

Immune Tolerant Hepatitis B: A Clinical Dilemma

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Abstract: Chronic hepatitis B virus infection remains a global health concern, with perinatal transmission still a problem in many countries. Several new therapies for chronic hepatitis B virus infection have recently been introduced that can safely and effectively suppress viral replication with a low risk of resistance; thus, it has become increasingly tempting for many clinicians to treat patients in the immune tolerant stage of infection who have high levels of viremia yet persistently normal levels of transaminases. However, understanding the natural history of hepatitis B virus infection and how it pertains to disease progression, as well as how current therapies alter or do not alter this natural history, is important when deciding whether to treat these patients. This article will review the definition and natural history of immune tolerance, the current world guidelines and recommendations for treatment of immune tolerant patients, and data on the effectiveness of current therapies in this patient population.

Chronic hepatitis B (CHB) remains a global health problem, affecting 300 million people worldwide.¹ Despite the availability and efficacy of the hepatitis B virus (HBV) vaccine, HBV continues to be transmitted perinatally and via blood and bodily fluids in high-risk individuals. In many countries that are considered by the World Health Organization to have an intermediate or high prevalence of HBV, birth dose vaccination schedules still do not include the HBV vaccine in 40–50% of births (Table 1). This shortfall highlights the ongoing worldwide problem of continued infection and transmission despite vaccine availability.²

In the United States, the Institute of Medicine recently issued a report on the current status of HBV and hepatitis C virus infection, finding a continued lack of knowledge of the risks of transmission among both healthcare providers and at-risk populations. Many opportunities exist for improving surveillance, vaccination, and access to care.³

Keywords

Hepatitis B virus, immune tolerant, management, HBeAg, alanine aminotransferase

Table 1. Hepatitis B Virus (HBV) Infection in World Health Organization Member Countries and Inclusion of Birth Dose HBV Vaccinations

Chronic HBV prevalence	Number of countries	Countries with HBV birth dose in schedule
High (>8%)	87	38 (44%)
Intermediate (2–8%)	62	33 (53%)
Low (<2%)	44	10 (23%)

Over the past decade, significant advances have been made in the treatment paradigm for chronic HBV infection as new therapies have become available. However, 1 of the challenging clinical dilemmas remaining in HBV management is the question of whether treatment should be initiated in the immune tolerant stage of chronic infection.

Natural History of Hepatitis B Virus Infection

Two of the major determinants of the outcome of acute HBV infection are age and immune competence at the time of infection. In neonates and young children, initial HBV infection is usually subclinical and results in high rates of chronic infection. In adult-acquired HBV, symp-

tomatic disease often leads to clearance of the hepatitis B surface antigen (HBsAg).

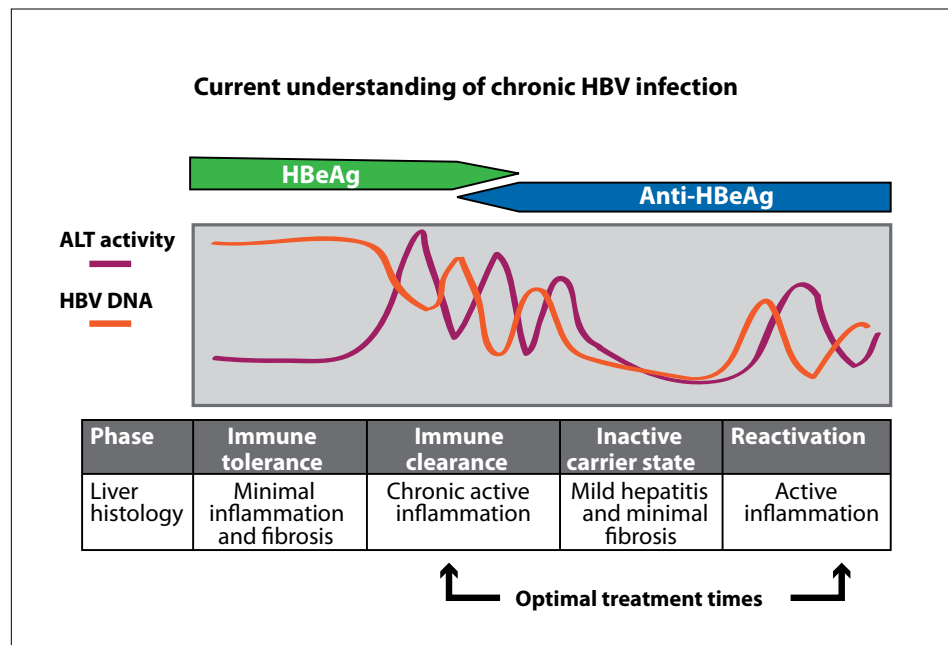
The natural history of perinatally acquired, chronic HBV can be broadly classified into 4 stages: immune tolerance, immune active/clearance, inactive carrier state, and reactivation (HBeAg-negative CHB; Figure 1).⁴ Children who are infected perinatally remain in the immune tolerant phase into adolescence or early adulthood, with the longest duration of this stage reported in 1 study to be in genotype C patients.⁵ Immune tolerance is clinically described as HBeAg positivity with DNA levels at or above 20,000 IU/mL and no significant immune response to the virus; thus, these patients have persistently normal alanine aminotransferase (ALT) levels. Biopsies in immune tolerant patients are generally benign, without signs of significant inflammation or fibrosis.⁶ Spontaneous loss of HBeAg in this stage is very low, and these patients are highly contagious due to their high levels of viremia.

