Revisiting the Natural History of Chronic Hepatitis B in Asian Americans

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Abstract

Worldwide, there are estimated to be 400 million people chronically infected with hepatitis B virus (HBV). In Asia, perinatal transmission of HBV from mother to newborn accounts for the high incidence of CHB infection Perinatally acquired CHB patients have unique features in their natural history, characterized by a long duration of immunotolerance phase, unpredictable patterns of disease reactivation and inactivation, and high risk for cirrhosis or HCC. Asian Americans, 60% of whom are foreign born, thus have similar patterns in the natural history of their disease. This article is a systemic review on the natural history of CHB in the Asian and Asian American population. Future research directions in this special population will also be explored.

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Abbreviations:

HBV, hepatitis B virus; HBIG, hepatitis B immunoglobulin; CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBsAb, anti-HBsAg antibody; HBcAb, anti-hepatitis B core antibody; HBeAb, anti-HBeAg antibody; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase ; AST aspartate aminotransferase.

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Introduction

Hepatitis B is one of the most common infections worldwide with an estimated two billion people infected with hepatitis B virus (HBV), resulting in 400 million people with persistent chronic infection[1] and an additional 50 million new cases of HBV infection diagnosed annually.[2] HBV is characterized by its high resilience and its ability to survive outside the body for significant periods of time, which contributes to its high infectivity. HBV has the ability to integrate into the host genome, making the virus difficult to eradicate by the immune system or by pharmacotherapy. However, most evidence suggests that liver injury is caused by the host's immune response against HBV, rather than by the virus itself.[3] Persistent HBV infection can lead to severe complications. Eventually, approximately 25% of the HBV carriers (over 1 million people annually) will develop liver cirrhosis and/or hepatocellular carcinoma (HCC).[1] The global geographic distribution of CHB infected populations are predominantly concentrated in endemic countries (**Figure 1**) with high (> 8%) and intermediate (2-7%) prevalence rates of hepatitis B surface antigen (HBsAg). Although United States (US) is listed as a country with low prevalence, CHB screening events in predominantly Asian communities of New York City, found similar prevalence results comparable to Asia, where prevalence of HBV infections is significantly higher than 8%.[4] The prevalence of chronic hepatitis B infection in the US is underestimated. In the past, the CDC estimated the total burden of CHB in the US to be 1.25 million individuals.[5] This estimation was based on the National Health and Nutrition Examination Survey (NHANES) for the period 1988-1994, which excluded institutionalized and incarcerated individuals. While African Americans and Hispanics were well represented, Asians, Pacific Islanders, Native Americans, and other migrants from native countries endemic with HBV were under-represented. Supplemented with data from the American Community Survey and from other published studies on CHB specific rates from the literature, the latest 2008 CDC update increased their estimates to as high as 1.4 million.[5] Recent publications have suggested that the total prevalence of

chronic hepatitis B in the US may be as high as 2 million with Asians and Pacific Islanders contributing close to 800,000 individuals.[6,7] The highest reported estimate of CHB in the US is potentially 3 million. This estimate was calculated by using the number of foreign born (FB) persons living in the US from 93 countries/regions provided by the US Census and factoring in the rate of chronic hepatitis B from their country of origin using > 900 prevalence studies with priority given to large peer reviewed. The number of FB with CHB in the U.S. ranges from 850,000 to 2,240,000 with over half from Asia. With the addition of 400,000 to 800,000 U.S.-born with CHB, this increases the total CHB disease burden to potentially as high as 3 million.[8] The growing prevalence in the US, especially in Asian-Americans, is contributed by the long duration of HBV infection, the influx of a large number of new immigrants in recent years from Asia.[9,10] improved public awareness and screening activities in Asian community in the US.[11] As the disease burden of CHB increases in the US, treatment candidate selection and the timing of treatments are even more difficult without fully understanding the risk factors and their impact on disease progression with complications. This article provides a systemic review on the natural history of CHB in Asians and Asian American population, unique groups that deserves further research endeavors.

