Natural history of hepatitis B and outcomes after liver transplantation

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Hepatitis B virus (HBV) infection affects approximately 400 million persons worldwide. Globally, it is the single most common cause of cirrhosis and hepatocellular carcinoma (HCC) although the impact of HBV infection varies depending on the geographical region [1]. The outcome of HBV infection is determined by the interplay of host, virus, and environmental factors.

HBV genotypes and molecular variants

Hepatitis B virus is a member of the hepadnaviruses. The HBV genome consists of a circular, partially double stranded DNA of approximately 3200 base pairs. The four open reading frames overlap and encode the envelope (pre-S/S), core (precore/core), polymerase, and X proteins. The precore/core open reading frame has two initiation sites. The translational product of the precore polypeptide undergoes N and C terminal processing into a soluble protein (hepatitis B antigen [HBeAg]) while the translational product of the core peptide encodes the nucleocapsid protein (hepatitis B core antigen [HBcAg]) [2].

The traditional classification of HBV into four serotypes (adr, adw, ayr, and ayw) has been supplanted by the division of HBV into seven genotypes (A–G) based on an intergroup divergence of 8% or greater in the complete nucleotide sequence [3]. The genotypes differ in their geographic distribution. Genotype A is predominantly found in Northwest Europe, North America, and Central Africa; genotypes B and C are mostly found in Southeast Asia, China, and Japan; genotype D is mainly found in the Mediterranean area, and India; the distribution of genotypes E, F, and G are less certain [4].

HBV genotypes have been implicated to play a role in the progression of liver disease. HBV genotype C has been reported to be associated with more active necroinflammation in the liver and a higher rate of cirrhosis compared with genotype B [5]. Some studies found that HBV genotype B is associated with an increased risk for HCC, but other studies have refuted this finding [3,6]. Explanations for the more active and progressive liver disease among patients with genotype C include a lower rate of spontaneous HBeAg seroconversion and a lower rate of sustained biochemical remission after HBeAg seroconversion [7]. The role of other HBV genotypes in the natural history of HBV infection is less clear. HBV genotype is related to precore and core promoter mutations, which may in turn influence liver disease severity.

The most common naturally occurring HBV mutations include the precore stop codon mutation (G1896A), which abolishes the production of HBeAg and the dual mutation in the core promoter region (A1762T, G1764A), which decreases precore mRNA synthesis and HBeAg expression [8]. The precore mutation is related to the nucleotide sequence at position 1858, which is base-paired with nucleotide 1896 in the stem-loop structure of the pregenome encapsidation sequence ε [9]. HBV genotypes B, D, E, G and some strains of genotype C, have thymidine (T) at nucleotide 1858, and permit the selection of the precore G1896A mutation. Genotypes A, F, and some strains of genotype C, have cytosine (C) at nucleotide 1858, and are rarely associated with the precore G1896A mutation. The correlation between HBV genotypes and core promoter mutation is less clear. The dual mutation has been found in association with genotypes A, C, D and less commonly genotype B.

Precore and core promoter mutations were initially reported to be more common in patients with fulminant hepatitis and those with more active chronic liver disease [10]. These mutations however, have also been detected in patients with self-limiting acute hepatitis and in inactive hepatitis B surface antigen (HBsAg) carriers [11]. Thus, the pathogenic significance of these mutations is unclear. Precore stop
codon mutations are generally selected around the time of HBeAg seroconversion but selection of the precore stop codon mutation is not a prerequisite of HBeAg clearance. In addition, some studies found that selection of precore stop codon mutation after HBeAg seroconversion is not necessarily associated with higher HBV DNA or aminotransferase levels [8].

The geographic distribution of HBV genotypes influence the prevalence of precore and core promoter mutations, and in turn, the prevalence of HBeAg-negative chronic hepatitis B in different parts of the world. Thus, HBeAg-negative chronic hepatitis B is more common in Asia and in Mediterranean countries where HBV genotype B, C, and D prevail, although it has been reported in all parts of the world [3,4].

Epidemiology and transmission

There is a wide range in HBsAg carrier rate in different parts of the world. Chronic HBV infection is common in Asia, most of Africa, and the South Pacific where 5% to 20% of the population are carriers and more than 50% of the adult population have markers of prior infection. In the United States and Western European countries, only 0.2% to 1% of the population are carriers.