The mechanism behind immune tolerance has not been fully elucidated, but HBV-specific T-cell hyporesponsiveness may be partly due to ineffective antigen processing and transport to major histocompatibility complex class I molecules.⁷ This inefficient T-cell response—with anergy, deletion, altered maturation of virus-specific effector cells, and expansion of regulatory T cells—may be a factor in immune tolerance.⁸ It has also been noted that lymphocytes bearing the classic NK phenotype dominate the immune effector cell population in immune tolerant patients, and the distribution

Figure 1. Four phases of chronic hepatitis B virus (HBV) infection.

ALT=alanine aminotransferase.

Reproduced from Yim HJ, et al. *Hepatology*. 2006;43:S173-S181.



of NK cells, CD4+ cells, and CD8+ cells resembles that seen in normal liver.⁹ In a recent study, intrahepatic and peripheral NK cells in immune activated and immune tolerant patients were studied, and researchers found that NK cells were activated with higher levels of interleukin (IL)-12, IL-15, and IL-18. Hepatic NK cells were also found to be more cytolytic than peripheral NK cells, which correlated with more inflammation and higher ALT levels in individuals who were immune activated.

As most immune tolerance is associated with perinatal transmission, knowing the mechanism for immune tolerance in early infancy is key; however, this mechanism is still not fully known. It is postulated to be associated with transplacental, maternal HBeAg induction of T-cell intolerance to hepatitis B core antigen (HBcAg) and HBeAg in the neonate.¹⁰ It has also been noted that neonates infected in utero do not have immunoglobulin (Ig)M antibodies to HBcAg, manifesting a lack of primary immune response.^{11,12} HBsAg is not believed to cross the placental barrier, but it is usually acquired at birth or shortly afterward.¹³ Thus, the presence of HBsAg in cord blood may indicate intrauterine infection.

One study conducted in 402 HBsAg-positive pregnant women showed that 15 newborns had detectable levels of HBsAg within 24 hours of birth; these infants were presumed to be cases of intrauterine HBV infection. Maternal serum HBV DNA levels, HBeAg status, and HBsAg titers were reported, along with data from histologic examination of the placenta, including in situ hybridization of HBV DNA and immunohistochemistry. Transplacental transmission was significantly associated with maternal HBeAg positivity, HBsAg titers, HBV DNA level, and history of threatened preterm labor. In addition, placental examination revealed a significant association between intrauterine infection and HBV infection in villous capillary endothelial cells. Thus, evidence of HBV infection decreased gradually from placental cell layers on the maternal side to layers on the fetal side.¹⁴

Clinically, the natural history of immune tolerant disease was studied by Hui and colleagues, who examined 57 adults (mean age, 31 years) with a normal serum ALT level of 30 IU/L (range, 4–42 IU/L) on 3 consecutive readings and liver biopsies at baseline showing minimal disease.¹⁵ Follow-up ensued every 6 months for 5 years, and 16% of patients developed ALT elevations during the study period. All 48 patients who remained in the immune tolerant phase for 5 years were biopsied at the end of the study: 85% of patients remained unchanged on repeat biopsy, while 6.3% (3/48) showed disease progression. Using a lower ALT serum cutoff value (30 IU/L for men and 19 IU/L for women) would have improved the test's sensitivity (from 84% to 94%) for predicting which patients would stay in the immune tolerant phase.¹⁵ This

study and others emphasize that the key to determining true immune tolerance is close, long-term follow-up. Patients who have persistently normal ALT levels are more likely to have little disease progression, while those with borderline or fluctuating ALT levels may have disease progression.

