Chronic Hepatitis B: An overview

Vaibhav Banait

Abstract

Hepatitis B is a global problem. India has intermediate prevalence of chronic hepatitis B. The approach to patients who have chronic hepatitis b necessorily involve counseling regarding strategies to prevent the spread of disease, and treatment of patients who are likely to develop progressive liver disease.The aims of treatment of chronic hepatitis B are to achieve sustained suppression of HBV replication and remission of liver disease. The ultimate goal is to prevent cirrhosis, hepatic failure and HCC. Judicious use of nucleoside Analogues in patients with chronic hepatitis B is the most eective prophylaxis against the development of antiviral-resistant HBV.

Preamble

The global prevalence of HBsAg varies greatly and countries can be defined as having a high, intermediate and low prevalence of HBV infection based on a prevalence of HBsAg carriers of 8%, 2% to 7%, and 2% respectively. India has intermediate prevalence of hepatitis B[1]. HBV is transmitted by perinatal, percutaneous, and sexual exposure, as well as by close person-to-person contact presumably by open cuts and sores, especially among children in hyperendemic areas. HBV can survive outside the body for prolonged periods. The risk of developing chronic HBV infection after acute exposure ranges from 90% in newborns of HBeAg-positive mothers to 25% to 30% in infants and children under 5 and to less than 5% in adults[1]. In addition, immunosuppressed persons are more likely to develop chronic HBV infection after acute infection. When a patient who is HBsAg positive visits family consultant's oce, there are certain questions that family physician need to address. This article attempts to answer these concerns.

Address for correspondence

MD, DNB (Medicine),
DM (Gastroenterology)

I have a patient who is HBsAg positive. What should I counsel him? [2]

1. Patients who are HBsAg positive should be counseled regarding prevention of transmission of HBV.

(a) Have sexual contacts vaccinated

(b) Use barrier protection during sexual intercourse if partner is not vaccinated or naturally immune.

(c) Not share toothbrushes or razors.

(d) Cover open cuts and scratches.

(e) Clean blood spills with detergent or bleach.

(f) Not donate blood, organs or sperms .

2. Sexual and household contacts of carriers who are negative for HBV seromarkers should receive hepatitis B vaccination.
3. Newborns of HBV-infected mothers should receive HBIG and hepatitis B vaccine at delivery and complete the recommended vaccination series.
4. Persons who remain at risk for HBV infection such as infants of HBsAg-

positive mothers, health care workers, dialysis patients, and sexual partners of carriers should be tested for response to vaccination with anti-HBs antibody.

5. Post vaccination testing should be performed at 9 to 15 months of age in infants of carrier mothers and 1-2 months after the last dose in other persons.

Children and adults who are HBsAg-positive:

- **Can participate in all activities including contact sports.**
- **should not be excluded from daycare or school participation and should not be isolated from other children.**
- **Can share food, utensils, or kiss others**

Does my patient have chronic hepatitis B or is a chronic inactive carrier?[3, 4]

Chronic hepatitis B is a chronic (>6 months) necroinammatory disease of the liver caused by persistent infection with hepatitis B virus.

It is further subdivided into

1. HBeAg positive

2. HBeAg negative chronic hepatitis B.

Diagnostic criteria Chronic hepatitis B

1. HBsAg-positive for 6 months

2.Serum HBV DNA 20,000 IU/mL (105copies/mL), lower values 2,000- 20,000 IU/mL (104-105 copies/mL) are often seen in HBeAg-negative chronic hepatitis B

3. Persistent or intermittent elevation in ALT/AST levels

4. Liver biopsy showing chronic hepatitis with moderate or severe necroinammation

Inactive HBsAg carrier state

Persistent HBV infection of the liver without significant, ongoing necroinammatory disease.

Criteria for diagnosis of carrier state:

1. HBsAg-positive for 6 months

2. HBeAg, anti-HBe +ve

3. Serum HBV DNA <2,000 IU/mL

4. Persistently normal ALT/AST levels

5. Liver biopsy confirms absence of significant hepatitis Resolved hepatitis B

Approximately 4% to 20% of inactive carriers have one or more reversions back to HBeAg +ve state. Among those who remain anti-HBe positive, 10% to 30% continue to have elevated ALT and high HBV DNA levels after HBeAg seroconversion, and roughly 10% to 20% of inactive carriers may have reactivation of HBV replication and exacerbations of hepatitis after years of quiescence.

Therefore, serial testing is necessary to determine if an HBsAg-positive, HBeAg-negative carrier is truly in the inactive carrier state and life long follow-up is required to confirm that the inactive state is maintained.

