Review Article

Hepatitis B : A Review

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ABSTRACT

Approximately 4% of Indian population has evidence of chronic hepatitis B. Development of chronicity is related to age at infection and immune status of the individual. Chronic hepatitis B is a dynamic disease with various phases. Majority of the adults are in immune tolerance phase and do not require treatment but require follow up. Treatment decisions are based on presence or absence of cirrhosis, immune status of the patient and presence or absence of active hepatitis, Tenofovir or Entecavir are the agents of choice for treatment. Surveillance for Hepatocellular carcinoma is necessary in all individuals especially after 40 yr of age. Hepatitis B is completely preventable disease and universal vaccination is recommended.

Key words : Hepatitis B, Chronic Hepatitis B, Management of chronic HBV

Introduction -

Hepatitis B is a 42 nm, DNA virus belonging to family of hepadenaviruses. With more than 300 million HBV carriers globally it accounts for over 6,50,000 deaths/annum from HBV related liver disease[1]. India has an intermediate prevalence of approximately 4% with geographical variations within the country. India is estimated to harbor approximately 50 million carriers amounting to nearly 15% of the world burden[2].

The virus exists in a wild form or a mutant form most common being the pre-core mutant with inability to secrete e antigen. Patients with e Ag negative chronic hepatitis have a rapidly progressive disease with higher risk of cirrhosis and hepatocellular carcinoma (HCC). They also have a higher risk of relapse after therapy.

Ten genotypes (A to J) and various subtypes have been identified. The genotypes have geographic distribution and vary in their response to therapy especially to interferon. Genotype C is associated with more aggressive disease while genotype D is associated with a poorer response to interferrons. In India the predominant genotypes are A or D[3, 4] while another study from north India found genotype D predominance (68.3%) followed by Genotype A (25.7%) and C (5.9%)[5].

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Modes of spread -

Vertical mode of transmission is more common in high prevalence areas. In India the predominant mode of transmission is horizontal. In a North Indian study HBsAg carrier rates in ANC patients was reported to be 3.7% while HBeAg carrier rate was 7.8% and vertical transmission was seen in 18.6%[6].

In another study of 722 family members of 215 HBV index cases and in another study from North India of 12 families of chronic liver disease patients horizontal transmission was found in 60% & vertical transmission in 17% and both patterns in rest[7,8].

1. The risk of post transfusion hepatitis B has substantially, decreased after HBSAg screening of donor blood. If anti HBc is included in the screening the risk can be virtually eliminated but would lead to discarding of substantialportion of donor blood pool.
2. Sexual transmission is a major route of spread in developed countries probably accounting for nearly 1/3rd of cases. Male homosexuals are particularly prone for this mode of transmission.
3. Percutaneous inoculation of blood and body, fluids with needle sharing can occur in intravenous drug abusers, during tattooing, acupuncture and ear piercing.

4. Perinatal transmission occurs in 90% of neonates if the mother is HBeAg + with high viral load unless the baby is given passive + active immunization immediately after birth. Maternal-fetal transfusion during delivery and contact withmaternal blood in the birth canal are major ways of transmission.
5. Family members of HBV infected persons are at risk of acquiring infection if they share razors / tooth brushes / with close body contacts with minor skin breaks.
6. Health care workers are at risk of acquiring infection through accidental needle prick injuries, infection through minor cuts.

How are patients detected -

During the experience of hepatitis B registry with more than 700 patients I have experienced that patients HBS Ag positive status are detected by following means.

Table 1 : **Showing common ways by which HBs Ag positivity is detected**

Pre-operative work up	During hospital work up for unrelated disease
Investigation of chronic liver disease	Investigation of jaundice
ANC screening	During voluntary blood Donation
Executive health check up	Pre employment work up
Family screening of an Index case.	

Majority of asymptomatic patients are in chronic inactive phase and remain so on follow up. (unpublished data)

Pathogenesis -

Acute hepatitis B is usually a self limiting disease with a case fatality ratio of 0.5-1%.

Age is a key factor in determining the risk of chronic infection. Following an acute infection in neonates 90% become chronic carriers, in young children between age of 1 to 5 yrs. 20-60% become chronic carriers while in adults < 5% become chronic carriers[9,10].

Longitudinal studies of untreated persons with CHB show an 8-20% cumulative risk of developing cirrhosis over 5 yrs. In those with cirrhosis, there is an approximately 20% annual risk of hepatitis decompensation and the annual incidence of hepatitis B related HCC is high, ranging from 1 to 5%. Untreated patients with decompensated cirrhosis have a poor prognosis with 15-40% 5 year survival[11,12].

