Background

Over 350 million people worldwide are infected with Hepatitis B virus (HBV) and globally around 1 million die due to consequences of this infection annually. Bangladesh belongs to the intermediate prevalence region for HBV infection. Here the lifetime risk of acquiring HBV is between 20-60%. Studies from our as well as other groups have shown that HBV is responsible for 31.25% cases of acute hepatitis, 76.3% cases of chronic hepatitis, 61.15% cases of cirrhosis of liver, and 33.3% cases of hepatocellular carcinoma (HCC) in Bangladesh.

There is high prevalence of HBeAg negative CHB in our population. In our series we found 48.7% CHB patients positive for HBeAg, while the rest 51.3% tested negative.

We have also observed that the most prevalent HBV genotype in Bangladesh is D (49%) followed by C (38%). In our patients with genotype C, we found more often serum ALT and AST elevation than those with genotype D. Also, HBV DNA level is high in patients with genotype C (88%) compared to genotype D (32%). Histologic activity index (HAI) tends to be higher in patients with genotype C infection. Since specialist healthcare to chronic HBV infected individuals in Bangladesh is delivered primarily by Internists, the aim of this guideline is to offer to them scientific approach in handling such patients in an easily understandable way that can be readily applied.

Chronic inactive HBsAg carrier state

Persistence of HBsAg in blood for more than 6 months is termed as chronic hepatitis B. HBeAg negative HBV infection may imply chronic inactive carrier state characterized by HBV DNA <104 copies/ml and normal or near normal hepatic histopathology. In carriers, sero-conversion of HBeAg to anti-HBe generally implies reduction of viral activity and improvement in biochemical and histologic parameters.

HBeAg negative CHB

However the inactive carrier state must be differentiated from chronic hepatitis by mutant variety of HBV resulting from mutation in pre-core or core promoter region of the viral genome giving rise to HBeAg negative CHB.

Besides HBeAg sero-conversion does not necessarily mean complete cessation of viral replication. It has been observed that over an 8 year follow up period, in a study population of 283 patients, 33% had ALT and HBV DNA elevation and 8% progressed to cirrhosis of liver.

The biologic role of HBeAg in the replication of HBV is uncertain. Expression of HBeAg is not essential for viral replication in humans or in animal models. It has been suggested that HBeAg acts as a tolerogen or as a target for immune response. In addition HBeAg appears to modulate the host immune response.

In one of our studies where we recruited 80 CHB patients, we found that 7.69% patients with HBeAg positive CHB had minimal chronic hepatitis, 69.23% had mild chronic hepatitis, 19.23% had moderate chronic hepatitis, while severe chronic hepatitis was seen in 3.85%. In case of HBeAg negative CHB, these figures were 10.71%, 53.57%, 25% and 10.71% respectively. Later we studied a larger sample size and compared not only hepatic necro-inflammation, but also fibrosis between HBeAg positive and negative CHB patients. This study included 155 patients, 102 HBeAg positive and the rest 53 negative for HBeAg. It was observed that 20.8% patients with HBeAg positive CHB had moderate to severe chronic hepatitis (CH). In contrast, moderate to severe CH was seen in 18.6% patients with HBeAg positive CHB. Significant hepatic fibrosis (i.e. HAI-F score >3) was also more frequent in the HBeAg negative CHB group. 28.3% patients in this group had significant hepatic fibrosis as opposed to 19.6% patients with HBeAg positive CHB. In both these studies, we observed that patients with HBeAg negative CHB tend to develop more severe hepatic histologic involvement compared to their HBeAg positive counterparts. In one of our more re-
cent works, we studied 42 HBeAg negative CHB patients with very low HBV DNA count (i.e. <105 copies/ml) only to discover that even in them, 26.2% patients had significant hepatic necro-inflammation (i.e. HAI-NI score 4-8) while significant fibrosis was seen in 19% patients12. Similar experience is also shared by studies from Korea13, Turkey14, Egypt16, Greece15, China16 and India17, 18, 19.

