Abstract

Hepatitis B: New strategies for diagnosis, monitoring, and referral

Chronic hepatitis B (CHB) infection is a global public health issue. It is estimated that 400 million people are infected worldwide and that it is associated with 500,000–700,000 deaths per year. While approximately 75% of infected individuals reside in Asia, other areas of endemicity include Africa, and Southern and Eastern Europe. However, even in areas with low prevalence there exist sub-groups in whom the infection rate is far higher than in the general population.

Epidemiology in Canada

In Canada, it is estimated that approximately 600,000 individuals have CHB infection. While the overall prevalence of infection in the general population is low, there are sub-populations with higher prevalence rates, particularly immigrant groups, the Inuit population, and intravenous drug users. Furthermore, the overall number of individuals with CHB infection is increasing because of immigration from endemic areas e.g., South-East Asia, including China, Korea and Vietnam, and Southern and Eastern Europe.[1]

Natural history of chronic hepatitis B infection

Our understanding of the natural history of CHB infection has evolved significantly over the past decade.[2] It is now recognised that CHB infection follows a dynamic course which varies between individuals.

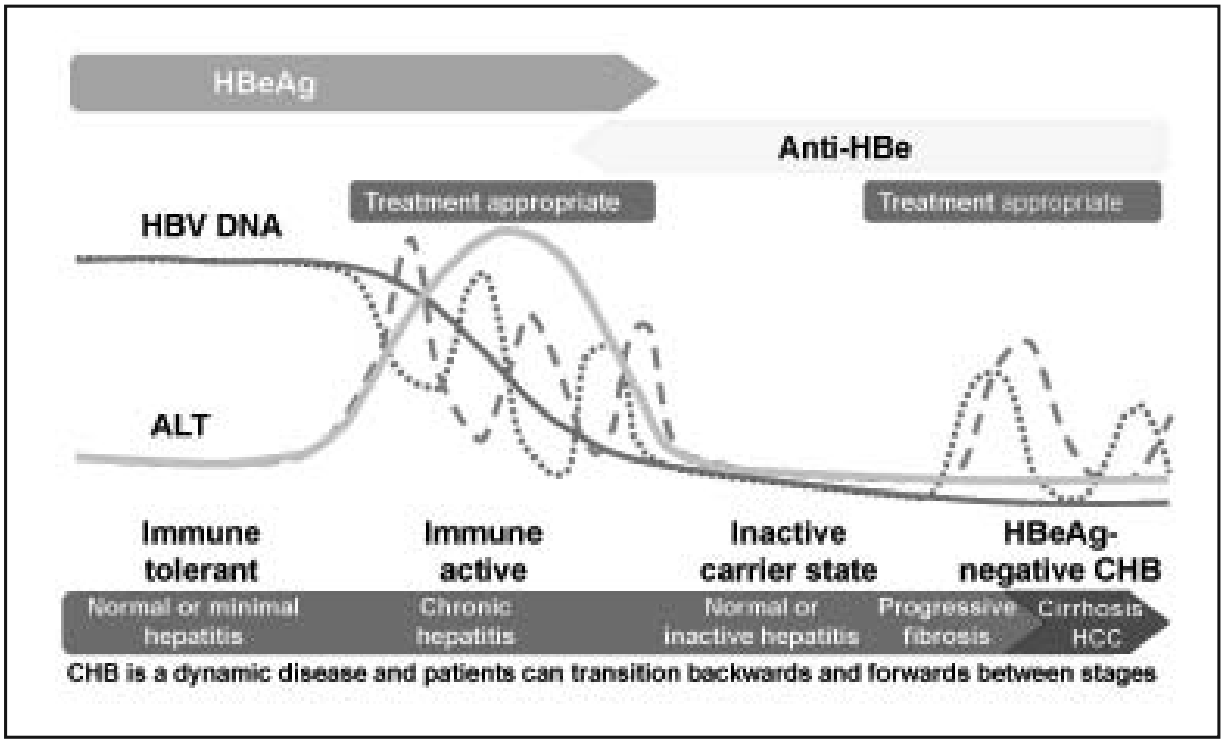

Figure 1. Chronic HBV infection has a dynamic disease course

Adapted from Yim & Lok, Hepatology 2006; 43: S173

Although four phases have been identified, these do not necessarily follow a linear course and patients may switch between stages at any time. Furthermore, treatment is not warranted at every stage and it is therefore important to undertake regular monitoring of patients with HBV infection to identify their current disease stage and to thereby determine whether they require treatment.

