INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem and it is estimated by the World Health Organization (WHO), approximately one-third of the world population has been infected with HBV with serological evidence of past or present infection with HBV. Of the approximately 2 billion people who have been infected worldwide, more than 350 million (5-7% of the world’s population) suffer from chronic HBV infection. Approximately 15-40% of patients infected with HBV will develop life-threatening liver consequences (including cirrhosis, liver failure and hepatocellular carcinoma) resulting in 600,000 to 1.2 million deaths per year due to HBV.\textsuperscript{1,4}

Based on the prevalence of Hepatitis B surface antigen (HBsAg), countries are classified as having high (where ≥8% of the population is HBsAg positive), intermediate (2-7%) or low (< 2%) HBV endemicity. Areas of high endemicity include South-East Asia, China, most of Africa, most of Pacific Islands, the Amazon basin and parts of the Middle-East. The areas of intermediate endemicity (2-7%) include South Asia, Eastern and Southern Europe, Russia and Central and South America. On the other hand, the areas with low endemicity (< 2%) include United States, Western Europe and Australia.\textsuperscript{5}

While South Asia including India has been grouped as countries with intermediate endemicity, the sheer enormity of the population of the region accounts for a large chunk of the entire pool of HBV carriers of the world.\textsuperscript{6}

EPIDEMIOLOGY OF HEPATITIS B VIRUS IN INDIA

India has over 40 million HBV carriers and accounts for 10-15% of the entire pool of HBV carriers of the world. Of the 25 million infants born every year in India, it is estimated that over 1 million run the lifetime risk of developing chronic HBV infection. Every year over 100,000 Indians die due to illnesses related to HBV infection.\textsuperscript{7,8}

There are varying reports of overall rate of HBsAg positivity ranging between 2-4.7%.\textsuperscript{8,10} A meta-analysis of the prevalence of HBV had estimated that the point-prevalence of hepatitis B among nontribal and tribal populations was 3.07% (95% CI: 2.5-3.64) and 11.85% (CI 10.76–12.93) respectively and the overall prevalence was 3.70% (CI: 3.17–4.24) (corresponding to a chronic carrier rate of 2.96%).\textsuperscript{11}

A high endemicity of HBV infection has been reported in the tribal populations which has been attributed to inbreeding, poor hygienic living conditions, close person-to-person contact and certain socioculture practices which may facilitate transmission of HBV.\textsuperscript{11}

Very high levels of HBsAg positivity have been reported in the tribes of Andaman and Nicobar Islands (Nicobarese tribe-23.3%, Shompen tribe-37.8%, Jarawa tribe-65%).\textsuperscript{13,14} There are hyperendemic foci of HBV infection in Arunachal Pradesh where the point prevalence of HBsAg in the Idu Mishmi tribe has been found to be 21.2%.\textsuperscript{15} A higher prevalence of HBV infection has also been reported in patients with human immunodeficiency virus (HIV) positive intravenous drug users in Manipur in northeast India.\textsuperscript{16}

The prevalence of HBsAg positivity in pregnant women has been reported to range from 0.9–6.3%.\textsuperscript{17-21} Unlike previous data, a recent report by Dwivedi, et al.\textsuperscript{17} has shown a high replicative rate with 56.8% of HBV infected pregnant women being HBeAg positive.

The common genotypes reported from India are genotype A followed by D.\textsuperscript{22-28} Genotype C has been reported from eastern India\textsuperscript{29,30} and there are few reports of genotypes E, F and G from India.\textsuperscript{30-32}

TRANSMISSION OF HEPATITIS B VIRUS IN INDIA

Spread of HBV infection in many South Asian countries is attributed to unsafe blood supply, reuse of contaminated syringes, lack of maternal screening to prevent perinatal transmission and delay in the introduction of hepatitis B vaccine.\textsuperscript{33} The predominant mode of transmission is horizontal rather than vertical in India.\textsuperscript{34} The specific modality of horizontal transmission is unknown but it may be due to contact of nonintact skin or mucous membranes with tears, saliva or blood containing secretions or through sharing of toothbrushes. While it is generally accepted that the modality of transmission of HBV in India is horizontal, the recent report by Dwivedi, et al.\textsuperscript{17} showing a high prevalence of replicative markers in India suggest that there may be a significant role of vertical transmission as well.