Management of HBeAg negative CHB

It is very important to distinguish chronic inactive HBsAg carriers from HBeAg negative CHB, as the later group has the potential of developing marked viral reactivation and has less chance of response to anti-viral medications20. A recent paper from Taiwan reports that the cumulative probability of hepatitis relapse in HBeAg carriers is 26.9% in males and 12.5% for females over a 20 year follow up period. Moreover 1.14% patients included in the study progressed to cirrhosis per annum. The sample size in this study was 124121.

Definitive diagnosis of pre-core mutation involves sequencing of viral genome20. However this is more of a research toll with practically no implication in the clinical setting. In an inactive carrier, ALT usually remains normal on serial monitoring with undetectable to low levels (i.e. <105 copies/ml) of HBV DNA. However the same may also occur in a patient with HBeAg negative CHB. HBV DNA is also not a very useful indicator as a Chinese study, involving 165 patients, reported that a single HBV DNA measurement misdiagnoses 45% HBeAg negative CHB as chronic inactive HBsAg carriers. The study further revealed that even HBV DNA measurement on three separate occasions also misdiagnoses 30% cases22. Besides a study of 196 CHB patients revealed that 10.5% HBeAg negative CHB patients had HBV DNA <30,000 copies/ml23.

The only way to distinguish between these two entities in a clinical set up is therefore performing a liver biopsy24.

The goal of treatment of any CHB patient is to prevent the development of cirrhosis, hepatic failure and hepatocellular carcinoma (HCC). In HBeAg negative CHB, response to treatment is said to have been obtained when one becomes negative for HBV DNA by PCR along with normalization of ALT and sero-conversion to anti-HBe. The problem however is that many HBeAg negative CHB patients test positive for anti-HBe at baseline and have persistently normal or near normal ALT. Moreover there is high incidence of relapse in this group of patients, even after HBV DNA becomes undetectable by PCR with treatment, the reason why initiating as well as determining the end-point of treatment in this group remains extremely difficult. The American Association for the Study of the Liver (AASLD) in it’s recent CHB guideline advocates treatment of HBeAg negative CHB patients till HBsAg becomes undetectable25. This is an approach that is perhaps not too appropriate in the Asian setting. The reason for saying so is multifold including lack of trained specialists, poor socioeconomic condition, lack of patient awareness, poor follow up, high cost of drugs etc. This means that there will be high risk of introducing mutant HBV strains. However a better answer to this question is not yet known.

Besides all oral anti-virals currently approved for CHB treatment are also associated with variable risk of inducing viral resistance on long-term use. This risk is highest with lamivudine (LAM) and minimal with entecavir (ETV).

Emergence of HBV mutant can lead to negotiation of initial treatment. Patients are also at increased risk of developing hepatitis flares and decompensation. Such mutation is initially characterized by viral breakthrough, where there is a >10 log rise in HBV DNA. Viral breakthrough precedes biochemical breakthrough by months. In the later, there is rise in serum ALT. Such patients also develop cross-resistance to other anti-virals, like patients resistant to LAM will have cross-resistance to talbivudine (LdT) and vice-versa.

Interferon-α (IFN) for 48 weeks is associated with 38-90% response as opposed to 0-39% response in controls26, however approximately 50% responders relapse post-treatment, some as late as up to 5 years later27. The sustained response may however be increased with prolonged treatment28. Besides 30-40% of these relapsers show sustained response following a second course of IFN-α29. Pegylated IFN for 48 weeks yields better results and the viral suppression is also better if LAM is added to pegylated IFN, however the sustained virologic response does not improve with this combination30.

LAM is a nucleoside analog that yields 60-70% HBV DNA negativity at 1 year in HBeAg negative CHB31, but 90% of these responders unfortunately relapse post-treatment30. With longer duration of treatment, the response progressively reduces to 73% at 1 year and 34% at 2 years due to emergence of LAM resistant strains, usually YMDD mutants32, where addition of adefovir (ADV) is usually effective.