The major mechanism of liver injury in chronic hepatitis B is immune mediated. The virus itself is not cytopathic. The cytotoxic T Lymphocyte mediated hepatocellularlysis is the major mechanism of liver damage. Cytokines like TNF and interferon also contribute. The integrations of viral genome into hepatocytes and the X gene of the virus have been implicated in development of heaptocellularcarcinoma. The virus persist in the hepatocytes in the form of ccc DNA (covalently coiled circular DNA). This ccc DNA acts as a template for viral replication in future and is inaccessible for antiviral agents. Hence it is not possible to eradicate the virus with presently available therapies.

Serology : Persistence of HBS Ag for more than six months denotes chronic HBV infection and needs to be documented.

Anti HBcIgM is a marker of acute infection but can also be found to be positive in low titers in reactivation of chronic HBV infection.

HB eAg is a marker of viral replication and infectivity but precore mutant viruses can cause.

HB eAb negative chronic hepatitis.

AntiHB eAg is a marker used to denote serocon version and its presence in a patient with illness resembling acute hepatitis indicates that we are dealing with reactivation of chronic HBV infection rather than acute hepatitis B. This usually happens in upto 40% of infections in adults[13].

HBV DNA is a gold standard of viral replication and used to monitor response to therapy. All values must be reportedin IU/ml and same technique should be used to compare two values..

Anti HBs is a marker of protectivity and should be more than 10 IU/ml. These antibodies develops after an infection which getscured or following vaccination.

Phases of chronic HBV infection : The phases of chronic HBV infection are of variable duration and are not necessarily sequential. Chronic HBV is a dynamic infection and patients can shift between various phases of infection over a period of time.

1. Immune tolerance phase : Typically seen in patients who acquire infection perinatally. HBeAg is positive and viral load is very high but transaminases are entirely normal. Such phase typically lasts for 2-3 decades. These patients do not require nor do they respond to treatment. EAg positive adults older than 40 yrs. of age with high normal or marginally elevated liver enzymes can have significant liver necroinflammation and need evaluation to rule out significant liver disease[14].
2. Immune clearance phase : These patients are eAg positive and likely to convert to HB eAb positive state. They are usually jaundiced and have intermediate viral loads, enzyme levels are in hundreds to thousands. Low level IgM Anti HBc positivity can be seen.

   Outcomes of immune clearance phase

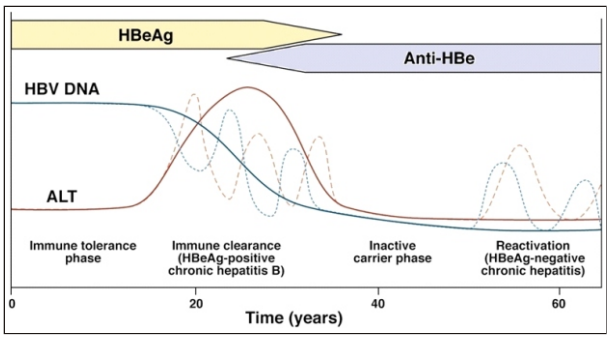
   A. Cure with loss of HBeAg, seroconversion to anti HBeAb positive state and loss of HBsAg spontaneously.

   B. Conversion to chronic inactive HBV infection stage which can.

      a. Remain inactive
      b. Show persistent low level activity
      c. Intermittent reactivation

   Patients with last two categories are likely to progress to cirrhosis if untreated.
3. Chronic inactive HBV infection can follow an immune clearance phase or after acquiring infection in adults. These patients are eAg negative, eAb positive and have low viral loads. They have normal enzymes. They require continuous follow up to keep a track of their viral activity.
4. Immune active phase : These patients have abnormal serum enzymes, are eAg positive, have intermediate viral loads. Symptoms may or may not be present but there is histological activity which if untreated progresses to significant fibrosis and cirrhosis. These patients need therapy.
5. Immune escape phase these patients have mutant virus. Most common mutation being in the YMDD motif of precorepromotor region because of which eAg is not expressed. These patients have a rapid progression of disease, have higher degree of relapse rates following treatment and increased risk of HCC.
6. Reactivation of HBV may occur spontaneous or may be triggered by cancer chemotherapy or other immunosuppressive therapy.
7. Occult HBV infection is defined as persistence of HBV DNA in the liver of person in whom HBs Ag is undetectable .This infection can get reactivated after immunosuppression due to any cause.

Figure 1 : **Showing serological events and phases innatural history of Hepatitis B infection.**



Diagnosis and categorization of patient -

Routine assessment of HBs Ag positive person includes additional serological markers of HBV infection (HBeAg, anti HBeAb, IgM anti HBC and HBV DNA titer),measuring aminotranferase to determine liver inflammation, assessing synthetic function of liver (Serum protines, prothrombin time) and assess liver fibrosis (non invasive test like APRI score, fibrotest, transient elastography using Fibroscan, or invasive test like liver biopsy).

