of the world without performing further and elaborative investigations. In addition, patients with resolved AHB are informed that they will never experience any future HBV-related illness because they harbor anti-HBs. However, flare of HBV of resolved AHB patients may occur in future due to change in life style or use of medications.

## Different Faces of the HBV-infection

Despite extensive and continuing intrahepatic replication of the virus, many HBV-infected persons are asymptomatic with almost no or minimum liver injury. This supports the concept that HBV is not directly cytopathic to the infected hepatocytes. In fact, HBV is not endowed with any cell destroying mechanisms; it does not harbor pathogenic island and incapable of producing toxins or cytolytic agents. The severity of hepatocellular injury is modulated by the nature and strength of the host immune responses to the virus. Infection with the HBV may induce an acute and self-limiting infection, fulminant and life-threatening hepatitis or chronic and persistent HBV-infection. Acute and fulminant infections by the HBV would be discussed in other chapters of this book and an account of chronic HBV-infection would mainly be provided in this chapter.

## Host Immunity; the Determinant of Chronic HBV-infection

Due to improved detection technologies, it is now evident that persistent presence of HBV DNA (a dominant marker of chronic HBV-infection) and anti-HBs (a hallmark of resolved AHB) are not so specific markers of chronic and acute HBV-infection, respectively. Both HBV DNA and anti-HBs are detected in patients with resolved AHB and chronic HBV carriers. However, the magnitude of replication of the HBV and the levels of concentrations of anti-HBs are different in resolved AHB patients and chronic HBV carriers. These markers represent a matter of quantitative concern, not a fundamental and qualitative difference. Thus, it is of utmost important to develop insights about why and how HBV replication and liver damages are usually controlled in acute HBV-infected subjects. However, these remain either semi-controlled or uncontrolled in chronic HBV carriers. Recent investigations have indicated that the replication of the HBV and expression of different HBV-related antigens and antibody are regulated by different subsets of helper T cells and cytotoxic T lymphocytes (CTLs). The role of HBV-specific and non HBV-specific adaptive immunity plays important role in this context. Also, the initial priming of innate immune system is related during determining the course of future HBV-infection.

## Ineffective Innate Immunity

After the entry of the HBV, cccDNA are produced in the liver. As mentioned before, cccDNA serves as the template for transcription of both messenger RNA

(for translation of viral proteins) and pre-genomic RNA (for reverse transcription into genomic DNA). HBV replication continues at the liver and viral antigens are expressed in the liver and the sera. Although HBV and its antigens are capable of stimulating different arms of innate immunity, it is poorly understood why there is no symptoms of acute infection within first 2–8 weeks of virus entry. It implies that cells of innate immunity are incapable of destroying HBV-infected hepatocytes. This is true for the neonatal or perinatal or adult HBV-infection. It is also true in the context of both acute and chronic HBV-infection. Thus, mere impaired innate immunity during acquisition of HBV-infection may not be accounted for pathogenesis of chronic HBV carrier state. The additional factors that may play critical role in the context of HBV-infection has not been explored in human.

## Nature of Adaptive Immunity in Infected Subjects and Chronic HBV Carriers

The nature of innate immunity should dictate the nature and magnitude of viral-specific adaptive immunity. In resolved acute HBV-infection, HBV-specific adaptive immunity is detected in some patients after so-called incubation period. This controls HBV replication and is followed by regulated and controlled production of HBsAg. Features of liver injuries are detected in some patients with acute HBV-infection. This seems to be due to destruction of hepatocytes by non HBV-specific immunocytes. Also, some HBV-specific CTLs may play a role in hepatocyte destruction, either by their direct cytopathic effect or indirectly by allowing migration of other immunocytes and cell-destroying factors. However, the infection is resolved because HBV-specific immunocytes including CTLs control viral replication and tissue damages to a minimum level. More important, HBV-specific immunity persist for decades in subjects with acute HBV-infection and these usually control further flare up of HBV replication in these subjects. However, immune suppression due to co-infection with immune suppressive virus or use of immune suppressive drugs may disrupt the HBV hemodynamics and may cause flare of HBV replication in these subjects. Some acute HBV-infected subjects may also progress to develop chronic HBV-infection, possibly due to waning of HBV-specific protective immunity.