HBV Genotypes and Mutants

HBV is a member of the hepadnavirus family featuring a partially double-stranded DNA and a very complex structure. It has four overlapping open reading frames (S, C, P and X region) which enable the virus to condense its coding information into a length of DNA that would otherwise need to be 1.5 times longer.[3] The genotypes of HBV have geographical distributions associated with anthropological history (**Table 1**); there are presently 8 viral isolates, genotypes A-H, identified by the sequence divergence of the entire DNA genome in excess of 8%. HBV genotypes B and C are predominantly in Asia. Several genotypes have been linked to severity of the disease but a causal relationship leading to hepatocellular carcinoma has yet to be established. HBV genotype C has been associated with cirrhosis and HCC;[12,13] it was more prevalent in those with HCC who were older than 50 compared with age-match asymptomatic carriers (41% vs. 15%, $p < 0.005$).[14] However, other studies did not conclude such association.[15,16] There is some evidence that shows HBeAg seroconversion occurs at a younger age among individuals infected with genotype B, and thus leading to a possibly improved prognosis.[12,16,17] HBV strains of the same genotype can be further divided geographically by subtypes, which not only differ by region but can behave virologically and clinically distinct.[18,19] For genotype B, there were formerly two major groups, HBV Bj specific to Japan and HBV Ba or B Asia found throughout Asia.[20] Bj may have a lower incidence of HCC that develops at an older age. In contrast, HBV Ba in Taiwan may have a higher incidence of HCC and occur at a younger age.[21] Although some virological differences such as presence of HBeAg and double mutation in the core promoter have been noted between the two subtypes, current studies have not concluded an influence on long-term clinical outcome.[22,23] Recently, Bj has been reclassified to B1 found in Japan and Ba into four distinct subtypes, B2 (China) B3 (Indonesia), B4 (Vietnam) and B5 (Philippines).[24] HBV sub-genotype Ba is a compilation of subtypes derived from the recombination of core regions of HBV genotype C onto the genotype B core HBV. B6, the newest subtype of genotype B, was found in the Artic indigenous people of Alaska, Canada and Greenland.[25] This virus is phylogenetically related to B1 and may have evolved from B1 (Japan) centuries ago. Genotype C is presently divided into C1, C2 and C3 and can be found in China, Korea, Southeast Asia and the South Pacific. A recent large prospective study from Hong Kong showed genotype C had a higher risk of HCC than genotype B with the highest risk from genotype C2, followed by C1.[26]

HBV has a reported mutation rate 10 times greater than other DNA viruses, some occurring naturally or under selective pressure from the host immune system or from antiviral therapy. There are at least four clinically relevant HBV natural variances or mutated types: wild-type HBV, precore mutants, core promoter mutants, and polymerase mutants in both naïve and treatment experienced patients.[27] Mutations in the precore and core promoter regions result in the reduction or loss of the virus's ability to produce hepatitis B e antigen (HBeAg) and development of HBeAg-negative HBV infection.[28,29] In a US conducted study, the precore variant of HBV was rarely found in CHB individuals with genotype A, but it was found in almost 50% of those with genotype C and in > 70% of individuals with genotype D.[30] Infection with precore variant and core promoter mutations lead to higher observed HBV DNA levels in sera than infections without these mutations. Among patients with biochemical flares related to chronic HBV, an increase in the concentration of precore mutations in proportion to wildtype HBV develop. As exacerbations subside with time, genetic heterogeneity disappeared and patients became exclusively infected with precore HBV.[31] A recent study in Asians and Asian Americans found that as high as 23% of treatment naïve wild type (HBeAg positive) infected patients have co-existing precore or basal core mutants.[32] These individuals tended to be older (age> 30) and have serum HBV DNA levels > 5 x log10 c/ml. Precore mutants were commonly found with genotype B infection, while basal core promoter mutants were with genotype C. The impact of these mutants on HBeAg sero-reversion, disease exacerbations or disease progression in HBeAg positive patients remains to be ascertained.