ADV on the other hand is a nucleotide analog that leads to HBV DNA negativity in 64% HBeAg negative CHB patients at 1 year of treatment33. ADV is a weaker drug compared to LAM and is unlikely to yield impressive results if
the initial HBV DNA load is high. However in HBeAg negative CHB patients with low HBV DNA load at baseline, ADV may be a useful first-line option, as it is associated with much lower resistance rate compared to LAM. Addition of ADV to LAM benefits LAM-resistant CHB patients and vice versa, although the later is much less common.

The drug that is of much discussion these days is a carbocyclic analog called entecavir (ETV). It is much superior to LAM or ADV and is effective in LAM-resistant cases\textsuperscript{31}. At 48 weeks, ETV yields HBV DNA negativity in 90% HBeAg negative CHB patients, compared to 78% with LAM\textsuperscript{29}.

Telbivudine (LdT), a L-nucleoside analog, is a newer addition to growing list of oral anti-virals for CHB and at 1 and 2 years shows much better response to LAM in HBeAg negative CHB\textsuperscript{34}. However these relatively newer drugs like ETV or LdT are yet to be time tested for long-term outcome.

Patients with HBeAg negative CHB must therefore be managed judiciously and in certain situations kept under close follow-up instead of rushing to treatment. However this does not mean advocating adoption of a too conservative approach, allowing many to proceed to irreversible and progressive liver disease (figure 1).

**Recommendation**

We would opt for treating HBeAg positive CHB patients with elevated ALT more times above baseline. However per-cutaneous liver biopsies should be performed routinely in them if HBV DNA is positive by PCR irrespective of the viral load and/or normal ALT level. The reason being that the definition of chronic inactive HBsAg carrier is not satisfied unless the liver histology is shown to be normal or near normal\textsuperscript{22}.

We also recommend treating these patients if there is significant hepatic necro-inflammation (i.e. HAI-NI >3) and/or significant hepatic fibrosis (i.e. HAI-F >3). Else we recommend following up the patients with regular, periodic ALT estimation and treat when ALT shows a rising trend (figure 2).

**Management of HBeAg positive CHB**

Treatment of wild type or HBeAg positive CHB is much more straightforward compared to HBeAg negative CHB. Viral resistance is the main drawback of long-term antiviral therapy. Lamivudine monotherapy is associated with higher resistance (year 1, 10-27%; year 2, 37-48%, year 4, 60-65%) than adefovir (year 1, 0%; year 2, 3%; year 5, 29%) or telbivudine (year 1, 3-4%; year 2, 9-22%). Entecavir resistance is rare in naive individuals (year 4, <1%), but increases over time in lamivudine-resistant patients (year 4, 43%)\textsuperscript{35}.

Antiviral resistance and poor adherence are the most important factors in treatment failure of hepatitis B. On-treatment monitoring strategies to define early virologic responses that might be predictive of better outcomes and a reduced risk of viral resistance were proposed for further study. This treatment plan, labeled the roadmap concept, recommends monitoring of serum HBV DNA levels to identify outcomes of therapy. Primary treatment failure was defined as a reduction of serum HBV DNA levels by <1 log\textsubscript{10} IU/mL from baseline at week 12. Measurement of the HBV DNA level at week 24 was considered essential to characterize virologic responses as complete, partial, or inadequate. Complete virologic response was defined as negative HBV DNA by a sensitive assay (<60 IU/mL or <300 copies/mL); partial virologic response was defined as HBV DNA levels less than 2000 IU/mL (4 log\textsubscript{10} copies/mL), and inadequate virologic response was defined as HBV DNA levels of 2000 IU/mL or greater (4 log\textsubscript{10} copies/mL)\textsuperscript{36}.