Different scenarios may be considered during genesis of chronic HBV-infection. Epidemiological data indicates that infection during neonatal period or perinatal period usually leads to chronic HBV-infection. In addition, immune suppressed subjects are more prone to develop chronic infection after initial exposure to the virus. Similar to acute HBV-infection, the magnitudes of innate immunity are almost undetected in patients that develop a chronic infection after HBV-infection. Some chronic HBV-infected persons that acquire the HBV during neonatal or perinatal period develop features of liver damages about 2-3 decades after initial infection. On the other hand, some chronically HBV-infected persons never experience any features of hepatitis during their life time. It is now evident

that HBV-specific adaptive immunity including HBV-specific CTLs and anti-HBs are detected in patients with chronic HBV-infection. However, these immunocytes are incapable of controlling HBV replication to the levels of resolved AHB patients. The extent of liver damages is controlled by different mechanisms. Persistent and substantial levels of replicating HBV may cause influx of non HBV-specific immunocytes that cause liver damages without inducing effective virus-controlling immune responses.

## Sequel of Chronic HBV-infection

Certain people with chronic HBV-infection develop progressive liver damages such as liver cirrhosis (LC), liver failure and hepatocellular carcinoma (HCC). On the other hand, complications are not detected in vast majority of chronic HBV carriers. Clinical studies have supported that ineffective control of HBV replication play some role in the pathogenesis of progressive liver damages. Although the mechanism of development of LC and HCC is not well understood, persistent viral replication and improper HBV-specific immunity seems to be responsible for progressive fibrosis. In addition, persistent inflammation of the hepatocytes predisposes to oncogenetic changes of the hapatocytes. The oncogenic potentials of HBV and some of its antigens have been documents in animal models, but, these are yet to confirmed in the pathogenesis of human HCC.

## Magnitude of Problem with Chronic HBV Carriers

Of the 2 billion individuals infected by hepatitis B virus (HBV), over 350 million are chronic HBV carriers. Chronic HBV-infection is not only a personal problem rather, its impact on the society is tremendous. Considerable numbers of chronic HBV carriers develop chronic hepatitis B (CHB), and complications like LC, liver failure, or HCC during their life time. It is estimated that over a million individuals die annually of HBV-related chronic liver diseases. Chronic HBV-infection never represents a medical emergency, like influenza virus, cholera infection, bird flu virus, Ebola virus or even human immune deficiency virus. Thus, proper attention is merely focused to this disease. In addition, about 90% of chronic HBV carriers reside in developing countries of the world. The health care delivery system of these countries is not properly developed. Emerging infectious diseases like bird flue, human immune deficiency viruses and re-emerging infectious diseases like tuberculosis and malaria have attracted the attention of the government and mass media. Accordingly, there are few national programs to find out and tackle chronic HBV-infection in most Asian and African countries. Most of the chronic HBV carriers remain undetected in these countries. HBV-infection is detected when the patients become severely ill or develop serious complications. In some cases, their state of infection is detected incidentally when they visit the physicians for different causes. Study about the epidemiology of HBV-infection indicates that most chronic HBV carriers become infected with the HBV during their neonatal or perinatal

period. This indicates that majority of chronic HBV carriers would remain as living and permanent reservoir of the HBV for decades. In fact, they transmit the virus to healthy and non-infected individuals in most developing countries. This process is a dynamic one. Accordingly, it is less likely that the numbers of chronic HBV carriers will be reduced in near future. This is in sharp contrast with that what is seen in developed countries of the world. In most of these countries, HBV-infected persons are declining. Most of the patients have been detected by screening or there is an operational system that can detect chronic HBV-infection routinely. At least, further transmission of the HBV from HBV carriers have been brought to almost zero by proper screening of donated blood and using clean transfusion apparatuses in many developed countries.

