ESR,Hb%, platelet count.

(b) Chronic HBV infection

The diagnosis of chronic HBV infection typically is based on evaluation of serological and

virological markers of HBV infection in serum and biochemical and histological markers of liver disease.

i) Serological markers

HBsAg is the first serological marker to appear after infection. Its persistence for > 6 months indicates chronic HBV infection. Antibody to HBsAg (anti HBs) implies recovery and/or immunity to HBV. Anti HBs also is detectable after immunity conferred by hepatitis B vaccination. Occasionally, anti HBs and HBsAg are both detectable in patients with chronic infection. The presence of HBeAg indicates active replication of HBV. However, its absence cannot be assumed to equate to absent viral replication because HBeAg is not detectable in patients with HBeAg negative (precore or core promoter mutant) HBV infection. Loss of HBeAg and seroconversion to anti HBe usually are preceded by a marked decrease in serum HBV DNA levels to < 10⁵ copies/ml¹⁴ and typically are followed by normalization of ALT levels. HBeAg seroconversion (HBeAg loss and detection of anti HBe) generally has been considered the end point for HBV therapy for HBeAg positive patients because it has been associated with a lower risk for disease progression¹⁵, although not protective against the later development of HCC.

ii) Virological markers

The amount of HBV DNA in serum is a measure of the level of viral replication. The National Institutes of Health Workshop on management of hepatitis B recommended that treatment to be considered for patients with detectable HBV DNA by nonamplified assay (i.e., with serum HBV DNA > 10⁵ copies/ml)⁸. However, some HBeAg

positive patients and many HBeAg negative patients have fluctuating HBV DNA levels that decrease to $<10^5$ copies /ml.¹⁶ The current target amplification assays, such as polymerase chain reaction (PCR) assays, have a much lower limit of detection (as low as 100-1000 copies/ml). These assays becoming more widely available and are preferable in the initial evaluation of patients and even more importantly, monitoring of both treated and untreated patients.

iii) Biochemical markers

Elevated serum ALT levels (i.e. greater than the upper limit of the normal range) are an indicator of necroinflammatory activity. Moreover, patients with normal ALT levels tend to have a poor serological response to antiviral therapy and often are not considered for treatment. However, some patients with normal ALT levels and elevated HBV DNA levels have significant inflammation and fibrosis on biopsy¹⁷. In such cases, treatment may be indicated.

iv) Histological markers

Histological evaluation of liver biopsy specimen is a more sensitive and accurate indicator of liver disease than ALT level. It is useful to establish the base line status of liver histological characteristics at initial evaluation before initiation of therapy and exclude other causes of liver disease.

Management approaches

a) Acute hepatitis B

There are no specific treatments necessary for acute viral hepatitis. Many patients will feel thoroughly miserable and some supportive measures may need to be instituted for symptoms control, such as anti-emetics for nausea and vomiting and, for some, an intravenous infusion. Most patients can be managed at home, but for some, a short in-patient stay during the initial phase of illness may be necessary to ensure that the patient remains adequately hydrated and that symptoms are controlled¹.

b) Chronic hepatitis B

Currently there are five drugs approved by US Food and Drug Administration (USFDA) for the

treatment of chronic hepatitis B infection¹⁸. Two immunomodulatory agents (interferon- α and pegylated interferon) and three antiviral agents (Lamivudine, adefovir and entecavir). The other immunomodulatory agents named thymosin- α 1 has also been approved in more than 30 countries, mainly in Asia¹⁹.

IFN- α

The recommended IFN- α dose for adults is 5 MU daily or 10 MU thrice weekly by subcutaneous injections. A smaller dosage (5-6MU thrice weekly) has been used in Asian patients with similar efficacy^{20,21}. The recommended IFN- α dose for children is 6MU/m² thrice weekly a maximum of 10MU. The recommended treatment duration for HBeAg positive chronic hepatitis B is 4-6 months and HBeAg negative chronic hepatitis B is 12 months.

Peg IFN- α

The recommended peg-IFN- α dose is 180 μ g subcutaneously weekly. The recommended treatment duration for HBeAg positive chronic hepatitis B is 6 months and HBeAg negative chronic hepatitis B is 12 months.

Lamivudine

The recommended lamivudine dose for adults with normal renal function is 100mg orally daily. The recommended lamivudine dose for children is 3mg/kg/day with a maximum of 100mg/day. The recommended treatment duration for HBeAg positive chronic hepatitis B is a minimum of one year. Patients in whom HBeAg seroconversion has occurred should maintained on treatment for 3-6 months after HBeAg seroconversion is confirmed (two occasions at least 2 months apart) to reduce post-treatment relapse. Treatment may be continued in patients who have not developed HBeAg seroconversion. Treatment may be continued in patients who have breakthrough infection due to lamivudine resistant mutants as long as benefit to the patient is maintained. The recommended treatment duration for HBeAg negative chronic hepatitis B is longer than one year but the optimal duration has not been established.

Adefovir

The recommended adefovir dose for adults with normal renal function is 10mg orally daily. The recommended treatment duration for HBeAg positive chronic hepatitis B is a minimum of one year and HBeAg negative chronic hepatitis B is longer than one year. The benefits versus risks of longer duration of treatment are unknown.

Entecavir

Entecavir is available in 3 dosage forms- 0.5mg film-coated tablet, 1.0mg film-coated tablet, 0.05mg/ml oral solution. Optimum dose and duration of treatment remain to be settled.

Thymosin- α 1

The recommended thymosin- α 1 dose is 1.6mg twice weekly by subcutaneous injections. The recommended treatment duration for both HBeAg positive and HBeAg negative chronic hepatitis B is 6 months.