HBV Perinatal Transmission in Asians and Asian Americans

In Western countries with low endemic rates of less than 2%, HBV remains predominantly a disease of adolescents and adults as a result of high risk sexual behavior or injection drug use.[33] However, perinatal or horizontal infections early in childhood are the main routes of HBV transmission in the high endemic regions of Asia, Africa, Pacific Islands and the Arctic; the rate of HBsAg positivity ranges from 8% to 15%.

Perinatal transmission is believed to account for 35-50% of hepatitis B carriers.[34-37] Prior to standard passive-active immunoprophylaxis adopted in Asia, about 70 to 90% of children who born to the mother with both HBsAg and HBeAg positive CHB became chronically infected.[38] Postnatal hepatitis B immunization is by far the most effective treatment and is recommended by both the CDC in the US5 and the Advisory Committee on Immunization Practices in Asia[39] for preventing perinatal transmission of HBV. According to the recommendations, all infants born to HBsAg positive women should receive hepatitis B immune globulin and the first dose of hepatitis B vaccine within 12 hours of birth, followed by the completion of the hepatitis B vaccine series within the first year of age. In Asia, where there is a high preponderance of CHB mothers with the high viral loads (HBV DNA>9 logs10 copies/mL), prenatal transmission can still occur despite the use of HBV immunoprophylaxis. In mothers with HBV DNA concentrations > 108-9 copies/mL, transmission rates from 9-32% have been reported in infants receiving HBIG and hepatitis B vaccine at birth.[40,41] In the US, 97% of pregnant women received prenatal screening before delivery.[42] However, many of the identified CHB pregnant women did not receive additional diagnostic testing to identify those with high risks for transmitting the HBV to their newborns. Despite ACIP recommendations for HBIG and vaccines, some newborns are not receiving HBIG within 12 hours of birth or their first dose of hepatitis vaccine before discharge from the hospital. Cases of perinatal HBV transmission has been reported in the US by CDC and these numbers may underestimate the actual incidence.[43]

Natural History and Complications in Asian Patients Infected with HBV Early During Childhood

In those who acquire HBV early in childhood, the typical disease model of their CHB can be divided into four distinct continuous phases. Most HBV infected individuals will generally transition through most of these phases before achieving disease remission or unfortunately, developing complications of cirrhosis or HCC. However, there are distinct differences in the natural history of CHB infection between Asian (majority from perinatal transmission) and Caucasian populations (mainly from horizontal transmission) although their disease is caused by the same hepatitis B virus. Chronic HBV infections in Asian patients frequently are waxing and waning; it goes through alternating cycles of high-replicative and low-replicative phases with unpredictable patterns on disease reactivation or inactivation. Such patterns are rarely seen in Caucasian population or other ethnic groups infected with HBV from horizontal transmission.

