Natural History of Chronic HBV

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Module 3: Screening and Diagnosis
Lesson 4: Natural History of Chronic HBV

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Classification and Phases of Chronic HBV Infection

From a conceptual standpoint, the National Institutes of Health originally classified chronic hepatitis B virus (HBV) infection into three phases (or types of immune responses): immune tolerant, immune active, and inactive carrier phase.[1,2] Some experts have included a fourth phase, described as an immune-reactivation phase.[3,4] These distinct phases of chronic infection correspond with characteristic serologic patterns and correlate with the patient's immune response to HBV (**Figure 1**).[1,5,6] The initial immune response and subsequent initial phase of chronic infection generally depends on the age at which the patient acquired HBV, with immune-tolerant phase usually following vertical perinatal acquisition, HBeAg-positive immune-active phase following horizontal acquisition after birth in early childhood (**Figure 2**).[4] Although the majority of adults with acute HBV infection generate an effective immune response and have complete resolution of the HBV infection, a small proportion will develop chronic infection and eventually enter an immune-active phase.

Natural History and Phases of Chronic HBV

The phases of chronic HBV infection are not considered permanently static and patients who initially develop the immune-tolerant phase usually progress to the immune-active phase and then on to the inactive chronic carrier state (**Figure 2**).[4] Progression in the reverse direction, from the inactive to the immune-active phase (manifested as a flare of HBV disease activity), can develop spontaneously or (1) following the reappearance of HBV DNA or a rise in the HBV DNA level after cessation of HBV nucleoside/nucleotide therapy (including reversion from HBeAg-negative to positive, (2) after withdrawal of corticosteroids, or (3) when starting or stopping a biologic agent or a cancer chemotherapy regimen.[7] In addition to the four stages of chronic HBV infection discussed, some chronically-infected patients will resolve their HBV infection, either naturally or occasionally following interferon-based therapy or less frequently, with oral nucleoside/nucleotide therapy; these patients typically show clearance of HBsAg, are anti-HBc positive, and most develop anti-HBs (along with anti-HBc). In some patients with resolved acute HBV, reactivation of HBV infection may develop if they become severely immunosuppressed, as can occur following immunosuppressant medications used for transplantation, receipt of potent chemotherapy regimens, or immunosuppressive biologic agents that target B cells.[8,9,10,11]

Immune-Tolerant Chronic HBV Infection

Patients with immune-tolerant chronic infection usually have acquired HBV perinatally or in early childhood, as often seen in Asia and the South Pacific Islands.[4,5,12] Although the immune response to HBV remains incompletely understood, it is thought that exposure to HBV antigens and high levels of HBV DNA very early in life lead to "immune tolerance" that presumably results from a suboptimal immune response. Laboratory studies characteristically show normal hepatic transaminase levels, presence of HBeAg, minimal or no liver inflammation or fibrosis, and high serum HBV DNA levels.[3,4] The AASLD 2015 guidelines define immune-tolerant chronic hepatitis B infection as characterized by positive HBeAg, very high HBV DNA levels (generally exceeding 1 million IU/mL) and ALT levels less than or equal to 30 U/L in men and less than or equal to 19 U/L in women; the guidelines recommend use of these ALT upper limits of normal as opposed to using local laboratory upper limits of normal.[3] Patients with immune-tolerant chronic infection usually remain in this phase for a few decades, until they experience an up-regulation in the immune response and transition to the immune active phase. In adults with immune-tolerant chronic HBV, treatment courses of 24 to 48 weeks with interferon or oral antiviral therapy have been associated with higher rates of HBeAg loss than placebo, but no studies in this patient population have demonstrated a reduction in rates of hepatocellular carcinoma, cirrhosis or liver-related deaths with such therapy.[3,5,12,13] Even with the use of current more potent antiviral agents, it is difficult to completely suppress the high levels of HBV DNA found in patients in the immune-tolerant phase. Accordingly, the AASLD guidelines recommend against routine use of antiviral therapy for adults with immune-tolerant chronic HBV infection.[3] Patients with immune-tolerant HBV should have ALT levels checked every 6 months to monitor for potential transition from immune-tolerant HBV to either immune-active HBV or inactive chronic HBV.[3] The AASLD guidelines recommend treating a select subset of patients with immune-tolerant HBV if they meet all of the following criteria: older than 40 years of age with normal ALT, HBV DNA of 1 million IU/mL or greater, and liver biopsy showing significant necroinflammation or fibrosis. In addition, the AASLD guidelines state that patients who undergo liver biopsy and have moderate-to-severe inflammation on liver biopsy should be considered for hepatitis B therapy if other causes of liver disease have been excluded.[3]