The mode of transmission and the age at infection are the key determinants of the risk of chronic HBV infection. The risk of progression to chronic HBV infection after an acute exposure ranges from 90% of neonates born to HBeAg positive mothers, to 25% to 30% of infants and children below the age of 5, to less than 5% of immunocompetent adults [12]. The high rate of chronic infection in individuals with perinatally acquired HBV infection has been attributed to the immature immune system in the neonate [13–15]. Perinatal infection also leads to a prolonged period of high level HBV replication, which in turn perpetuates the cycle of maternal-infant transmission. Thus, more than 50% of chronic HBV infections in Asia and Oceania are attributed to perinatally acquired HBV infection [16,17].

Acute HBV infection

The clinical manifestations of acute HBV infection range from subclinical infection to acute hepatitis to, rarely (less than 1%), fulminant hepatitis. Acute HBV infection is, in general, subclinical in neonates and children although there have been reports of fulminant hepatitis in neonates. Many of the latter instances have been attributed to de novo infection with precore HBV variants from maternal anti-HBe positive carriers [18]. As discussed earlier, precore and core promoter variants have been reported to be more commonly associated with fulminant hepatitis, but these variants have also been found in inactive HBsAg carriers, and in several reported outbreaks of fulminant hepatitis B—in the source patient, who had asymptomatic chronic HBV infection [19]. Thus, the role of HBV mutations in the course of acute HBV infection remains to be established. Indeed, one study in Germany analyzed the complete HBV sequence of seven patients with fulminant hepatitis B along with one post-transplant patient with fulminant recurrent hepatitis B and concluded that no specific HBV mutation could be identified [20].

Other factors that may influence the course of acute HBV infection include co-infection with other hepatitis viruses, such as hepatitis C or D virus (HCV or HDV) along with immunosuppression. Acute co-infection of HBV and HCV or HBV and HDV are most likely to occur among injection drug users. In these clinical settings, one virus may exert inhibitory effect on the other virus [21,22]. Nonetheless, the hepatitis is usually more severe and the risk of fulminant hepatitis is higher than infection with HBV alone [23]. Individuals who are immunocompromised secondary to administration of immunosuppressive medications such as corticosteroids or cancer chemotherapy, or underlying illness such as chronic renal failure may develop a more severe or protracted illness and have a higher rate of progression to chronic infection.

As discussed earlier, the age at infection is the primary determinant of the risk of progression from acute to chronic HBV infection. The immune status of the host is also important. More recently, one study on 55 patients suggests that genotype C is associated with a higher risk of progression to chronic infection than genotype B (Fig.1)[24].
Recovery from acute HBV infection is marked by HBsAg to HBs antibody (anti-HBs) seroconversion. Recent studies using sensitive techniques such as polymerase chain reaction (PCR) showed that low levels of HBV DNA can be detected in the serum and more often in the peripheral blood mononuclear cells (PBMC) and liver of individuals many years after recovery from acute HBV infection [25]. These findings indicate that HBV is not eradicated in patients who appear to have recovered from an acute infection, and account for the reactivation of HBV replication when the immune system in these individuals is suppressed.

**Chronic HBV infection**

Chronic HBV infection is defined as presence of HBsAg in the serum for a minimum of 6 months. The clinical manifestations of chronic HBV infection range from asymptomatic infection to chronic hepatitis, cirrhosis, liver failure, and HCC. In general, the course of chronic HBV infection consists of an earlier phase with high levels of HBV DNA and presence of HBeAg and a later phase with low or undetectable HBV DNA levels and presence of anti-HBe (Fig. 2).

**Immune tolerant phase**

Chronic HBV infection acquired by perinatal infection is distinct from chronic HBV infection acquired during childhood or adult life in having an initial and often prolonged immune tolerant phase (characterized by presence of HBeAg, very high HBV DNA levels and normal ALT). This phase often lasts for 10 to 30 years [26]. The rate of spontaneous HBeAg clearance is low and has been estimated to be about 2% during the first 3 years of infection and only 15% after 20 years [17]. As a result, most individuals with perinatally acquired chronic HBV infection remain infectious when they reach adulthood accounting for the perpetuation of vertical transmission of HBV infection in Asian countries.