## Phases of Chronic HBV-infection

Most of the chronic HBV carriers are infected with the virus at their young ages: neonatal period, perinatal period or early school-go going ages. HBV is never eradicated from these subjects, but, exhibit variable kinetics. The levels of HBV replication are extremely high in some period of life, whereas, it is low at other times. In addition, the kinetics of the HBV show marked individual variations. The extents of liver damages also vary considerably in these patients. Some patients never develop any features of considerable liver damages, whereas, the others exhibit features of hepatitis and complications. HBV-infected subjects may present: (1) in a state of immune tolerance, (2) with HBeAg+ CHB, (3) as an inactive HBsAg carrier, and (4) HBeAg-negative CHB. The patients with AHB that progress to chronic HBV-infection usually do not show immune tolerance phase. Chronic HBV carriers also develop complications like LC, liver failure or HCC. HBeAg+ CHB and anti-HBe+ CHB represent a phase of immune clearance or immune active state in their life cycle. Accordingly, some investigators have mentioned about three phases in chronic HBV carriers. These are immune tolerance phase, immune active phase, and inactive HBV carrier state. In Table 8.2, different phases of chronic HBV-infection in relation to presence of HBV DNA, HBsAg, HBeAg and anti-HBe have been shown. In addition, all chronic HBV carriers express

**Table 8.2: Different phases of chronic HBV-infection**

| | *HBV DNA* | *HBsAg* | *HBeAg* | *Anti-HBe* |
|---|---|---|---|---|
| Immune tolerance phase | Positive | Positive | Positive | Negative |
| Immune clearance phase | Positive | Positive | Positive or negative | Positive or Negative |
| Reactivation phase | Positive | Positive | Positive or Negative | Positive or Negative |
| Inactive carrier state | Positive | Positive or negative | Positive or negative | Positive or negative |

anti-HBc. Anti-HBs can also be detected in the course of chronic HBV-infection, however, the neutralizing capacities of these anti-HBs are yet to be confirmed.

### *Immune Tolerance Phase*

Patients who acquire HBV at birth or early child hood exhibit an initial immune tolerance phase that can be characterized by the presence of high levels of serum HBV DNA, HBsAg and HBeAg. In spite of active HBV replication, these patients do not exhibit features of considerable liver damages. This has been described as a consequence of immune tolerance to HBV-related antigens. However, HBV-specific immunocytes are detected in these patients. Thus, immune tolerance in its strict sense may not be applicable in these patients. Rather, these patients suffer from impaired or distorted immune responses. Although it is told that there is no liver damage in these patients, histological findings of minimal liver damages have been shown in these patients. The duration of so-called immune tolerance phase may be highly variable. In some patients, clinical liver damages or subjective symptoms are never detected throughout their life. Some patents become negative for HBsAg in the course of life and previous HBV-infection is manifested by presence of anti-HBc antibody. Some patients even develop anti-HBs and HBV replication is efficiently controlled in these subjects. It is elusive if these patients suffer from subclinical hepatitis or not. On the other hand, some of these patients enter into immune reactive phase and develop features of hepatitis.

### *HBeAg+ CHB*

In patients with perinatally acquired HBV-infection, transition from the immune tolerance to the immune reactive phase (HBeAg-positive chronic hepatitis) occurs during the second or third decade of life. This phase is characterized by the presence of HBeAg, high levels of serum HBV DNA, elevation of serum aminotransferase (ALT) levels, and histological findings of active inflammation and often fibrosis in the liver. Also, the levels of hepatitis may be highly variable. Some patients remain almost asymptomatic and damages of the liver may be detected by biochemical test only. On the other hand, moderate to severe hepatitis are detected in others. Patients in immune clearance phase may become negative to HBeAg with development of anti-HBe. In others, HBeAg continue to persist after flare of ALT. Even hepatic decompensation may occur after these flares. Immune active phase may appear spontaneously or may be induced by antiviral drugs.