1. Stages of Chronic HBV Infection

Individuals with acute HBV infection can achieve immune clearance of the virus and develop lifelong immunity which is recognized by the loss of HBsAg and the appearance of anti-HBs. However, an alternate fate of the host is the development of chronic hepatitis B. Prior to hepatitis B immunoprophylaxis, the age of acute hepatitis B exposure influenced the risk of developing chronic hepatitis. After exposure to HBV, CHB can develop in 90% of newborns from HBeAg positive CHB mothers, 25-30% in those under 5 years and 5% of adults.[44-46] There are four stages of CHB based on viral-host interaction: immune tolerant phase, immune clearance phase, inactive carrier phase and reactivation phase (**Figure 2**). The immune tolerance phase is characterized by little or no symptoms, HBeAg positive status, high levels of serum HBV DNA, normal ALT levels and minimal histological activity in the liver. This first phase can last for years in those who acquired the infection during the perinatal period[2] and is considered a highly infectious period for transmitting HBV via blood or bodily fluids. In a recent Chinese study of immunotolerant patients with documented persistently normal ranges of ALT values (< 40 U/L) and liver biopsies that demonstrated minimal histological activity, 15 percent of the subjects developed progression of their disease over a five year period.[47] The second stage of CHB is marked by the loss of tolerance of the HBV infection by the host immune system. The immune clearance phase, defined by immune-mediated lysis of infected hepatocytes, is generally characterized with decreasing HBV DNA levels and increasing ALT levels, duration of which can lasts from months to years. Successful immune control of the HBV virus can result in seroconversion of HBeAg to anti-HBe, non-detectable or low level serum HBV DNA and normal ALT levels, a phase of quiescence or inactive disease that can last years or lifetime. However, a subset of individuals after reaching this disease point can develop spontaneous or immunosuppression-induced reactivation of their chronic hepatitis. Partial immune control of the HBV replication, often attributed to precore or basal core mutations, may lead to HBeAg negative CHB. This is the most frequent described scenario for the fourth or reactivation phase of CHB, patients with elevated levels of ALT, high levels of DNA, moderate to severe liver histological activity and anti-HBe status. However, in terms of disease progression of CHB over time, the reactivation phase includes not only patients with HBeAg negative disease but also those with the HBeAg sero-reversion, the reappearance of HBeAg positive active hepatitis after HBeAg sero-conversion. In a natural history study of 283 Taiwanese patients, the long outcome of individuals with spontaneous HBeAg seroconversion over 8.6 median years showed 4% developed HBeAg reversion and 24% progressed to HBeAg negative CHB.[48] Chu et al. observed that reactivation occurred at 3.3% per year in HBeAg negative patients.[49]

2. Cirrhosis

The survival of patients diagnosed early with CHB is excellent, an estimate of 97% at 5 years.[50] However, the long-term complications of chronic HBV infection are cirrhosis and hepatoma which significantly increases morbidity and mortality. In untreated, non-cirrhotic patients, the incidence of liver related death is low, ranging from 0 to 1.06 per 100 person years. Unfortunately, the mortality rate dramatically increases to 16% in 5 years for those with

compensated cirrhosis and 65% to 86% for decompensated cirrhosis.[51,52] In a study of treatment naïve individuals with predominantly HBeAg positive chronic hepatitis B, the incidence of cirrhosis ranges from 2 to 5.4 per 100 person years with a 5-year cumulative incidence of cirrhosis of 8% to 20%.[33] Higher rates of cirrhosis have been reported in HBeAg-negative as compared to HBeAg-positive patients. Older age and persistent viral replication were consistently found to be positive predictors of cirrhosis and higher mortality. The REVEAL study analysis which included more than 3500 patients from Taiwan with a mean follow-up period of 11 years, showed the cumulative risks of cirrhosis and HCC increased significantly with increased baseline serum HBV DNA concentration. The incidence of cirrhosis increased respectively from 4.5% to 36.2% (relative risk 1.4 vs.9.8) in patients with baseline serum HBV DNA < 300 copies/mL versus patients with ≥ 6x log10 copies/mL or higher. Although the relative risk of cirrhosis was only 2.5 for serum HBV DNA concentrations between 4xlog10 and 5xlog10 copies/mL, 40% of the patients with cirrhosis had serum HBV DNA concentrations of ≤ 4log10 copies/mL. This relationship remained statistically significant after the analysis was adjusted for age, sex, cigarette smoking, alcohol consumption, ALT activity, and HBeAg status. It was also statistically significant in chronic carriers of HBsAg who were HBeAg negative with normal ALT level and no evidence of cirrhosis at study entry. The presence of any other independent hepatotoxic factors such as alcohol ingestion and HCV co-infection can contribute to progression to cirrhosis. Once cirrhosis is established, individuals can decompensate over time.[53] In the EUROHEP cohort study, the 5-year cumulative incidence of hepatic decompensation was 16%, the incidence per 100 person years was 3.3 and the mean interval between the time of diagnosis of cirrhosis and the onset of first episode of decompensation was 31 months (range 6-109).[54] After decompensation, the survival drops to 55% to 70% at 1 year and to 14% to 28% at 5 years. Interestingly, an improvement in liver function activity has been observed in those individuals who subsequently lose their HBsAg positivity.