**Immune clearance phase / “HBeAg positive chronic hepatitis”**

Patients who acquired chronic HBV infection perinatally usually transition from the immune tolerant to the immune clearance phase during the second to third decade whereas patients with childhood or adult acquired chronic HBV infection often present initially in the immune clearance phase. During this phase, spontaneous clearance of HBeAg occurs annually at a rate of 10% to 20%. HBeAg seroconversion rates of 70% over a 10 year span has been reported in a population based study of Alaskan natives who acquired HBV infection during childhood or adult life [27].

Biochemical perturbation, notably an abrupt increase in serum ALT, often accompanies HBeAg seroconversion. This is likely caused by a sudden increase in immune-mediated lysis of infected hepatocytes [28]. It has been hypothesized that immune clearance of HBeAg may be triggered by an increase in viral load or changes in the presentation of viral antigens because increase in ALT is often preceded by an increase in serum HBV DNA level and a shift of HBcAg from nuclear to cytoplasmic sites in the hepatocytes [29,30]. Not every exacerbation will lead to HBeAg seroconversion and long-term suppression of HBV replication. These exacerbations may reflect abortive immune clearance, and recurrent exacerbations may occur until sustained suppression of viral replication is achieved [31].
Factors that have been reported to be associated with a higher rate of spontaneous HBeAg seroconversion include older age, female gender, elevated ALT, and more recently HBV genotype B (compared with genotype C) [7,32,33].

Biochemical exacerbations observed during the immune clearance phase are often asymptomatic. Occasionally, the exacerbations are associated with symptoms of acute hepatitis, and may be mistaken for acute hepatitis B if the exacerbation occurs in an individual who is not aware of the pre-existing chronic HBV infection [34]. This is further complicated by the fact that an elevation in the anti-HBc IgM titer may occur during these exacerbations. Rarely, these exacerbations will precipitate hepatic decompensation and may be fatal [35]. These patients should be referred for transplant evaluation. Treatment with lamivudine may result in improvement or stabilization of liver disease and may delay or avert the need for liver transplantation [36]. Interferon is contraindicated in this setting. Serum alphafetoprotein may also be increased during an exacerbation, sparking concerns about a diagnosis of HCC. Exacerbations are more common in men than in women [37]. The higher frequency of exacerbations in men may explain the higher rate of cirrhosis and HCC in men because recurrent necroinflammation leads to fibrosis and regeneration increases the susceptibility to malignant transformation.

**Inactive carrier state**

Most patients with chronic HBV infection who seroconvert remain HBeAg-negative and anti-HBe positive with normal ALT and very low HBV DNA levels that are only detectable by PCR assay. These individuals are considered to be in the “inactive carrier state” [28,38,39]. Most of these patients follow a benign course, but the clinical outcome is dependent on the severity and duration of chronic hepatitis before reaching the “inactive carrier state.” Laboratory monitoring should be continued as up to 20% of patients may experience spontaneous reactivation of HBV replication manifested as ALT elevation, increase in serum HBV DNA level with or without seroreversion to HBeAg positivity [32,40,41].

**HBeAg negative chronic hepatitis**

Most patients have normal ALT and low HBV DNA levels after HBeAg seroconversion. Some patients however, continue to have elevated ALT, high HBV DNA levels, and persistent necroinflammation in the liver. These patients are said to have “HBeAg negative chronic hepatitis” [8]. Some patients transition from HBeAg positive chronic hepatitis directly to HBeAg negative chronic hepatitis while others enter into the inactive carrier state for varying duration—years to decades, before HBV replication is reactivated. Most of these patients have mutations in the precore or core promoter region that abolish or decrease the production of HBeAg [8,42]. HBeAg negative chronic hepatitis was initially reported in Mediterranean countries and in Asia, but it is present worldwide, with a higher prevalence in countries where the predominant HBV genotype permits selection of the precore stop codon mutation. Patients with HBeAg negative chronic hepatitis are typically older than HBeAg positive patients, are more often men, and tend to have more advanced liver disease at presentation [43]. The older age, the more advanced liver disease, and the observed progression from HBeAg positive chronic hepatitis indicate that most cases of “HBeAg negative chronic hepatitis” represent a later stage in the natural history of chronic HBV infection. De novo infection with “HBeAg-negative HBV variant” can occur and may be associated with a higher risk of fulminant hepatitis but the risk for progression to chronic infection appears to be low [44].