### *Inactive HBV Carrier*

After immune active phase, some patients remain negative for HBeAg and positive for anti-HBe antibody. Seroconversion is usually, but not always, accompanied by control of hepatic flare. These patients show normalization of ALT levels and decreases in HBV DNA to low or undetectable levels. This condition is commonly referred to as the 'inactive carrier state'. Histologically, minimal to mild hepatitis

may be observed, although the degree of fibrosis may be variable. Most patients remain in this phase for many years, if not indefinitely. Their prognosis is generally favorable, particularly if this phase is reached early in the disease course. Immune active phase may persist for long or there may be reversion to HBeAg+ phase with increased viral replication. There may be complications like LC and HCC after immune active phase. Although HBeAg seroconversion is seen in some patients in immune active phase, seronegativity of HBsAg is not so common. Seroconversion to anti-HBs is more uncommon. However, the levels of HBsAg negativity or anti-HBs development are seen more in European natives than in patients from Asian countries. HBV genotype is considered to be a factor in this regard.

### *HBeAg-negative CHB*

Although HBeAg negativity and development of anti-HBe is usually considered as good prognostic marker of chronic HBV carriers, chronic hepatitis may recur in up to one third of inactive HBV carriers without reversion of HBeAg in their serum. Some of these carriers are likely infected with one of the HBV variants that cannot express HBeAg because of mutations in the precore or core-promoter regions of the HBV genome. Most patients progress to this phase after a variable length of time in the inactive HBV carrier state, whereas some progress to HBeAg-negative chronic hepatitis directly from HBeAg-positive chronic hepatitis. This phase is characterized by the absence of HBeAg, the presence of anti-HBe antibody, detectable levels of HBV DNA, elevated levels of serum ALT, and histological findings of continued necroinflammation of the liver. Compared to those with HBeAg-positive chronic hepatitis, patients with HBeAg-negative chronic hepatitis are generally older, have more advanced disease as evidenced by liver histology, and have lower serum HBV DNA levels.

## RISK FACTORS FOR PROGRESSIVE DISEASE

HBV can cause both acute and chronic infection. Once a person is infected with the virus, it is never completely eradicated from the hosts. Patients with acute HBV-infection or resolved AHB may develop flare of HBV-infection or develop progressive chronic infection. Infection with the HBV is related with development of complications like LC, liver failure and HCC. Accordingly, there is need to develop understandings about the risk factors for progressive diseases. At present, it seems that several factors will increase the likelihood of developing liver damage and HCC in chronic HBV-infection. Viral factors include HBV genotype; persistently elevated HBV DNA levels; and specific mutations in the HBV genome, including mutations in the precore (PC) and core promoter regions of the virus. Eight genotypes of HBV (A–H) have been identified that differ in complete genomic sequence by $\leq 8\%$ from each other. In addition, many subgenotypes, which differ by 4 to 8% are now also recognized. Although genotyping of the HBV is not a routine procedure in HBV management, some insights about their

influence are needed. Genotype A is found in sub-Saharan Africa (A1) and northern Europe and the United States (A2). Genotype A1 is associated with HCC in young males, often without cirrhosis, whereas genotype A2 is associated with cirrhosis and HCC in older persons. Genotypes B and C are found in the Far East, Southeast Asia, and the Pacific. Genotype B comprises 2 subgroups, one where part of genotype C is recombined into the core region of genotype B (B2–5) and one without recombination (B1 and B6). Genotype C is believed to be linked to a more aggressive disease course, associated with high rates of HCC and cirrhosis. Genotype D is found in the Mediterranean countries, eastern Europe, the Middle East, and the Indian subcontinent and has been associated with chronic anti-HBe-positive hepatitis B. Comparison studies have suggested that genotype D is associated with a more adverse outcome than genotype A2. Genotype E is found in Central Africa, but little is known about the outcome of those infected with this genotype. Genotypes F and H are found in indigenous populations in the Americas; genotype F has been associated with HCC in children and young adult Alaska natives, often without cirrhosis. Although information about different genotypes has been published, little is known about genotype of HBV in most developing countries. There are some pilot studies about HBV genotype in developing countries, but, more epidemiological studies are needed in this regard.