It is important to distinguish between patients with HBeAg-negative disease and those in the inactive carrier state, as the former is associated with a high risk of complications, including cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Patients with HBeAg-negative disease have higher serum HBV DNA levels than inactive carriers.

In addition, in patients with HBeAg-negative disease, serum ALT level is intermittently elevated, whereas it is persistently normal in inactive carriers. As the serum levels of HBV DNA and ALT often fluctuate in those with HBeAg-negative disease, a “normal” measurement on one occasion does not exclude HBeAg-negative disease. Regular monitoring over a period of 6–12 months should be undertaken to distinguish HBeAg-negative disease from inactive carriage.

Screening for HBV infection

Individuals with CHB infection are often asymptomatic until late in the disease course, therefore, screening is vital to identify individuals who are infected and require monitoring and/or treatment.[4] A number of high risk groups exist, as detailed in Table 1, and these should be actively targeted for screening. It is also important to screen household and sexual contacts of people diagnosed with HBV infection to enable vaccination to be undertaken in those who are not infected but remain at risk.

Evaluating the newly diagnosed patient

Individuals who are diagnosed with CHB infection should undergo testing for HBeAg and anti-HBe, serum HBV DNA level, and serum ALT/AST levels.[5] These will assist in the determination of disease phase and the identification of patients who require immediate treatment (see Figure 3).

It is also important to assess liver function by measuring the complete blood count, INR, albumin, and bilirubin. An ultrasound examination should also be performed.