Role of liver biopsy : Liver biopsy is considered to be the gold standard to assess fibrosis, inflammatory activity and presence or absence of cirrhosis. However it is not mandatory in all patients for treatment decisions. Secondly it is invasive, associated with bleeding albeit < 5%.

It is indicated in following situations.

1. Patients with borderline liver enzyme elevations with intermediate viral load where treatment decision cannot be done by these tests alone.
2. Where coexisting causes which can alter the liver function tests like NASH, Alcoholic liver disease, Wilson's disease exist. In these patients documentation of histological activity as well s clues to possible etiology could be sought by doing a liver biopsy.
3. In a research protocol. As an alternatives to liver biopsy for assessing fibrosis non invasive tests (NITs) have been proposed.

   APRI score is based on two indirect markers of fibrosis (AST and platelet count) which are easily available. APRI score is calculated by following formula

   APRI = (AST/ULN X100)/Platlet count 109/L

   APRI of >2 has been recommended for identifying adults with cirrhosis and in need of antiviral therapy.

   Measures liver stiffness using ultrasound technology have been use in last few years Transient Elastography using (Fibroscan) or ARFI (acoustic radiation force impulse imaging) are two available methods. However the cost of the equipment, expertise needed to get the desired examination, various other clinical condition affecting the values make a widespread use of these methods and standardization difficult. These methods also have limitation of tissue sampling errors and in future probably MR elastography which can measure the stiffness of entire liver may become the standard.

Indications of treatment[1] -

The aims of therapy are viral suppression and prevention of progression of liver disease. HBS Ag loss or cure rates are extremely low. Hence one of the intermediate goal in HBe Ag + patients is to achieve HB eAg serocon version (Loss of e Ag and development of e Ab). For others, keeping the virus suppressed, biochemical normalization and improvement in liver histology are the goals of therapy.

None of the available therapy can eradicate HBV infection as the agents cannot clear ccc DNA from hepatocytes. Hence treatment decisions need to be very cautions. In addition there is a risk of viral resistance which can have implications not only on patient but also on the community.

World Health Organization has published the most recent guidelines in March 2015[1] for managing and treating patients with Chronic HBV infection. The treatment recommendations are determined by age of the person, ALT levels, Viral load, presence or absence of cirrhosis. They can be summarized as follows

1. Patients in immune tolerance phase with normal transaminase do not need treatment and need observation with LFT repeated every 3-6 month.
2. Patients in chronic inactive infection with persistently normal enzymes also need only follow up with LFT repeated every 3 month.
3. Patients in immune clearance phase and those with chronic HBV infection with activity (ALT/Histology) need treatment. Patients with eAg negative chronic hepatitis need indefinite therapy in new of high likelihood of relapse following treatment withdrawal.
4. Patients with cirrhosis of liver require therapy and urgently if they are decompensated irrespective of their transaminase and DNA levels. Treatment is required indefinitely.
5. Patients with HBs Ag positive status undergoing chemotherapy or immunosuppressive therapy need therapy irrespective of disease activity/viral load, in order to prevent viral reactivation. Minimum duration of therapy is for 6 month post chemotherapy.

   Entecavir and Tenofovir are the first line therapies recommended at present because of their high barrier to resistance. Development of resistance

can be suspected is patient has clinical or biochemical or virological relapse. Changing to tenofovir is recommended for non tenofovir patients in case of resistance. PEG interferon was not even considered in WHO guidelines 2015 due to its less feasibility in resource limited settings, limitations on use in presence of cirrhosis, pregnancy, thyroid disease and psychiatric conditions.

The duration of therapy in patients of cirrhosis is lifelong. The response to treatment can be monitored by biochemical (ALT/AST), virological (HBV DNA) or serological status (HBs Ag, HBe Ag loss and conversion to anti HBeAb positive status for e Ag + ve patients).

Non cirrhotic patients stated on therapy can be considered for stopping therapy if persistent HBs Ag loss or persistent HBV DNA negatively along-with persistent biochemical normalization and stable e seroconversion is demonstrated on two occasions 1 year apart.

One year consolidation therapy post seroconversion or DNA negatively or HBs Ag loss is recommended. All patients who stop therapy should be carefully followed to assess reactivation.

Prevention -

HBV is completely preventable disease. HB vaccine is now included in universal program of immunization in India. For adults taking this vaccine, it is necessary to do at least Hbs Ag screening before vaccination in order to identify inactive HBV infection state. Hepatitis B vaccine is the first vaccine which can prevent cancer (Hepatocellular cancer).

Passive immunization with Hepatitis B immunoglobulin is recommended in newborns of HBS Ag + ve mothers andin unvaccinatedadults with exposure to Hepatitis B.