In addition to genotype, certain viral mutations, including the PC and basal core promoter (BCP) mutations have been associated with an increased risk of developing cirrhosis and HCC. The PC mutation is a single substitution at base pair 1896, resulting in a G to A mutation. This mutation results in the creation of a stop codon that prevents the formation of HBeAg (at the translation level) and down regulates HBV DNA, however, HBV DNA replication can still occur at a sufficiently high rate so as to result in liver inflammation and ongoing fibrosis. This mutation is more frequently found in individuals with anti-HBe-positive CHB, but can also be found in inactive anti-HBe-positive carriers. The BCP mutation is a double mutation in the core region of HBV that reduces the production of HBeAg by down regulating the transcription of precore mRNAs; this mutation is associated with HCC in individuals infected with genotypes A, B, C, and D, but not genotype F. Tests for both of these mutations are commercially available but because these mutations can occur in patients without serious liver disease, their interpretation requires a detailed analysis of the individual clinical situation.

Coinfection with hepatitis C virus increases the risk for cirrhosis, and especially for HCC. Coinfection with the hepatitis D or "delta" virus also increases the risk for cirrhosis. HBV and HIV coinfection is associated with more severe liver inflammation. Other risk factors for HCC in HBV-infected individuals are male sex, older age, and family history of HCC Persons with hepatitis B who have these risk factors should be screened semiannually with liver ultrasound and perhaps measurement of serum alpha-fetoprotein in an attempt to detect HCC at a treatable stage. All persons found to be HBsAg-positive should be tested for hepatitis C, HIV, and hepatitis D virus infection.

Hepatitis A virus and hepatitis E virus are present in developing countries of the world. HBV carriers are also predominant in these countries. The effect of co-infection of HBV with HAV and HEV should be studied.

## MANAGEMENT OF CHRONIC HBV CARRIERS

### What is Clear about Management of Chronic HBV Carriers and the Practical Problems

Treatment and management of chronic HBV-infected carriers will be discussed in details in other chapters of this book. We would discuss only some points that are relevant in the context of their management in developing countries.

Complete eradication of HBV from the infected hosts is an unachievable goal. Treatment is aimed at delaying complications and improvement of quality of life. The more specific objective of therapy is to reduce the levels of HBV replication as well as to restore host immunity that would control the virus, but, will not cause liver damages. Considering these factors, treatment is now internationally recommended for chronic HBV carriers with features of liver damages. In other word, the patients should be in immune active phase to be a recipient of antiviral drugs. This is because the immune modulatory capacities of commercially-available antiviral drugs are neither satisfactory nor uniform in different patients. These factors indicate that immune modulator agents may be used to restore immunity in chronic HBV carriers. More specifically, there is need to induce HBV-specific antiviral and protective immunity in chronic HBV carriers. In this regard, new types of immune therapy using HBsAg-based vaccine have been used in these patients. Although some pilot studies have shown some beneficial effects of HBsAg-vaccine therapy in CHB patients, it seems that the present regimen of HBV-specific immune therapy would not stand the test of time. Now, different types of immune therapy that uses HBcAg or cell-based immune therapy have been applied to these patients. Immune therapy may be used alone or as a part of combination therapy with antiviral agents in CHB patients. The duration of treatment may be finite (in case of interferon) or infinite (in case of nucleoside analogs). Patients receiving antiviral drugs should be regularly followed-up. This is especially true for patients receiving nucleoside analogs. It is true that if a patient is indicated to receive antiviral drug treatment, he or she deserves the treatment. But, the prescribing physicians should also consider whether the patient will be able to continue the therapy. Also, it is needed to assess if the health care delivery system of that society will be able to support the patient regarding adverse effects of these drugs. It is important that there is no viable health insurance system in most developing countries of the world, and all expenditures for treatment must be carried by the patients. There are several instances when it is better not to start treatment by antiviral drugs in many patients of the developing countries. In addition, drugs that are indicated for chronic HBV carriers are sold in open market and can be bought without any prescription. The traditional doctors are aware of the presence of different new antiviral drugs against the HBV. They prescribe the vast majority of chronic HBV carriers with these drugs for limited