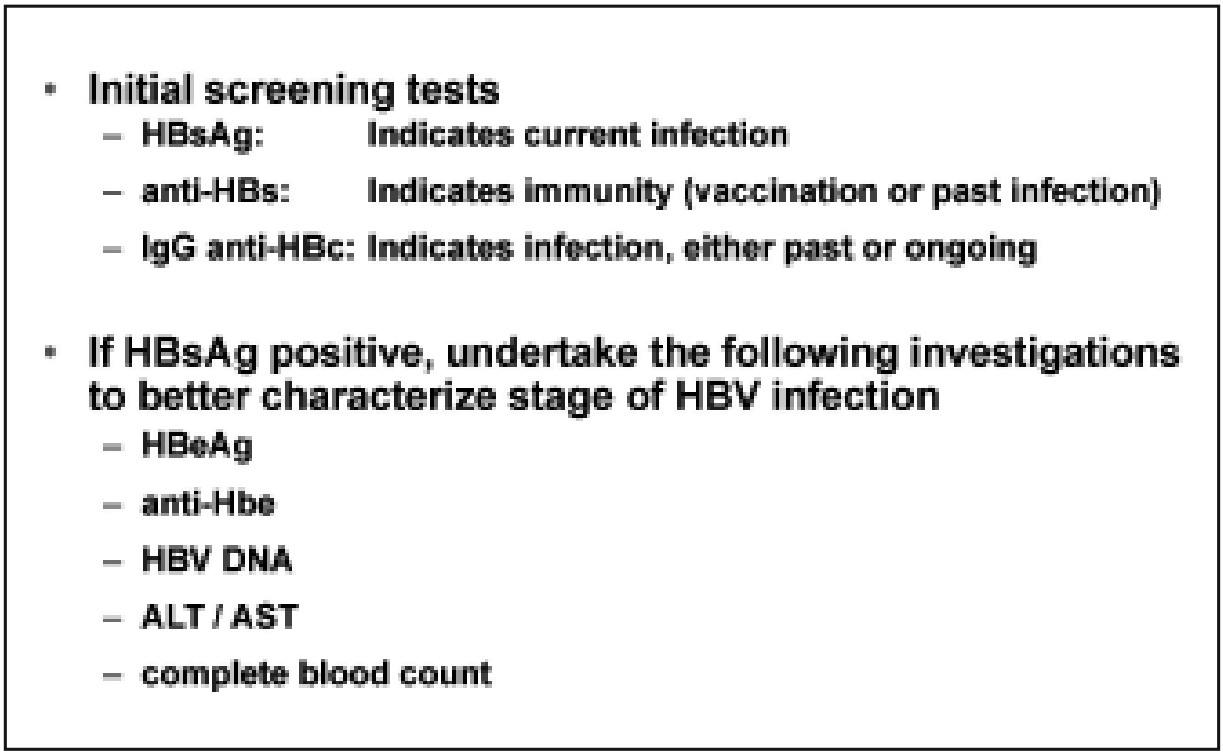

Figure 3. Evaluating the person at risk for HBV infection

Patient age and family history are important determinants of risk; older individuals and those with a family history of liver disease, including cirrhosis and hepatocellular carcinoma, are at higher risk for complications from HBV infection.

The role of HBV DNA and ALT/AST

Recent studies have highlighted the importance of serum HBV DNA levels in determining the risk of complications and the requirement for treatment.[6]

The REVEAL study evaluated the correlation between serum HBV DNA levels and the risk of complications in an untreated Taiwanese population. This study revealed that, in patients aged >35–40 years, the risk of cirrhosis or hepatocellular carcinoma significantly increased with higher viral loads (>1,000 IU/mL or 5,260 copies/mL).[7]

Persistently elevated serum HBV DNA levels were associated with the highest risk. This highlights the need for effective assessment of patients with CHB infection to determine which patients are appropriate for treatment.

Historically, ALT has been utilised to provide an indication of the level of hepatic damage and to thereby determine which patients are appropriate for therapy. However, studies have demonstrated that the normal range often quoted is too high to exclude clinically significant histology. The recommended upper limit of normal for ALT is now 30 IU/mL in men and 20 IU/mL in women. Furthermore, a normal ALT level cannot completely exclude significant liver damage as it is a marker of inflammation only and does not provide an indication of the degree of hepatic fibrosis. Consequently, patients should not be denied treatment solely on the basis of a normal ALT.

Specialist referral

The requirement for specialist referral is often determined by the severity of the disease and the comfort level of a physician in managing a patient with CHB infection. Patients at high risk of complications should be referred to a gastroenterologist or hepatologist with an interest in CHB infection.

This group includes those with high serum HBV DNA and ALT levels, patients who have been treated previously, patients who fail to respond to current therapy, and those requiring a liver biopsy. General Practitioners opting to manage a patient within their own clinic should undertake regular monitoring.

On-treatment monitoring

It is important to monitor a patient's response to therapy. This can identify those who have responded and no longer require treatment, those who have not responded adequately, and those who had an initial response which is now declining.[8]

Lack of response to therapy can be divided into primary and secondary treatment failures. In primary treatment failure, the patient fails to exhibit a drop of at least 2 $\log_{10}$ IU/mL in HBV DNA levels by six months after commencing therapy. This is most commonly associated with poor compliance. In secondary treatment failure, there is an initial response to therapy followed by an increase in viral load of ≥1 $\log_{10}$ IU/mL from nadir value.

Secondary treatment failure can be due to a number of factors, including lack of compliance, but the possibility of antiviral resistance should be considered. This is extremely important as the development of resistance to an agent leads to a reduction in its efficacy and affects clinical outcomes. In a minority of cases, acute flares of hepatitis occur and these can be life-threatening in patients with advanced disease.

Antiviral resistance occurs due to mutations in the HBV polymerase allowing the virus to escape inhibition by the nucleoside or nucleotide analogue.