Patients with “HBeAg negative chronic hepatitis B” tend to have more severe necroinflammation and a much lower rate of sustained remission. Three patterns have been observed: (1) flares with ALT normalization in between (44.5%), (2) flares without ALT normalization (19.5%), and (3) persistently abnormal ALT levels (35.9%). [45]. Because of the fluctuating course, serial testing is often necessary to differentiate between “inactive carrier state” and “HBeAg negative chronic hepatitis.” When evaluating a patient who is HBeAg negative with elevated ALT for the first time, it is important that other etiologies of chronic hepatitis including other hepatitis viruses, excessive alcohol use, autoimmune or metabolic liver disease, and concomitant hepatotoxic medications, must be excluded.

**Resolution of chronic HBV infection**

Approximately 0.5% to 2% of HBsAg carriers will clear HBsAg annually, some will also seroconvert to anti-HBs. These patients appear to have a better outcome than those who remain HBsAg positive [46]. However, some patients may develop HCC even after clearance of HBsAg. In a series of 55 patients who had spontaneously cleared HBsAg, 33% developed complications including cirrhosis,
hepatic failure and HCC during a mean follow-up of 23 months [47]. Thus, long-term follow-up of all patients with chronic HBV infection is necessary even after HBsAg clearance.

**Clinical outcomes**

Adverse clinical outcomes of chronic HBV infection include progression to cirrhosis, hepatic decompensation, HCC, and death. Worldwide, chronic HBV infection is estimated to account for 1 million deaths each year.

Heavy alcohol intake and concomitant infection with either hepatitis C (HCV), hepatitis D (HDV), or HIV may increase the rate of disease progression [48]. In alcoholics, the prevalence of serum HBV markers has been estimated to be two to four times higher than the control population, implying an increased rate of HBV infection in these individuals [49]. Although no clear evidence has emerged that alcoholics are at an increased risk of chronic HBV infection, HBV DNA had been found in HBsAg negative alcoholics with cirrhosis or HCC suggesting that occult HBV infection may have worsened the liver disease in these patients [50].

Hepatitis D virus (HDV) requires the presence of HBV for complete virion assembly and secretion. HDV superinfection is in general associated with more severe liver disease and more rapid rate of progression to cirrhosis [21,51]. Intravenous drug users and men who have sex with men have increased risk of HBV and HIV coinfection. These patients have higher levels of HBV DNA, a lower rate of HBeAg seroconversion, and increased severity of liver disease [12,52]. Immune reconstitution after successful control of HIV infection may lead to exacerbations of chronic hepatitis B.

**Progression to cirrhosis**

Progression to cirrhosis occurs insidiously. Accurate assessment of the rate of progression to cirrhosis requires serial liver biopsy, which is impractical and ethically unjustified. Studies in Europe and Asia estimated the 5-year cumulative risk for developing cirrhosis as 8% to 20% for patients with HBeAg positive hepatitis [53,54]. The risk is higher for patients with HBeAg negative chronic hepatitis, in part related to the older age and the more advanced fibrosis at presentation [48,55,56]. Factors that have been reported to be associated with increased risk of developing cirrhosis include older age, ongoing HBV replication, coinfection with HCV, HDV, and HIV, alcohol use, and more recently HBV genotype (genotype C more than B) [7,56,57]

![Fig. 3. The difference in survival rates by HBeAg replication status over 96 months. Survival rates are equivalent up to 24 months. Solid line indicates HbeAg+ and broken line indicates HBeAg−. (From Niederau C, Heintges T, Lange S, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. NEJM 1996;334:1422-7; with permission.)](image)