duration, but not for adequate period of time. These patients will not be benefited from these drugs. Rather, the confidence of the patients will be reduced and many of these patients may suffer later from side effects or partial treatment. This will provide a tremendous negative impact on health care delivery system of these countries.

## ANTIVIRAL DRUGS, MUTANT HBV AND ITS FUTURE IMPACT

Rationale and irrational use of antiviral drugs, especially some nucleoside analogs, may give rise to mutant HBV in chronic HBV carriers. These patients should be properly followed-up and treated with combinations of antiviral drugs or other means. However, most of the patients with drug-induced mutant HBV in developing countries remain unaware about their pathological conditions. As both vertical and horizontal transmission of HBV has not been controlled in most developing countries, transmission of mutant HBV from chronic HBV carriers to healthy individuals is a reality. The ultimate outcome of this is yet to be explored by epidemiological studies, however, random transmission of mutant HBV may provide a tremendous burden on existing health care delivery system of developing countries.

## EPILOGUE

The world harbors about 350 million chronic HBV carriers that exhibit considerable levels of HBV replication and it is unlikely that these patients will ever be able to eliminate the virus. In addition, about 2 billion people have been infected with the HBV during their life time. Although the replication of the HBV is under control in these patients, some of them may enter into the list of chronic HBV carriers in future. Whatever the name we use to denote chronic HBV carriers, it is possibly true that once one is infected with the HBV, the virus remains in the host forever in some form either in the blood or in the liver or in both places. The cunningness of the interplay between the HBV and the host indicate that mankind has to live with this virus for more than one or more centuries. The challenge is to find out a strategy for peaceful coexistence of human race with this virus. Many features of this virus are already known. It is a tricky virus. It is localized not only in the liver, but, also in other extrahepatic sites including cells of the immune systems. The virus does not ensue an emergency situation for the host immediately after infection, rather it remains silent for decades. This allows the virus to alter tissue microenvironment and host immunity slowly and some times irreversibly. This virus is adapted to hide and fight strategy. It causes exacerbation of liver damages, which is usually followed by a stage of remission. Drugs that are effective against this virus can be found in the market and more and more potent antiviral drugs are on the list of development. Also, a potent vaccine against the HBV is available for the last 3 decades. The major limitations to conquer this virus lie in our limitation to fix global strategy. It is the time to admit that the world is extremely heterogeneous in the context of economy, medical infrastructure, social values, and also public health delivery system. Scientists of the developed countries provide

recommendations for management and therapy and these are supported by professional organizations like AASLD, EASL, APASL, and JSH. These messages are transmitted to developing countries, but, the health care delivery systems of these countries are not prepared to implement this. Defective implementation of scientific know how may cause devastating outcome in the context of chronic HBV-infection. The following strategies may help to overcome problems with chronic HBV-infection in global context:

1. Screening of chronic HBV carriers, especially those among high risk group.
2. Vaccination of healthy individuals with proper maintaining of quality of vaccines and immunization schedule. It would be better if anti-HBs is checked after vaccination to assess the efficacy of vaccination.
3. Proper controlling of drug legislation so that medical prescription is needed to buy antiviral drugs and the man behind the machine can make a proper judgment about the scope and limitations of these drugs in the context of patient's socioeconomical conditions.
4. Formation of treatment guideline for individual countries on the basis of scientific knowledge and socioeconomic conditions.
5. Development of medical facility to detect mutant HBV.
6. Frequent transmission of knowledge among developed and developing countries so that a bridge can be developed so that a mutually-beneficial clinical research net work can be materialized.