The therapeutic endpoints for chronic hepatitis B treatment are²²

1. Sustained suppression of HBV replication, as indicated by HBsAg and HBeAg loss.
2. Decrease of serum HBV DNA of an undetectable level by a non-PCR method.
3. Remission of disease, as shown by normalization of ALT.
4. Improvement in liver histology.
5. Reduction of the acute exacerbation, cirrhosis and HCC.

Recommendation for treatment and monitoring patients with chronic HBV infection^{5, 19, 22}

1. Thorough evaluation and counseling is mandatory before considering drug therapy.
2. The primary aim of treating chronic HBV infection is to eliminate or permanently suppress HBV, thus reducing infectivity and hepatic necroinflammation, which can lead to cirrhosis, liver failure and hepatocellular carcinoma.
3. HBeAg positive patients with elevated ALT levels and compensated liver disease may be

observed for 3-6 months for spontaneous seroconversion from HBeAg to anti HBe antibody prior initiation of treatment.

4. Patients who meet the criteria for chronic hepatitis B (serum HBV DNA $> 10^5$ copies/ml and persistent or intermittent elevation in aminotransferase levels) should be evaluated further with a liver biopsy.
5. Patients in the inactive hepatitis B surface antigen (HBsAg) carrier state should be monitored with periodic liver chemistries every 6-12 months, as liver disease may become active even after many years of quiescence.
6. Patients with HBeAg positive chronic hepatitis B:
 - a) ALT greater than 2 times normal or moderate/severe hepatitis on biopsy. These patients should be considered for treatment. Treatment may result in virological, biochemical, and histological response and also appear to improve clinical outcome. Treatment may be initiated with IFN- α , peg IFN- α , lamivudine, adefovir, entecavir or thymosin- α 1.
 - b) ALT persistently normal or minimally elevated (< 2 times normal). These patients should not be initiated on treatment.
 - c) Children with elevated ALT > 2 times normal. These patients should be considered for treatment if ALT levels remain elevated at this level for longer than 6 months. Both IFN- α and lamivudine are approved treatments for children with chronic hepatitis B.
7. Patients with HBeAg negative chronic hepatitis B (serum HBV DNA $> 10^5$ copies/ml, elevated ALT > 2 times normal or moderate/severe hepatitis on biopsy) should be considered for treatment.
8. During therapy, ALT, HBeAg and/or HBV DNA should be monitored at least every three months. Renal function should be monitored if adefovir is used. During IFN therapy, monitoring of adverse effects is mandatory.

9. After the end of therapy, ALT and HBV markers (including HBV DNA) should be monitored monthly for the first 3 months to detect early relapse and then every 3 months (for cirrhotic patients and those who remain HBeAg/HBV DNA positive) to 6 months (for responders). For non-responders, further monitoring is required to recognize a delayed response and to plan re-treatment when indicated.
10. Patients who failed to respond to prior IFN- α therapy may re-treated with lamivudine or adefovir if they fulfill the criteria.
11. Patients with compensated cirrhosis are best treated with lamivudine or adefovir because of the risk of hepatic decompensation associated with immunomodulatory agent related flares of hepatitis.
12. Patients with decompensated cirrhosis should be considered for lamivudine treatment. Adefovir may be used as an alternative to lamivudine, although it has not been evaluated as a primary treatment in these patients. IFN- α should not be used in patients with decompensated cirrhosis.
13. For patients with an inactive HBsAg carrier state, antiviral treatment is not indicated.

Prevention

- a) **Reduction of exposure:** Parenteral transmission can be reduced by avoiding high risk practices where the skin is pierced, such as acupuncture, tattoos and body piercing. The sharing of items such as razors and tooth brushes should also be avoided. Injecting drug use should be discouraged. The sexual risk of transmission can be reduced by safe sex practice such as the use of condoms and by immunization of the sexual partners of known carriers. Every donor of blood should be screened for HBsAg before transfusion.
- b) **Pre-exposure prevention:** Universal recombinant HBV vaccine should be given intramuscularly to everybody in a dose schedule of either 0, 1 and 6 months, with a booster dose at

varying time intervals, or 0, 1, and 2 months, with a fourth (booster) injection at 12 months. The hepatitis B vaccine is also effective in preventing infection with delta virus.

Unresolved issues need further study⁷

The treatment of chronic hepatitis B has advanced into the era of nucleoside analogues. However, the results are still unsatisfactory. In particular, the following issues remain unsettled;

1. Should patients with an ALT level of $<2 \times \text{ULN}$ be treated, and if so when and how?
2. What is the role of HBV genotypes in therapy?
3. Which is the first (line) choice among the currently available direct antiviral agents?
4. What is the role of combination therapy?
5. Cost-effectiveness of each therapeutic strategy?

Conclusion

The future of chronic hepatitis B therapy seems to be in the combination of different drugs. Ideally, the optimal drugs to combine would meet the following criteria; they should have different sites of action on HBV DNA replication, a potent antiviral effect, an excellent safety profile and they should induce a sustained response with a limited duration of therapy. However, so far few combinations have been evaluated; no combination therapy demonstrated a benefit as compared with mono-therapy. Newer approaches for treatment of chronic hepatitis B are inhibitors of reverse transcriptase/DNA polymerase, virus entry, core assembly, cytokines, therapeutic vaccine, monoclonal antibodies, antisense oligonucleotides, antifibrotic therapy. More potent drugs and new combinations together with the understanding of the mechanisms of resistance to therapy are important challenges to improve the efficacy of treatment and decrease in the future the global burden related to chronic hepatitis B.

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