How should I evaluate a patient who is HBsAg+ve? [2]

Initial evaluation

1. History and physical examination

2. Family History of liver disease, HCC. This increases the likelihood of development of serious liver disease in patient

3. Laboratory tests to assess liver disease

(a) complete blood counts with platelets,

(b) hepatic panel, and prothrombin time

(c) Tests for HBV replicationHBeAg/anti-HBe, HBV DNA

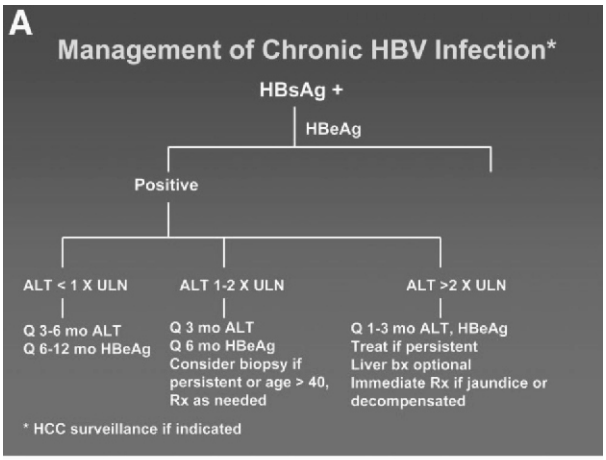
(d) Tests to rule out viral co-infections anti-HCV, anti-HDV (in persons from countries where HDV infection is common and in those with history of injection drug use), and anti-HIV in those at risk

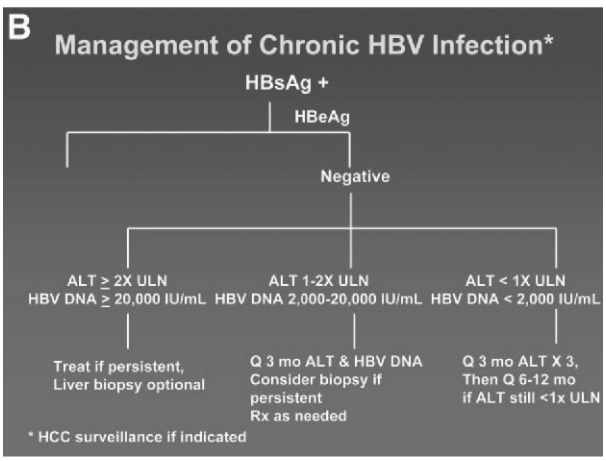
(e) Tests to screen for HCCAFP at baseline and, in high risk patients, ultrasound

(f) Consider liver biopsy to grade and stage

liver disease - for patients who meet criteria for chronic hepatitis (Not mandatory)

How should I follow up these patients? When should I start treatment?[2]





How should I treat a treatable chronic hepatitis B?

The aims of treatment of chronic hepatitis B are to achieve sustained suppression of HBV replication and remission of liver disease. The ultimate goal is to prevent cirrhosis, hepatic failure and HCC.

Currently, seven therapeutic agents have been approved for the treatment of adults with chronic hepatitis B. While IFNs are administered for predefined durations, nucleoside analogues are usually administered until specific endpoints are achieved. The difference in approach is related to the additional immune modulatory effects of IFN. For HBeAg-positive patients, viral suppression with currently approved treatments can be sustained in 50% to 90% patients if treatment is stopped after HBeAg seroconversion is achieved. For HBeAg-negative patients, relapse is frequent even when HBV DNA has been suppressed to undetectable levels by PCR assays for more than a year; thus, the endpoint for stopping treatment is unclear [2].

In choosing which antiviral agent to use as the firstline therapy, consideration should be given to the safety and efficacy of the treatment, risks of drug resistance, costs of the treatment (medication, monitoring tests, and clinic visits), and for women when and whether they plan to start a family.

Although the efficacy is not substantially different, pegIFN- is likely to supersede standard IFN-because of its more convenient dosing schedule. In view of the high rate of drug resistance during long-term treatment, lamivudine and telbivudine are not preferred except where only a short course of treatment is planned (pregnant women to reduce risk of transmission to foetus). Since adefovir is less potent than other NA and is associated with increasing rate of antiviral resistance after the rst year of therapy, it is best utilized as a second line drug in treatment-na¨ve patients. The first-line drugs recommended for treatment of hepatitis B are pegIFN, entecavir or tenofovir[2]. Denovo combination therapy seems to be a logical approach but none of the combination regimens tested to date is clearly superior and it remains to be shown if a clinical meaningful decrease in the rate of antiviral-resistance results from combination therapy as compared to entecavir or tenofovir mono therapy.

Judicious use of nucleoside Analogues in patients with chronic hepatitis B is the most effective prophylaxis against the development of antiviral-resistant HBV. Thus, patients with minimal disease and those who

are unlikely to achieve sustained response should not be treated with nucleoside analogue, particularly if they are young (30 years). When possible, the most potent nucleoside analogue with the lowest rate of genotypic resistance should be administered and compliance reinforced. Although combination therapy has been shown to prevent antiviral resistance in patients with HIV infection, the promise of combination therapy has not yet been fulled for patients with HBV infection. Once antiviral-resistant HBV mutants have been selected, they are archived (retained in the virus population) even if treatment is stopped and lamivudine-resistant HBV mutants had been detected up to four years after withdrawal of lamivudine[2] .