Chronic HBV-infection is not just a disease entity, rather it a major challenge to mankind that test our preparedness to tackle other chronic emerging and re-emerging diseases in the global context.

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# Comprehensive Textbook of Hepatitis B

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Chapter 11

# HBeAg-Negative Chronic Hepatitis B

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## INTRODUCTION

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-infection is between 20% and 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 liver cirrhosis and 66% cases of hepatocellular carcinoma in Bangladesh.

There is high prevalence of HBeAg-negative chronic hepatitis B in our population. In our series, we found 48.7% chronic hepatitis B (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.

## 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 $<10^4$ copies/mL and normal or near normal hepatic histopathology. In carriers, seroconversion 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 precore or core promoter region of the viral genome giving rise to HBeAg-negative CHB.

Besides, HBeAg seroconversion 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 the 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 55 negative for HBeAg. It was observed that 20.8% patients with HBeAg-negative 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 $\leq 3$) was also more frequent in the HBeAg-negative CHB group (28.3% patients 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 recent 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% patients. Similar experience is also shared by studies from Korea, Turkey, Egypt, Greece, China and India.

## 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 antiviral medications. A recent paper from Taiwan reports that the cumulative probability of hepatitis relapse in HBsAg carriers was 26.9% in males and 12.5% in 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 1241.

Definitive diagnosis of precore mutation involves sequencing of viral genome. 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. $<10^4$ 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 mis-diagnoses 45% HBeAg-negative CHB as chronic inactive HBsAg carriers. The study further revealed that even HBV DNA measurement on three separate occasions also mis-diagnoses 30% cases. Besides, a study of 196 CHB patients revealed that 10.5% HBeAg-negative CHB patients had HBV DNA <30,000 copies/mL.

The only way to distinguish between these two entities in a clinical setup is, therefore, performing a liver biopsy.

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 seroconversion 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 endpoint of treatment in this group remains extremely difficult. The American Association for the Study of the Liver (AASLD) in its recent CHB guideline advocates treatment of HBeAg-negative CHB patients till HBsAg becomes undetectable. 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.

Besides this, all oral antivirals 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). This means that there will be high risk of introducing mutant HBV strains.

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 antivirals, like patients resistant to LAM will have cross-resistance to telbivudine (LdT) and vice versa.

Interferon-α (IFN) for 48 weeks is associated with 38–90% response in HBeAg-negative CHB patients as opposed to 0–39% response in controls; however, approximately 50% responders relapse posttreatment, some as late as up to 5 years. The sustained response may, however, be increased with prolonged treatment. 30–40% of these relapsers show sustained response following a second course of IFN-α. 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 combination.

LAM is a nucleoside analog that yields 60–70% HBV DNA negativity at 1 year in HBeAg-negative CHB, but 90% of these responders unfortunately relapse posttreatment.30 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 mutants, where addition of adefovir (ADV) or switching over to double dose entecavir (ETV) 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 treatment. 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