3. Hepatocellular Carcinoma

The development of hepatocellular carcinoma (HCC) and liver failure are the main causes of death from chronic hepatitis B. It is estimated that over 662,000 deaths from liver cancer occur yearly worldwide,[1] 53% of which can be attributed to chronic HBV infection.55 In the US, the incidence of hepatocellular carcinoma for Asian men and women combined is nearly two times higher than Hispanics (11.0 vs. 6.8 per 100,000/year; P<0.0001) and more than four times higher than Caucasians (11.0 vs. 2.6 per 100,000/year; P<0.0001).[56] Among Asian Americans, ethnic differences are noted in the incidence of liver cancer and death due to liver cancer; the highest rates are seen in Chinese, Kampuchean, Korean, Laotian, Samoan, and Vietnamese men.[57] The various risk factors for hepatocellular carcinoma are summarized on **Figure 3**. Data from REVEAL study group demonstrated similar relationship between serum level of HBV DNA at cohort entry examination and the cumulative incidence of HCC.53, 58 Using patients with baseline serum HBV DNA < 300 copies/mL as a relative risk of 1.0, the incidence of HCC increased from 1.3% to 14.89% in patients with serum concentrations of 6x Log10 copies/mL or higher (relative risk, 6.1). This relationship remained statistically significant after the analysis was adjusted for age, sex, cigarette smoking, alcohol consumption, ALT activity, and HBeAg status. Spontaneous reduction in serum HBV DNA concentration over time was protective against the development of HCC. After a median follow-up of 10 years, subjects with persistently elevated serum HBV DNA concentrations > 5xlog10 copies/mL were at greater risk of HCC than those with similar elevated baseline serum HBV DNA concentrations that > 5 x log10 copies/mL at study entry but decreased to < 4 x log 10 copies/mL upon follow-up. HCC incidence is three to six times higher in males than females, suggesting a tumorgenic effect of androgens.[59,60] Several studies have indicated that older age (> 45 years) in Asians is an important risk factor for HCC as this may be an independent risk factor or reflect the longer duration of viral infection and liver disease . Having a first degree relative with HCC, the presence of cirrhosis, and reversion activity are all thought to contribute to HCC development.59-62 Chronically infected subjects have a 100 times increased risk of hepatocellular carcinoma compare with non-carriers.48 A recent study suggested positive HBsAg increased one's risk of developing HCC by 10 folds, and with positive HBeAg, the risk increased by 60 folds. Detectable HBV DNA levels yielded a 4 fold increase risk of HCC.[63] The additional use of alcohol, consumption of aflatoxin in diet and co-infections with HCV or HDV were found to be independent factors for HCC in HBV infected patients. Unlike hepatitis C, hepatitis B virus is considered a proto-oncogene and does not require underlying cirrhosis for the development of HCC. A recent presentation of 89 HCC patients from a large public hospital in New York City found that 90% of the HBV related HCC were of Asian descent; 26% were ≤ 40 years of age upon diagnosis and 78% had cancers larger than 10 cm compared with 41% in those > 40 year of age.[64] At Mount Sinai School of Medicine in New York, a detailed subset analysis of their twenty year retrospective- prospective database of HCC patients, found 44% of their 241 liver resected HBV-HCC patients had non-cirrhotic disease and 15% had both absence of cirrhosis and fibrosis.[65]