Current therapy of chronic hepatitis B does not eradicate HBV and has limited long term efficacy.

Thus, careful consideration of the patient's age, severity of liver disease, likelihood of response, and potential adverse events is needed before treatment is initiated[2]. Treatment is indicated if the risk of liver-related morbidity and mortality in the near future (5-10 years) and the likelihood of achieving maintained viral suppression during continued treatment are high. Treatment is also indicated if the risk of liver-related morbidity and mortality in the foreseeable future (10-20 years) and the likelihood of achieving sustained viral suppression after a defined course of treatment are high. Treatment is not indicated if the risk of liver-related morbidity or mortality in the next 20 years and the likelihood of achieving sustained viral suppression after a defined course of treatment are low. Because of the fluctuating nature of chronic HBV infection, the risk of liver-related morbidity and mortality and the likelihood of response may vary as patient progresses through the course of chronic HBV infection. Thus, continued monitoring is essential for risk assessment.

What is response to antiviral drugs?

Biochemical (BR) Decrease in serum ALT to within the normal range

Virologic (VR) Decrease in serum HBV DNA to undetectable levels by PCR assays, and loss of HBeAg in patients who were initially HBeAg positive

Virologic relapse Increase in serum HBV DNA of 1 log10 IU/mL after discontinuation of treatment in at least two determinations more than 4 weeks apart

Histologic (HR) Decrease in histology activity index by at least 2 points and no worsening of fibrosis score compared to pre-treatment liver biopsy

Complete (CR) Full criteria of biochemical and virological response and loss of HBsAg

Depending upon Time of Assessment

End-of-treatment At the end of a defined course of therapy

Off-therapy After discontinuation of therapy

Sustained (SR-6) 6 months after discontinuation of therapy

Sustained (SR-12) 12 months after discontinuation of therapy

Management of Antiviral-Resistant HBV Prevention [2]

If the biochemical or virological relapse occur while the patient is on treatment, drug resistance has to be suspected and can be confirmed with readily available tests.

To contain and manage drug resistance, following ways are suggested

1. Prevention

(a) Avoid unnecessary treatment

(b) Initiate treatment with potent antiviral that has low rate of drug resistance or with combination therapy(c) Switch to alternative therapy in patients with primary non-response Monitoring

(d) Test for serum HBV DNA (PCR assay) every 3-6 months during treatment

(e) Check for medication compliance in patients with virologic breakthrough.

(f) Conrm antiviral resistance with genotypic testing

2. Treatment

Resistance	Treatment
Lamivudin resistance	Add adefovir Add tenofovir Stop lamivudine, switch to tenofovir-emtricitabin combination
Adefovir resistance	Add lamivudine Stop adefovir, witch to tenofovir-emtricitabin combination Switch to or add entecavir
Entecavir-resistance	Switch to tenofovir or tenofovir-emtricitabin combination
Telbivudine-resistance	Add adefovir or tenofovir Stop telbivudine, switch to tenofovir-emtricitabin combination

Comparison of Approved Treatments of Chronic Hepatitis B

	IFNα	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir
Indications						
HBeAg+, normal ALT	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated
HBeAg+ chronic hepatitis	Indicated	Indicated†	Indicated	Indicated	Indicated†	Indicated
HBeAg- chronic hepatitis	Indicated	Indicated†	Indicated	Indicated	Indicated†	Indicated
Duration of treatment						
HBeAg+ chronic hepatitis	4-12 months§	≥1 year**	≥1 year**	≥1 year**	≥1 year**	≥1 year**
HBeAg− chronic hepatitis	1 year	>1 year	>1 year	>1 year	>1 year	>1 year
Route	Subcutaneous	Oral	Oral	Oral	Oral	Oral
Side effects	Many	Negligible	Potential Nephrotoxicity	Negligible	Negligible	Potential Nephrotoxicity
Drug resistance	–	~20%, year 1 ~70%, year 5	None, year 1 29%, year 5	~1% up to year 5‡	~25% up to year 2	None, year 1 na beyond 1 year
Cost*	High	Low	Intermediate	High	Intermediate	Intermediate

*Based on treatment duration of 1 year.
**Treatment for at least 12 months continuing for at least 6 months after anti-HBe seroconversion.
†Not preferred drug due to high rate of resistance.
§PegIFN approved for 12 months.
‡Entecavir resistance reported within year 1 in patients with prior lamivudine resistance.

References

[1] Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004;11(2):97-107

[2] Anna S. F. Lok, Brian J. McMahon. Chronic Hepatitis B: Update 2009.Hepatology, 2009; 50(3):1-36

[3] Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000summary of a workshop. Gastroenterology 2001;120(7):1828- 1853.

[4] Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. HEPATOLOGY 2007; 45(4):1056-1075.