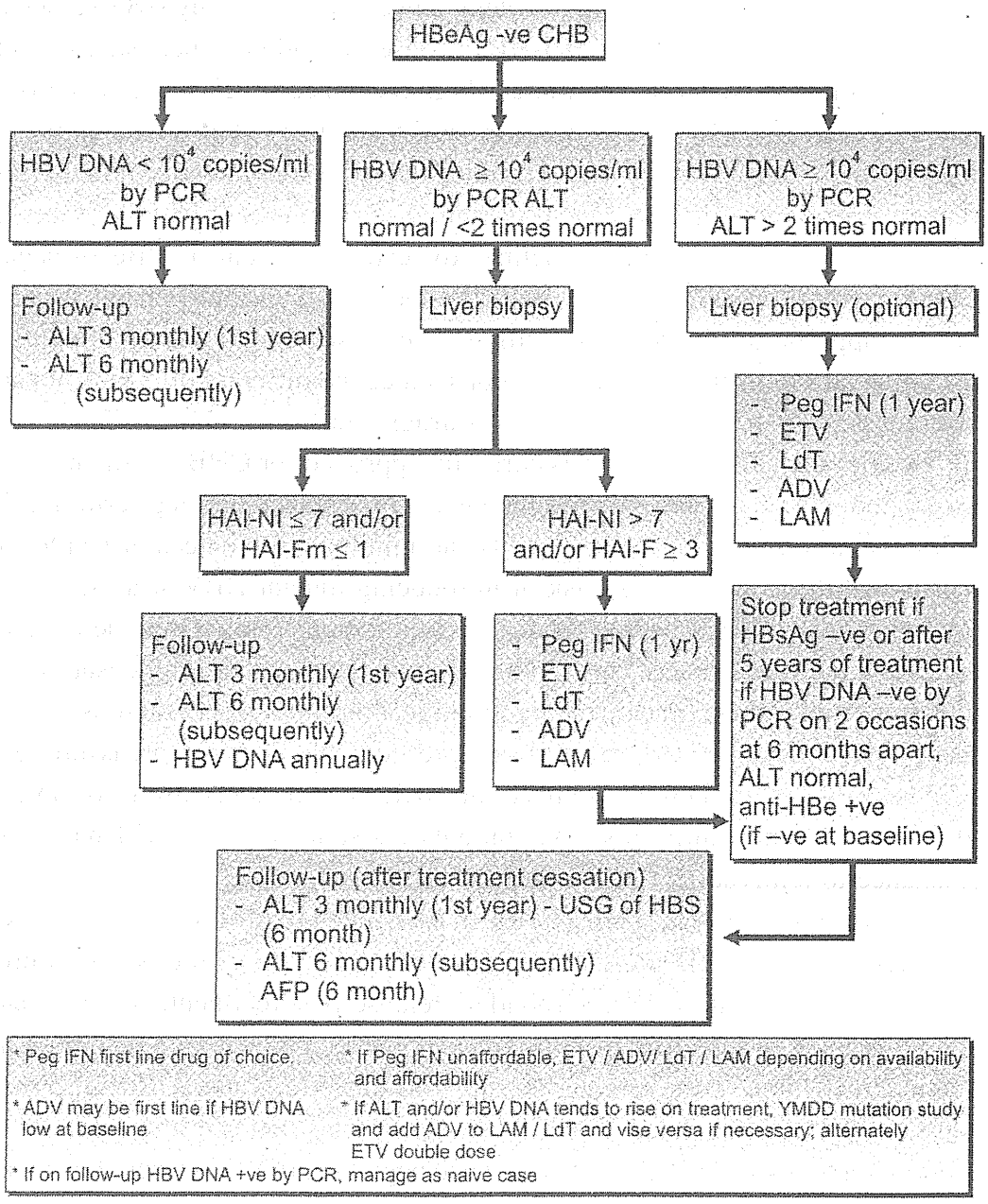


**Fig. 11.1:** Approach to HBeAg-negative CHB

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. It is much superior to LAM or ADV and is effective in LAM-resistant cases. At 48 weeks, ETV yields HBV DNA negativity in 90% HBeAg-negative CHB patients as compared to 78% with LAM.

Telbivudine, an L-nucleoside analog, is a newer addition to growing list of oral antivirals for CHB and at 1 and 2 years shows much better response to LAM in HBeAg-negative CHB. 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 (Fig. 11.1).

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# Comprehensive Textbook of Hepatitis B

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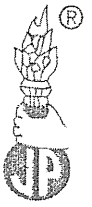

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