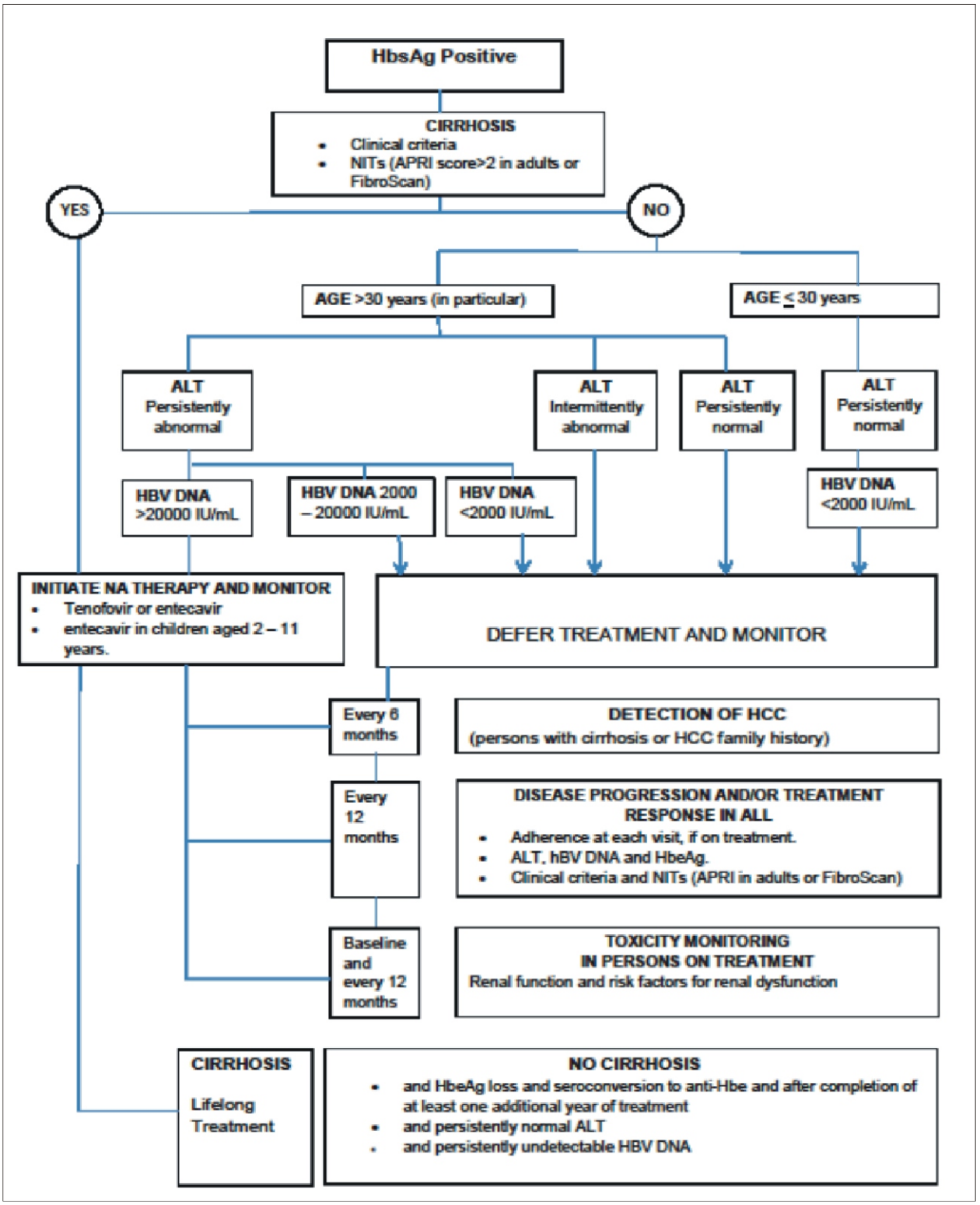
Family members of patients with chronic HBV infection need to be screened for HBs Ag and vaccinated if negative. Patients and family members need to be educated on not sharing tooth brushes or razors.

Health care workers must test for HBs Ag and get vaccinated. Universal precautions must be followed to avoid risk of infection. Disposal of waste sharp on site and avoiding needle recapping must be followed as most of the needle stick injuries occur during needle recapping.

Table 2 : **Showing rates of response to various agents for HBV therapy.**

Response Parameter	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir	Peg Ifn
HBe Ag+ patient At wk 48/52						
Undetectable HBV	36-44	13-21	67	60	76	25
HBE Ag	16-21	12-18	21	22	21	27
HBS Ag loss	<1%	0	2	0	3	3
Resistance	27	0	0	4.4	0	0
HBe Ag- vepts						
Undetectable HBV	60-73	57	90	88	93	63
HBS Ag loss	<1%	0	<1	<1	0	4

Modified from[15]



Algorithmic Approach in a Case of HbsAg Positive Patient

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