4. Serum Aminotransferase Activity and Disease Progression in Asian Patients

Elevation in serum ALT activity is an indicator of necro-inflammatory activity; normal values are considered predictive of histological quiescence. However, normal ranges of serum ALT levels can vary between laboratories. Patients with persistently normal ALT activity generally have milder liver inflammation than patients with ALT activity higher than normal. However, several studies suggest a significant risk for mortality from liver diseases remains for CHB individuals with persistently normal transaminase. Analyses of insurance data collected from a cohort of 142,055 Korean patients demonstrated a significant association between slight elevations in serum

aminotransferase activity and death due to liver disease. Although the study did not ascertain the etiology of liver disease, the liver-related mortality risks of patients with ALT and AST activity between 20 and 29 U/L (in men) or between 30 and 39 U/L (in both men and women) were significantly higher than those of patients with serum aminotransferase activity lower than 20 U/L.[66] Similar results have been demonstrated among patients in whom liver disease developed as a result of untreated chronic HBV infection. In fact, ALT or AST activity between 20 and 40 U/L is positively associated with increases in HBV-related mortality and complications. In the REVEAL data, the rate of liver disease progression correlated with elevated ALT values >45 U/L, but more than 80% of the cases of cirrhosis and HCC occurred in patients with ALT activity lower than 45 U/L.[53,58] There is poor correlation between liver histological damage and normal ALT. Yang et al studied the biopsies of 327 patients with normal serum aminotransferase activity for more than 6 months and found that 30% to 40% of patients had histological findings indicating at least grade 2 or stage 2 disease.[67] In their subset analysis based on HBeAg status, biopsies from 183 patients with HBeAg positive shown that 74 patients had grade 2 or 3 disease and 63 patients had stage 2, 3, or 4 disease; biopsies from 144 patients with HBeAg negative showed that 60 patients had grade 2 or 3 disease and 67 patients had stage 2, 3, or 4 disease. Similar results were found in a large study involving 3233 Chinese patients with CHB with median 4 year follow up; the risk of cirrhosis and HCC was greater for patients with ALT activity 0.5 to 6 U/L times the upper limit of normal (ULN), compared with less than 0.5 times ULN.[68] More than two thirds of the patients who experienced complications were HBeAg sero-negative. These findings suggest that serum ALT or AST activity within the normal laboratory range are not a reliable predictor of progression or death due to liver disease. Patients with mild elevations in ALT activity or ALT > 0.5 ULN appear to be at higher risk of cirrhotic complications and HCC than those with ALT activity below 0.5 ULN.

5. HBeAg Status and Disease Progression in Asian Patients

Among chronic HBV infected patients, HBeAg positive status ranged from 20 to 65%, increasing with age.[69] Several studies in Asian patients with HBV infection acquired in early childhood have demonstrated that HBeAg sero-positivity and HBV DNA levels of > 104-105 copies/ml are associated with an increased risk of cirrhosis and HCC.[58,70] Spontaneous HBeAg seroconversion was usually associated with remission of liver disease and cessation of active viral replication. However, many clinical observational studies suggest that HBeAg seroconversion might reduce, but did not eliminate the risk of cirrhosis and HCC in early acquired CHB Asian patients. Long term studies of post HBeAg sero-conversion patients with median duration of 5 to 13 years follow up have shown that 65-85% of the patients potentially sustained remission of the disease activity while 5% had active disease The remaining 10 to 30% of patients may have patterns of relapsing disease, alternating with remission.[71-73] 15% of the Asian patients with post HBeAg seroconversion can developed cirrhosis in 15 years median follow up.[48,74] In contrast, a recent long term study with follow up of 25 years in Italians, who were mostly infected with HBV in adulthood, sustained remission pattern with rare clinical complications after HBeAg seroconversion was seen.[75] The age at which HBeAg seroconversion occurred also had a significant impact on disease outcomes. The progression to cirrhosis decreased if HBeAg seroconversion before age 40.[76] In Asian patients, HBeAg negative status has been observed mainly in the elderly population. Multivariate analyses demonstrated that reactivation of hepatitis B correlated significantly with genotype C (P=0.003), male sex (P=0.03), ALT levels > 5 x upper normal limit (UNL) during the HBeAg-positive phase (P=0.02), and age at HBeAg seroconversion > 40 years (P=0.002). HBeAg negative patients may have active disease during the immune clearance stage or from the reactivation after being an inactive carrier. Most often, significant viral replication with pre core or basal core mutants could be found in these cases. HBeAg-negative patients are generally in a late phase of infection that is associated with significantly lower serologic HBV DNA levels but more severe inflammation and fibrosis and poorer prognosis relative to HBeAg-positive patients.[77]