**Development of hepatic decompensation**

Hepatic decompensation includes ascites, variceal bleeding, jaundice, and hepatic encephalopathy. Among patients with HBV-related cirrhosis, ascites is usually the first manifestation of hepatic decompensation. A longitudinal study of Asian patients with recent development of cirrhosis found that the 5-year cumulative rate of decompensation was approximately 20% [58]. In a multicenter longitudinal study performed by the investigators of the European Concerted Action on Viral Hepatitis (EUROHEP), the 6-year rate of hepatic decompensation among patients who present with compensated HBV-related cirrhosis was 16%. Multivariate analysis showed that six variables were associated with increased risk for hepatic decompensation: older age, low albumin, low platelets, splenomegaly, high bilirubin, and HBeAg. These factors were also predictive of HCC development and liver-related mortality [56,59].

**Development of hepatocellular carcinoma**
HCC is one of the most dreaded complications of HBV-related liver disease because it often presents late, treatment options are limited and frequently ineffective, and the mortality is high. The 5-year rate of progression from compensated cirrhosis to HCC has been estimated to be 6 to 15% [53,54,60]. Although HCC usually occurs in patients with cirrhosis, 30% to 50% of HBV-related HCC occur in patients without cirrhosis [55], possibly because of the potential oncogenic effect of integration of HBV DNA into host genome. HBV-related HCC has also been reported to occur in children and to cluster in families [61]. It has been suggested that Asians with chronic HBV infection have higher risk for HCC. One study based on retrospective data collected from 20 North American liver transplant centers found that Asians awaiting liver transplantation for hepatitis B were significantly more likely to have HCC than whites (26% versus 6%, \( P<0.0001 \)) [62]. Whether the higher risk of HCC among Asians is related to the longer duration of infection or as yet unidentified host, virus or environmental factors is unclear. Risk factors that have been reported to be associated with increased risk of HCC include older age, male gender, heavy alcohol consumption, presence of cirrhosis, exposure to aflatoxin, and co-infection with HCV [63]. Although HCC surveillance may lead to earlier detection, prospective data to support that it is cost-effective or improves survival is lacking. At this time, HBsAg carriers with high risk for HCC (male gender, over the age of 45 years, diagnosis of cirrhosis, family history of HCC) are recommended to undergo periodic screening with both AFP and ultrasound [2].

**Deaths**

The two main causes of death in chronic hepatitis B infection are HCC and liver failure. Annually, more than 1 million people die secondary to long term consequences of hepatitis B [64]. Survival rates at 5 years range from 99 to 100% in patients with chronic hepatitis B to 80 to 86% in patients with compensated cirrhosis, and only 14 to 35% in patients with decompensated cirrhosis [10,56,60]. Patients with decompensated cirrhosis have a 1-year probability of survival of 55 to 70%, the survival rate is worse in patients with more than one complication (Fig. 4)[65].

**Outcome after liver transplantation**

Once decompensation occurs in patients with HBV-related cirrhosis, orthotopic liver transplantation (OLT) should be considered. Although antiviral therapy such as lamivudine has been shown to stabilize or improve liver disease, clinical improvement is slow and may not be of help to patients with very advanced liver failure [66]. In addition, prolonged use of lamivudine may lead to drug resistance, negation of initial benefit, and increased risk of recurrent hepatitis B after OLT. OLT is also indicated for patients with fulminant hepatitis B and for patients with HBV-related HCC. The biggest obstacle plaguing OLT for hepatitis B was the high rate of reinfection and the rapid progression of recurrent hepatitis B. Significant advances have been made in the prevention and treatment of recurrent hepatitis B in the last 15 years and will be covered by Dr. Keeffe. The outcome of patients who had OLT for hepatitis B will be discussed later.