Viral breakthrough is defined as a ≥1 $\log_{10}$ IU/mL rebound in HBV DNA from the nadir on-treatment level. This is followed by biochemical breakthrough – a rise in ALT level from its nadir (see Figure 4). It is important to identify resistance to an agent as early as possible (at viral breakthrough), as intervention

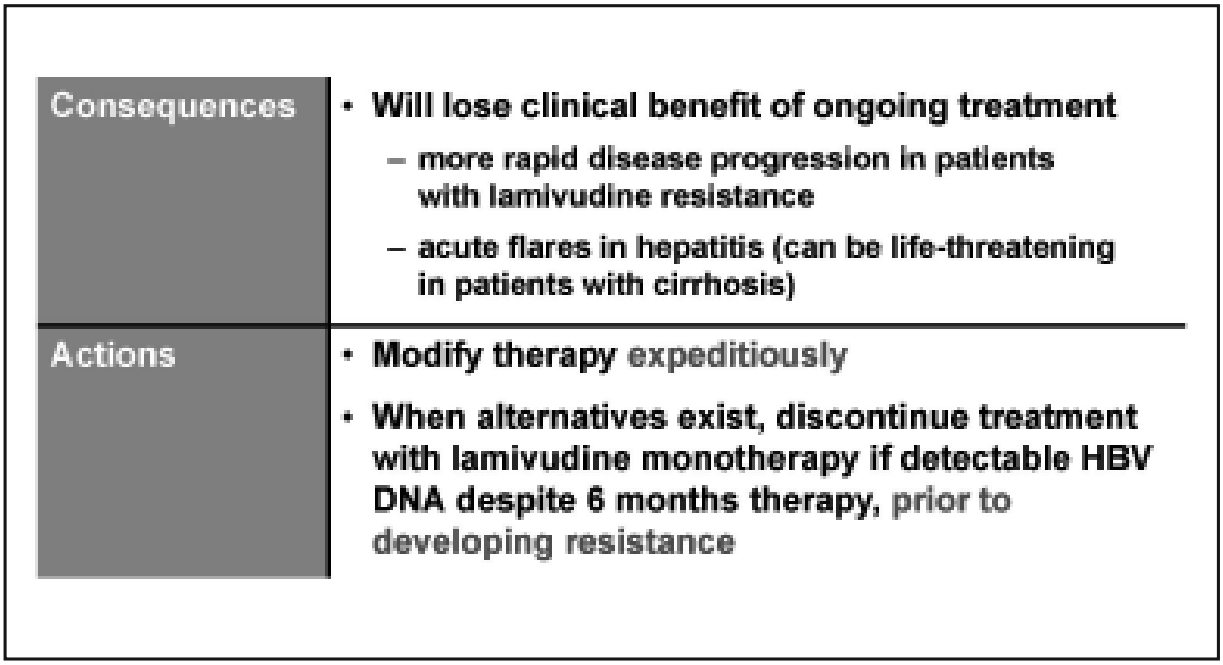

Figure 4. Manifestations of antiviral resistance
Adapted from Sherman et al, Can J Gastroenterol 2007; 21(Suppl C): 5C

(switching or adding an alternative agent) is more effective before the viral load returns to pre-treatment levels. Viral resistance can be diagnosed using genotypic testing which identifies mutations in the HBV genome. This is important as the pattern of mutations affects future management choices.

Cross-resistance can occur between the available oral anti-HBV agents based on their structure. Cross-resistance can occur between the L-nucleoside analogues, lamivudine, entecavir, and telbivudine. Adefovir and tenofovir may be appropriate choices in patients with resistance to an L-nucleoside analogue. Patients with suspected antiviral resistance should be referred for specialist assessment.

Summary

Chronic hepatitis B infection remains an important public health issue. It is associated with a significant risk of cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Despite the introduction of vaccination programs, the overall number of infected individuals in Canada is increasing due to immigration from endemic areas. It is important that at-risk individuals and, when appropriate, their families, are screened for HBV. Newly diagnosed individuals should be carefully assessed to determine their disease phase and the need for treatment. Infected patients, both those receiving treatment and those not currently receiving treatment, should be monitored regularly.

Effective screening, monitoring and referral practices are vital to identify and treat those with chronic hepatitis B infection, with the aim of reducing the morbidity and mortality associated with this disease.

Further reading

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