After a variable period of immune tolerance, immune activity may commence; at this point, patients may show clinical evidence of elevated or fluctuating ALT levels, fluctuating HBV DNA levels, and histologic activity on biopsies indicative of inflammation and injury. If this immune activity is successful, immune clearance occurs, with HBeAg loss and development of anti-HBe, which signifies a less active disease state and the transition to inactive carrier status. If the immune active phase persists, with the patient's immune system being unsuccessful at inducing serologic HBeAg clearance, then liver damage may occur, which can lead to fibrosis, cirrhosis, and a higher risk of hepatocellular carcinoma (HCC). Even after HBeAg seroconversion and entrance into a quiescent HBV inactive carrier state, the emergence of precore/basal core promoter mutations allowing viral replication and reactivation can lead to HBeAg-negative CHB, the fourth stage of disease.¹ It is important to understand that the natural history of HBV appears to be dynamic, with progression from 1 stage to another being variable in duration and severity, as well as being reversible.

Defining Normal Alanine Aminotransferase Levels

Without the benefit of a liver biopsy in all patients, the definition of immune tolerant disease requires that clinicians take into account ALT as a major determinant. Over the past several years, the definition of a "normal" ALT level has been redefined. In a large, retrospective analysis of 6,835 first-time blood donors, Prati and colleagues reported that the normal limit for ALT should be 30 IU/mL for men and 19 IU/mL for women.¹⁶ Interpretation of these data concluded that these lower levels may be more appropriate than current reference laboratory values (when adjusting for factors such as body mass index [BMI] or dyslipidemia).¹⁶ A more recent study assessed ALT levels in 1,105 healthy Korean potential liver donors with biopsy-proven normal liver histology; this study found that healthy ALT values were 33 IU/L for men and 25 IU/L for women. This Asian study also noted the impact of age, BMI, and metabolic factors on ALT levels.¹⁷ These studies emphasize that utilization of appropriate ALT levels is key when trying to determine the stage of a patient's HBV infection and may make an important difference in treatment decisions.

Table 2. Summary of Current International Guidelines and Clinical Recommendations Regarding Immune Tolerant Patients

Organization/Guidelines	Recommendations regarding immune tolerant patients
European Association for the Study of the Liver	Most patients under 30 years of age with persistently normal ALT levels, a high HBV DNA level (usually $>10^7$ IU/mL), no suspicion of liver disease, and no family history of HCC or cirrhosis do not require immediate liver biopsy or therapy. Follow-up is mandatory.
American Association for the Study of Liver Diseases	HBeAg-positive patients with persistently normal ALT levels should have their ALT levels tested at 3–6 month intervals. ALT and HBV DNA levels should be tested more often when ALT levels become elevated. HBeAg status should be checked every 6–12 months.
Asian Pacific Association for the Study of the Liver	Patients with viral replication but persistently normal or minimally elevated ALT levels should not be treated, except patients with advanced fibrosis or cirrhosis. Immune tolerant patients need adequate follow-up and HCC surveillance every 3–6 months.
National Institutes of Health Consensus	Therapy is not recommended for patients who are in the immune tolerant phase, which includes the presence of HBsAg, high HBV DNA levels, normal ALT levels, and liver histology showing mild or minimal inflammation and fibrosis.
US Algorithm	Younger patients are often immune tolerant. A biopsy should be considered, particularly if a patient is older than 35–40 years of age. Patients should be treated if there is evidence of histologic disease on liver biopsy. In the absence of biopsy, patients should be observed for elevation in ALT levels.

ALT=alanine aminotransferase; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCC=hepatocellular carcinoma.

If repeat monitoring shows ALT levels to be persistently normal, is it accurate to predict a benign liver biopsy? Lai and colleagues examined 192 patients with CHB: 59 had persistently normal ALT levels (defined as ALT ≤ 40 IU/L at the institutional laboratory), 26 had ALT levels 1.0–1.5 times the upper limit of normal (ULN), and 107 had ALT levels greater than 1.5 times ULN.¹⁸ Of those patients with persistently normal ALT levels, 34% had grade 2–4 inflammation, and 18% had stage 2–4 fibrosis.¹⁸ Older age was a significant factor in this study and in other studies, suggesting that even in patients with normal ALT levels, older patients with long-term infection may be candidates for liver biopsy to accurately assess the degree of ongoing liver injury.

Significance of Viral Levels: The REVEAL Study

Many clinicians, citing a strong association between viral replication and the risk of HCC and cirrhosis, are advocating treatment of patients with high viral levels, irrespective of serum ALT levels. This recommendation stems in part from the seminal REVEAL study, which was a very large, 11-year, population-based study of 3,582 Taiwanese patients with CHB who were followed every 6–12 months with ultrasound examinations and clinic visits. These

patients were studied before the Taiwanese national insurance instituted HBV treatment in 2003, so this study consisted of an untreated, natural history cohort.