**Patients with recurrent hepatitis B**

In the absence of prophylactic therapy or when hepatitis B immune globulin (HBIG) was administered for a limited period (less than 6 months), graft reinfection rate approached 80% to 100% [67–69]. In addition, recurrent hepatitis B post-OLT ran a rapidly progressive course. Left untreated, HBV reinfection of the graft led to recurrent cirrhosis within 1 to 2 years of reinfection, and a 2-year mortality of 50% compared with 20% among patients transplanted for other liver disease [67,70]. The high rate of HBV reinfection and the rapid downhill course are related to enhanced viral replication secondary to immunosuppressive therapy as well as direct stimulation of the glucocorticoid-responsive enhancer region of the HBV genome [71,72]. Another contributory factor to graft reinfection is the
presence of extrahepatic reservoirs of HBV such as peripheral blood mononuclear cells [73]. The importance of a high viral load is most evident in patients with fibrosing cholestatic hepatitis (FCH). FCH is an aggressive form of recurrent hepatitis B seen in 5% to 10% of patients with HBV reinfection post-OLT. It is characterized by a histologic picture of prominent cholestasis and fibrosis with very little necroinflammation, and intense expression of HBsAg and HBcAg [69]. The pathogenesis of FCH is believed to be caused by direct cytopathic effects of very high concentrations of HBV. The mortality of FCH in the pre-lamivudine era was 100%.

The use of HBIG and lamivudine monotherapy, and more recently combination prophylaxis of HBIG and lamivudine has reduced the HBV reinfection rate post-OLT to less than 10% [74,75]. In addition, the course of recurrent hepatitis B has been modified by the availability of effective antiviral therapy. In one study 60% of 52 patients who received lamivudine for recurrent hepatitis B post-OLT had undetectable levels of serum HBV DNA after 52 weeks of treatment. However, 14 (31%) patients developed breakthrough infection secondary to lamivudine resistance [76].

Although lamivudine resistant mutants have reduced replication fitness and most patients with lamivudine resistance have lower HBV DNA and ALT levels compared with pre-treatment values, some patients develop worsening liver disease over time, leading to hepatic failure, graft loss, and death [77]. Moreover, a recent report suggested that some patients subsequently select for mutations that are lamivudine dependent, (ie, these mutants replicate more efficiently in the presence of lamivudine) [78].

Adefovir dipivoxil, a nucleotide analog with inhibitory effect on wild type as well as lamivudine resistant HBV, has provided rescue for some patients who have developed worsening liver disease caused by lamivudine resistant HBV mutants. Preliminary data from an ongoing compassionate use program found that most patients had 3 to 4 log10 reduction in serum HBV DNA levels, and biochemical and clinical improvement of liver disease [79]. Whereas the long-term safety of adefovir and the durability of its antiviral effect are still unknown, the future for patients with recurrent hepatitis B post-OLT is bright as many new therapeutic options are being developed.

Advances in the prevention and treatment of recurrent hepatitis B post-OLT have resulted in significant improvement in survival of patients transplanted for hepatitis B in recent years. Survival rates of these patients are now comparable to and in some instances exceed that of patients transplanted for other liver disease [80].

**Patients with no evidence of recurrent hepatitis B**

Even in the absence of prophylactic therapy, a small percent of patients transplanted for hepatitis B escape reinfection. Predictors of a lower rate of reinfection include long-term administration of HBIG, HDV superinfection, fulminant hepatic failure, and undetectable HBeAg/HBV DNA pre-OLT [81]. Several studies have now shown that HBV DNA can be detected in serum in up to 67% of patients, and in peripheral blood mononuclear cells and liver in a higher proportion of patients who have no evidence of recurrent hepatitis B, as defined by absence of HBsAg in the circulation. Most of these patients have normal ALT level and studies that included liver histology showed that most of these patients have normal or minimal changes on their biopsy [82]. These data suggest that low-grade reinfection is present but the viral load is insufficient to cause significant liver damage. It is likely that these patients will not develop any adverse outcome. Nonetheless, these data raise concern regarding the feasibility of withdrawing HBV prophylactic therapy in patients who seem to have no evidence of reinfection many years after OLT.

**Summary**

HBV infection is the single most common cause of cirrhosis globally although the prevalence rate is influenced by geographic region. The natural course of HBV infection and the clinical outcome is dependent on the interplay between host, virus, and environmental factors. Understanding the natural history of HBV infection is important in determining treatment strategies. OLT is the ultimate cure for patients with HBV-related liver failure or HCC. The use of HBIG and new antiviral agents has resulted in significant decrease in HBV re-infection rate and survival of patients transplanted for hepatitis B in recent years is comparable to that of patients transplanted for other liver disease.

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