Immune-Active Chronic HBV Infection

Most patients in the immune-tolerant phase eventually mount an enhanced immune response to HBV infection and transition to the immune-active phase (**Figure 2**).[4,12] Patients with perinatally-acquired HBV most often have this transition between the ages of 20 and 50, especially those infected with HBV genotype C, whereas those who acquire HBV in childhood generally have an earlier transition (between the ages of 10 and 15) to this active phase.[12] Patients can also develop immune-active chronic HBV without an immune-tolerant phase as when infection occurs in childhood or adolescence, a pattern frequently seen in sub-Saharan Africa and some Mediterranean countries where HBV genotypes A and D predominate, or when infection is acquired as an adult, as seen more frequently in industrialized countries. The immune-active phase is characterized by elevated levels of HBV DNA (typically greater than 20,000 IU/mL), elevated ALT levels, and active liver disease (moderate-to-severe inflammation or fibrosis) on biopsy.[3] The AASLD 2015 guidelines define immune-active chronic HBV as (1) a two-fold or greater elevation of ALT above the upper limit of normal or significant histologic disease seen on liver biopsy plus (2) elevated HBV DNA level above 2,000 IU/mL (in patient who is HBeAg negative) or above 20,000 IU/mL (in patient who is HBeAg positive).[3]

Most patients in the immune-active phase have a positive HBeAg, but will eventually spontaneously clear HBeAg and seroconvert from a negative to a positive anti-HBe at a rate of 8 to 10% per year.[13] When this occurs, the patients will have undergone a transition to the inactive chronic carrier state, characterized by normal ALT levels and HBV levels below 2,000 IU/mL. Some patients, who remain HBeAg-positive or experience HBeAg seroconversion can remain in the immune-active phase for years and experience progressive liver fibrosis that can lead to cirrhosis and an increased risk of hepatocellular carcinoma.[13] The 2015 AASLD guidelines recommend treating adults with immune-active chronic HBV infection.[3] For patients with ALT levels greater than normal, but less than twice the upper limit of normal, the decision to initiate treatment should take into consideration the severity of the patient's liver disease, as determined by liver biopsy or noninvasive tests, such as a serologic marker for fibrosis or transient elastography.[3] In addition, treatment is recommended if the patient has immune-active chronic HBV, cirrhosis, and an HBV DNA level greater than 2,000 IU/mL, regardless of the ALT level. For patients who do not quite meet criteria for immune-active HBV and have ALT levels less than two times the upper limit of normal and HBV DNA levels below the threshold levels, other patient factors should be considered in the decision to initiate treatment: age greater than 40, family history of hepatocellular carcinoma, presence of cirrhosis, and presence of extrahepatic manifestations of chronic HBV.

Inactive Chronic HBV Infection

Transition to the inactive chronic carrier state is typically accompanied by a change from negative to positive anti-HBe antibody, normalization of ALT levels, a decrease of serum HBV DNA to low or undetectable levels, and improved liver histology (with evidence of minimal necroinflammation on liver biopsy).[3] Overall, 67 to 80% of patients in the inactive chronic carrier phase will remain anti-HBe positive and HBeAg negative, and among these inactive carriers, 4 to 20% will undergo one or more "HBeAg reversions" and again become HBeAg-positive.[3,14] The approach to and management of patients who spontaneously transition to inactive chronic HBV is not addressed in the 2015 AASLD guidelines. The 2009 AASLD guidelines recommend persons with inactive hepatitis B phase should initially have ALT levels checked every 3 months for 1 year and then if persistently normal the interval can be increased to every 6 to 12 months (**Figure 3**).[5] In addition, since these persons are still at risk for the developing hepatocellular carcinoma (HCC), most experts would consider performing HCC surveillance every 6 moths using liver ultrasound, particularly in persons with chronic HBV infection who are at a higher risk for developing HCC (males older than 40 years of age, females over 50 years of age, presence of cirrhosis, or family history of HCC).[12,15] Not infrequently, patients in the inactive phase of HBV may have elevated levels of aminotransferases from other causes, the most common being non-alcoholic fatty liver disease (NAFLD) due to metabolic syndrome or moderate to heavy alcohol intake. In these circumstances, clinicians should evaluate patients for other causes of elevated ALT besides NAFLD and alcohol, including but not limited to hepatitis C, autoimmune liver disease and medications.[16]

Summary Points

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