Researchers measured HBV DNA viral levels and gathered data on sociodemographics and risk factors such as smoking, alcohol use, family history, and ALT levels. After adjusting for age, sex, smoking, and alcohol use, an HBV DNA level at or above 10^6 copies/mL at enrollment was associated with the highest incidence of cirrhosis (relative risk, 9.8; 95% confidence interval, 6.7–14.4; $P < .001$). Increasing HBV DNA levels were associated with increasing risk for cirrhosis incidence ($P < .001$). The cumulative incidence of cirrhosis was 4.5%, 5.9%, 9.8%, 23.5%, and 36.2% in patients with serum HBV DNA levels of less than 300 copies/mL, between 300 copies/mL and 9.9×10^3 copies/mL, 1.0 – 9.9×10^4 copies/mL, 1.0 – 9.9×10^5 copies/mL, and greater than 10^6 copies/mL, respectively. Further analysis from the same investigators showed a similar relationship between HBV DNA levels and development of HCC.^{19,20}

While it is tempting to extrapolate from these data that all patients with high viral levels should be treated to bring their virus down to undetectable levels and thus reduce the risk of cirrhosis and HCC, closer examination of the REVEAL study cohort shows that although many

of these patients did have normal ALT levels, 85% of these patients were HBeAg-negative, and the median age was 45 years. Thus, the natural history of these older patients with longer durations of infection and HBeAg-negative CHB would not be the same as the natural history of a 20-year-old, immune tolerant patient with HBeAg-positive CHB, a normal ALT level, and a high viral load. Therefore, in discussing the correlation between high viral levels and the risk of cirrhosis and HCC, the REVEAL data cannot accurately be applied to the truly immune tolerant patient, as this relationship is still largely unknown.

Current Treatment Recommendations

There are little data to support treatment in the immune tolerant pediatric patient, as progressive disease is unlikely in the short term. Although close monitoring for immune activity is warranted, a panel that recently convened on HBV infection in the pediatric population recommended deferring therapy in immune tolerant children due to concerns about long-term therapy—including the risks of resistance and low yield for clinical serologic endpoints—as well as a lack of data that therapy would alter the natural history of the disease in children.²¹

Carey and colleagues reported results of a study involving 23 children with HBV infection acquired in infancy and biopsy-proven immune tolerance who received lamivudine treatment for 8 weeks followed by combination therapy with interferon for an additional 44 weeks.⁸ Those patients who showed a serologic response had a more vigorous T-cell proliferation and CD8 response and fewer mutations. Interestingly, DNA levels decreased in both responders and nonresponders during the 8 weeks of therapy with lamivudine alone, but increased mutations were already being seen in nonresponders during this period; after interferon was initiated, responders showed a gradual broadening and strengthening of core-specific T-cell proliferation.⁸ Although treatment is not currently recommended, therapy involving better antiviral agents in combination with the immunomodulatory stimulation of interferon continues to hold appeal and is being further studied in both children and adults. For adults, all current national and international guidelines do not recommend therapy for immune tolerant patients with normal ALT levels (Table 2).

In interferon treatment studies, HBeAg seroconversion rates were less than 10% when ALT levels were normal. In lamivudine studies, pretreatment serum ALT level was the strongest predictor of response among HBeAg-positive patients. Pooled data from 4 studies of patients who received lamivudine for 1 year found that HBeAg seroconversion occurred in 2%, 9%, 21%, and 47% of patients with ALT levels within the normal range,

1–2 times normal, 2–5 times normal, and greater than 5 times normal, respectively. In another study, lower seroconversion endpoints were noted in patients treated with newer antivirals, with entecavir (Baraclude, Bristol-Myers Squibb) having an HBeAg seroconversion rate of only 12% in patients with a pretreatment ALT level less than 2 times ULN.²²

Although guidelines do not recommend therapy in immune tolerant patients, clinicians should note the importance of taking into account the age of the patient, duration of infection, whether ALT levels are truly normal for that patient, whether ALT levels are fluctuating, whether there is a family history of cirrhosis or HCC, the severity of histology, and other comorbidities.

Conclusion

HBV infection is a perplexing and dynamic viral disease with a natural history that remains largely unpredictable to the clinician. Immune tolerant disease is best characterized by high viral replication in the setting of minimal liver inflammation and injury, and this stage can persist for decades. The risk of disease progression in the truly immune tolerant patient is believed to be low, but HCC risks are largely unknown and, again, unpredictable. We do not know whether current therapies will change the natural history of disease in these individuals, and whether we should commit these patients to long-term antiviral therapy—while enticing—is not yet a clinical question we can answer based on the currently available data. Many further studies are needed in this patient population.

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