NATURAL HISTORY OF HEPATITIS B VIRUS INFECTION

The natural history of HBV infection consists of five phases: the immunotolerant phase, the immune reactive HBeAg positive phase, the inactive HBV carrier phase, the HBeAg negative chronic hepatitis B phase and the HBsAg negative phase or resolution phase.\textsuperscript{35}

1. The “immunotolerant phase” is characterized by HBeAg positivity, very high levels of HBV DNA, normal alanine aminotransferase (ALT) levels with no or minimal liver inflammation or fibrosis on liver biopsy. The immune-tolerant phase is prolonged in individuals who acquire the infection at birth or in early childhood.
and may last for up to 40 years. In this immunotolerant phase, the immune system does not recognize the virus. However, with age, most such patients will go into the immune-reactive phase where the immune system mounts a response against the virus.

2. During the “immune reactive phase” is characterized by HBeAg positivity, elevations in ALT, elevated HBV DNA levels (though levels of replication are lower than in the immunotolerant phase) and active liver disease is found on biopsy. Most often, the immune response results in decline in HBV DNA levels and HBeAg seroconversion can occur. Once HBV seroconversion occurs, there are three possible outcomes: (1) inactive HBsAg carrier stage, (2) HBeAg negative chronic hepatitis B and (3) reversion back to HBeAg seropositivity. From 10 to 40% of persons, can develop one or more reversions back to HBeAg seropositivity, which may be associated with a flare of hepatitis that is usually subclinical.

3. The “inactive HBV carrier stage” is characterized by HBeAg negativity, normal ALT, and HBV DNA levels that are usually below 2,000 IU/mL and often undetectable by polymerase chain reaction (PCR) assay. The HBsAg levels are less than 1,000 IU/mL in inactive carriers.

4. “HBeAg negative chronic hepatitis B” may be seen in about 20% of persons after HBeAg seroconversion. They are HBeAg-negative/anti-HBe positive with fluctuating levels of ALT and elevated HBV DNA levels and patients with HBV DNA levels between 2,000 and 20,000 IU/mL may have active hepatitis and fibrosis on liver biopsy.

5. “The HBsAg negative phase” is characterized by loss of HBsAg. However, low levels of HBV DNA replication may persist in the liver and occasional reactivations after immunosuppression or cancer chemotherapy have been reported. Patients with HBsAg positivity presenting with jaundice may be due to acute HBV infection, superadded infections like hepatitis A or E or due to reactivation of the HBV virus. Acute exacerbations of chronic hepatitis B are common in endemic areas and may account for about 50% of patients presenting as presumed acute hepatitis B.66–69 Kumar et al. found that 40% of the patients first presenting clinically as acute icteric hepatitis B, and negative for markers of other hepatitis viruses, developed persistence of HBsAg with evidence of chronic liver damage, the majority of whom represented acute exacerbation of previously asymptomatic chronic HBV infection.70

GUIDELINES FOR MANAGEMENT OF HEPATITIS B VIRUS

Various international guidelines including the AASLD, EASL and APASL guidelines have been published for management of HBV.64–67 While these would provide management guide-lines in ideal situations, therapy and monitoring needs to be tailored in a resource-constrained nation like India.

Goals of Therapy

The ultimate aim of HBV management is to prevent progression of the disease to cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma and hence decreasing morbidity and mortality. The ideal aim is to eradicate HBsAg and the virus from the body. However, the virus persists as covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes, which may lead to HBV reactivation. It is recognized that the primary driver of inflammation and fibrosis is viral replication. Hence, the intermediate goal is to suppress viral replication by HBeAg seroconversion and/or HBV-DNA suppression leading to ALT normalization.