**Recommendation**

We would opt for treating HBeAg positive CHB patients with elevated ALT more times above baseline. However per-cutaneous liver biopsies should be performed routinely in them if HBV DNA is positive by PCR irrespective of the viral load and/or normal ALT level. The reason being that a percentage of these patients show mild to severe chronic hepatitis on hepatic histology.

We also recommend treating these patients if there is significant hepatic necro-inflammation (i.e. HAI-NI >3) and/or significant hepatic fibrosis (i.e. HAI-F >3). Else we recommend following up the patients with regular, periodic ALT estimation and treat when ALT shows a rising trend (figure 2).

**Recommended for children, pregnant women and cirrhotics**

The recommendation for treating these groups is in line with that of HBeAg negative and positive CHB respectively with some special points to note.

In children, the response is poor with any anti-viral and hence treatment should be initiated with care. Some groups including our group recommend treating these patients with sequential combination of lamivudine and interferon, based
on encouraging outcome in limited number of patients\textsuperscript{37}, but there is not enough data at the moment to recommend this treatment.

In case of cirrhotics all oral anti-virals are safe; however injectable anti-virals are contraindicated in those with decompensated cirrhosis as this will lead to hepatic failure. However in decompensated cirrhotics, combination treatment with lamivudine and adefovir may be given considering the fact that this group of patients will require long term treatment and perhaps life long. However renal function should be monitored.

We recommend treatment with lamivudine (pregnancy category B) in the third trimester of pregnancy in both HBeAg negative and positive CHB, if they fulfill treatment criteria. This is likely to reduce the risk of vertical HBV transmission significantly\textsuperscript{38,39}.

**Recommendation for vaccination**

1. First degree relatives and house-hold contacts of HBsAg positive individuals.
2. All newborns born to HBsAg positive mothers. They should receive HBV immunoglobulin in addition routine vaccination.
3. Injectable drug abusers.
4. All patients with congenital haemolytic anaemia and on renal dialysis.
5. All healthcare personnel.

**References**

18. Arankalle VA, Chanda MS, Chobe LP. Five year follow up of HBsAg carriers. Indian J Gastroenterol 1999; 18 (Suppl): 27.


27. Papatheodoridis GV, Manesis E, Hadziyannis SJ. The long-term outcome of interferon alfa treated an untreated patients with HBeAg negative chronic hepatitis B. J Hepatol 2001; 36: 306-313.


Figure 2: Approach to HBeAg positive CHB

HBeAg +ve CHB

- HBV DNA <10^5 copies/ml by PCR
  - ALT normal
  - Follow up
    - ALT 3 monthly (1st year)
    - ALT 6 monthly (subsequently)
    - HBV DNA annually

- HBV DNA ≥10^5 copies/ml by PCR
  - ALT normal / <2 times normal
  - Liver biopsy
    - HAI-NI ≤7
      and/or HAI-F ≤1
      - Follow up
        - ALT 3 monthly (1st year)
        - ALT 6 monthly (subsequently)
        - HBV DNA annually
    - HAI-NI >7
      and/or HAI-F ≥3
      - Peg IFN (1 yr)
        - LdT
        - ETV
        - LAM
        - ADV

- HBV DNA ≥10^5 copies/ml by PCR
  - ALT ≥2 times normal
  - Liver biopsy (optional)
    - Peg IFN (6 months)
      - LdT
      - ETV
      - LAM

Stop treatment if
- HBV DNA -ve by PCR on 2 occasions at 6 months apart
- ALT normal
- HBeAg -ve
- Anti-HBe +ve

* Peg IFN first line drug of choice if DNA<10^7 copies/ml; otherwise LdT/ ETV
* ADV may be first line if HBV DNA low at baseline
* If on follow up HBV DNA +ve by PCR, manage as naive case
* If Peg IFN unaffordable, LdT/ ETV / LAM depending on availability and affordability
* If ALT and/or HBV DNA tends to rise on treatment, YMDD mutation study and add ADV to LAM / LdT and vise versa if YMDD mutation +ve; alternately ETV double dose