Conclusions and Future Research Directions

The majority of chronic hepatitis B infections in the Asian population are from perinatal transmission. Therefore, prevention of perinatal transmission of HBV from an infected mother to her newborn is the most effective strategy in the global eradication of HBV infection. However, the growing prevalence of CHB in Asian-Americans can be attributed to the large number of foreign born immigrants to the US from Eastern and South-east Asia. Asian CHB patients have a unique natural history: a long immutolerance phase, unpredictable patterns of disease reactivation or inactivation, and high risk for cirrhosis and HCC despite achieving spontaneous HBeAg seroconversion. Further studies on the pathophysiology of the immutolerance phase including the role of HBeAg protein as a tolergent and the factors to trigger immune clearance are needed, so that the duration of host exposure to high level HBV replication may be shorten and liver injury due to ineffective intermittent immune reactions to the persistent HBV infection may be prevented. In addition to long duration of HBV infection, serum HBV DNA level and/or persistent viremia are considered important risk factors in the Asian population. Serum HBV DNA concentration may be more predictive of cirrhosis and HCC than ALT activity. However, it is still unknown if the patterns of ALT flares or intermittent elevation of ALT could have impact on disease progression independently from HBV DNA levels, especially patients with HBeAg negative status. Potential independent viral factors such as HBV genotype, natural mutations and treatment induced mutations on disease progression remain unclear and needs further investigation. A significant portion of Asian Americans with wild type infection have co-exiting pre core and/or basal core mutants; elucidation of their possible impact on natural history of disease progression, treatment response or cancer transformation is warranted. Finally, long term clinical

outcome on antiviral treatment in patients without advanced liver fibrosis should be evaluated for cost effectiveness and antiviral resistance prevention. In summary, future investigations in promoting HBV immune clearance by enhancing the host adaptive immunity against HBV or providing effective treatment to eradicate HBV infection may be the best solutions to combat HBV chronic infection and reduce its unfortunately high complication rates of cirrhosis or HCC in this special population.

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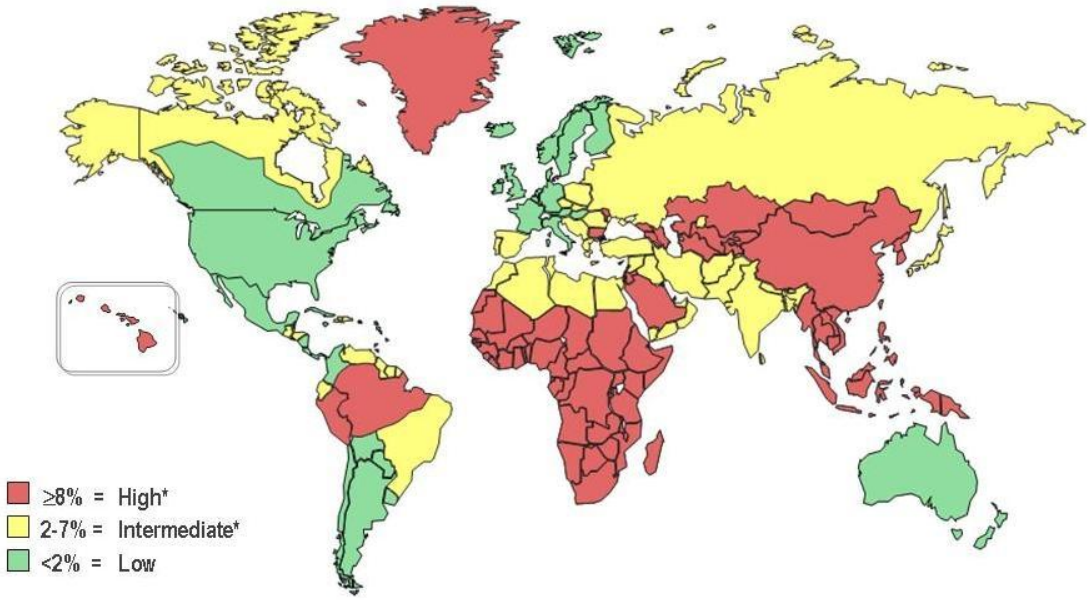
Figure 1. The global geographic distribution of chronic HBV infection