Indication for Treatment

Patients should be considered for treatment when they have evidence of disease activity (serum ALT levels above the upper limit of normal (ULN) and/or liver biopsy showing moderate to severe active necroinflammation and/or at least moderate fibrosis along with evidence of viral replication with HBV DNA levels above 2,000 IU/mL. Patients with cirrhosis or liver or obvious evidence of active chronic hepatitis B with ALT above 2 times ULN and serum HBV DNA above 20,000 IU/mL may start treatment even without a liver biopsy.

Currently Available Treatments

The currently approved treatment options include immunomodulatory therapies [including conventional interferon α (IFN α), pegylated interferon α (PEG-IFN α) and thymosin α], and nucleoside/nucleotide analogs (NA). The NAs include nucleoside analogs (lamivudine (LAM), entecavir, telbivudine and emtricitabine) and nucleotide analogs (adefovir, tenofovir). Advances of pegylated interferon are that it has a finite duration of action, there is no development of resistance and there are higher rates of HBeAg seroconversion and HBsAg loss. However, the disadvantages are that the efficacy is only modest, treatment has adverse effects that may limit tolerability and the fact that it involves prolonged injections. Nucleoside analogs can be easily administered orally but may often be given for an indefinite duration.

Conventional Interferon Alpha

HBeAg-Positive Chronic Hepatitis B

Meta-analyses of controlled trials in HBeAg-positive patients showed that treatment with IFN α at a dose of 5 MU daily or 10 MU three times weekly for 4–6 months achieved higher HBeAg loss (33 vs 12%), HBV DNA suppression (37 vs 17%), and ALT normalization than untreated controls with a risk difference of around 25% for each parameter. A lower dosage of IFN α (5–6 MU three times weekly) has been used in Asian patients with similar efficacy.71

HBeAg-Positive Chronic Hepatitis B

Conventional IFNα treatment for 4–6 months in HBeAg negative patients has shown low sustained virologic response (SVR) rates and 12 months treatment duration with conventional IFN α is preferable for HBeAg-negative chronic hepatitis B. In Asian patients, 6–10 months course of IFN α therapy achieved a 6-month post-treatment response in 30% patients.72

Pegylated-Interferon Alpha

HBeAg-Positive Chronic Hepatitis B

Twelve months therapy with PEG-IFN α resulted in 30% seroconversion as compared to 20% with NA. Sustained HBsAg loss after PEG-IFN α therapy was 3–7%. The predictors of response with PEG-IFN α in HBeAg positive CHB are:

- **Pretreatment:** Low viral load HBV DNA (< 2 × 10⁴ IU/mL), HBV genotype (A and B), high serum ALT levels (> 2–5 times ULN) and high activity scores on liver biopsy (≥ A2).
- **During treatment:** HBV DNA decrease to below 20,000 IU/mL at 12 weeks (associated with 50% chance of seroconversion), HBsAg levels less than 1,500 IU/mL at 12 weeks. If at 12 weeks, there was no decline of HBsAg levels or HBsAg levels were > 20,000 IU/mL there was low probability of seroconversion.
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**HBeAg-Negative Chronic Hepatitis B**

Sustained viral response rates after discontinuation of PEG-IFN α were 20% as compared to less than 5% with IFN.

Sustained HBsAg loss after PEG-IFN α therapy was 3% at the end of 6 months after therapy but increased to 9% at 3 years and 12% at 5 years. The predictors of response with PEG-IFN α in HBeAg negative CHB are:

- **Pretreatment:** Nil
- **During treatment:** HBV DNA decrease to below 20,000 IU/mL at 12 weeks (associated with 50% chance of seroconversion). A combination of no decline of HBsAg levels and more than 2log_{10} reduction in HBV DNA is suggestive of lack of response.

**NUCLEOSIDE/NUCLEOTIDE ANALOGS**

Tenofovir and entecavir are the most potent NA with highest barriers to resistance and can be used as first-line agents. Lamivudine is a cheap drug but has almost 70% resistance at 5 years. Adefovir is less effective and also has high resistance levels. Telbivudine also has high resistance, though this is low in patients with low baseline viremia.

**HBeAg-Positive Patients**

Virological remission can be maintained in more than 90% patients with ongoing entecavir or tenofovir after more than or equal to 3 years of therapy.

The HBsAg loss rates after 12 months in HBeAg positive patients are: 0% with adefovir, 0.5% with telbivudine, 1% with lamivudine, 2% with entecavir and 3% with tenofovir.

The factors predictive of anti-HBe seroconversion with NA in HBeAg positive CHB are:

- **Pretreatment:** Low viral load (HBV DNA < 2 \times 10^6 IU/mL), high serum ALT levels, and a high activity scores on liver biopsy.
- **During treatment:** Undetectable HBV DNA at 24–12 weeks with lamivudine or telbivudine and 48 weeks with adefovir were associated with higher seroconversion. A decline in HBsAg levels may identify patients with HBeAg or HBsAg loss.

**HBeAg-Negative Chronic Hepatitis B**

HBsAg loss is rarely seen in 4–5 years of NA therapy in HBeAg positive patients. Undetectable HBV DNA at 24–12 weeks with lamivudine or telbivudine and 48 weeks with adefovir were associated improved chance of maintained virological response.

**SPECIAL CONSIDERATIONS AND IMPLICATIONS FOR MANAGEMENT OF HBV IN INDIAN SCENARIO**

Therapy for HBV is expensive and often lifelong. The factors that would affect the management of hepatitis B in India are related to the epidemiological features, the viral and host characteristics and financial constraints. Some of these are as below:

- While the predominant mode of transmission is horizontal recent reports of high prevalence of replicating HBV suggest significant transmission may occur through the vertical route, thereby underscoring the importance of universal immunization at birth.
- The common genotypes reported from India are genotype A followed by D with genotype C having been reported from eastern India. The genotype distribution has relevance to both the prevention of transmission as well as management of chronic hepatitis B.
- Different genotypes may be preferentially transmitted by different modes. Pockets of high prevalence of genotype C in Arunachal Pradesh have a high prevalence of HBV. Genotype C is most prevalent in highly endemic areas where vertical transmission is the primary mode of transmission. It is, therefore, important to ensure universal immunization starting in these areas with vertical transmission of HBV.
- HBV genotypes A and B have been shown to be associated with higher rates of anti-HBe seroconversion and HBsAg loss than genotypes D and C, respectively, after treatment with PEG-IFN α. Hence, in patients, who do not have cost constraints, PEG-IFN α may be a reasonable option for Indian patients with genotype A.
- However, many patients are not even able to afford evaluation of HBV, leave alone the burden of cost of PEG-IFN α therapy. Hence, modifications of standard guidelines may have to be done to cut costs:
  - In HBeAg positive patients with raised ALT being planned for NA therapy, frequent or even initial HBV DNA monitoring could be avoided.
  - Since resistance to telbivudine is low in patients with low baseline viremia (< 2 \times 10^5 IU/mL for HBeAg positive patients and < 2 \times 10^6 IU/mL for HBeAg negative patients), it may be considered as a first line therapy in such patients to contain long-term costs of NA therapy.
  - In lamivudine resistance, addition of adefovir, rather than switching to tenofovir may contain costs.
  - There is some evidence that in among Asian patients (genotype B and C HBV infected patients), an HBsAg level of less than 100 IU/mL might predict lower risk of relapse and stopping treatment can be considered. Similar studies for Indian patients with dominant genotype A and D should be encouraged to identify patients in whom costs can be curtailed by stoppage of NA.
  - Further trials of low dose conventional interferon therapy in Indian patients should be encouraged.
  - There may be merit in considering Hepatitis B immunoglobulin free liver transplant protocols using nucleoside analogs to prevent viral recurrence in the graft.
  - There needs to be a concerted effort from the medical fraternity to provide universal immunization against HBV.

**CONCLUSION**

The viral characteristics, genotypes and host response in the Indian subcontinent are likely to be different. Hence, there is an urgent need for leading hepatologists from India to come together and formulate protocols that would be appropriate for our country rather than blindly following guidelines based on European or South-East Asian countries.

**REFERENCES**