*Individuals born in locations with intermediate or high prevalence should be routinely screened for HBV infection

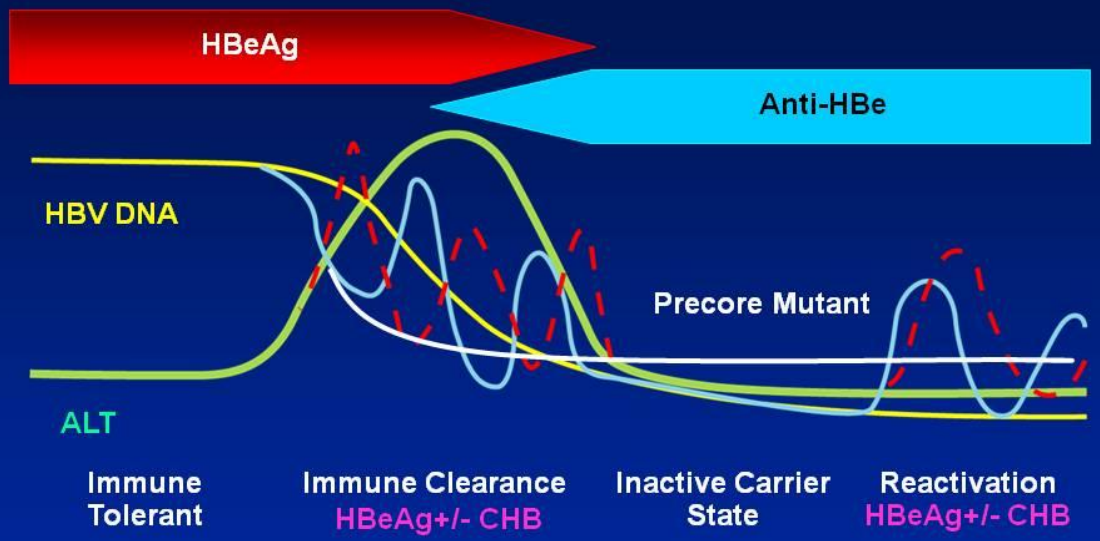
Adapted from: Centers for Disease Control and Prevention. *Morb Mortal Wkly Rep.* 2008;57:1-16.

Table 1. Genotypes of HBV and Geographic Distribution

Differ in HBsAg protein in different genotypes

Genotype	Geographic Distribution
A	Africa, India, Northern Europe, United States
B	Asia, United States
C	Asia, United States
D	India, Middle East, Southern Europe, United States
E	West and South Africa
F	Central and South America
G	Europe, United States
H	Central and South America, California in United States

Figure 2. Typical Disease Models of Chronic Hepatitis B



Liver Histological Activity			
Mild	Moderate/Severe	None/Mild	Moderate/Severe

Figure 3. Independent Risk Factors for the Development of HCC in CHB infection