Monograph

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.

Natural history of chronic hepatitis B infection

Our understanding of the natural history of CHB infection has evolved significantly over the past decade. It is now recognised that CHB infection follows a dynamic course which varies between individuals. Although four phases have been identified, these do not necessarily f

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.

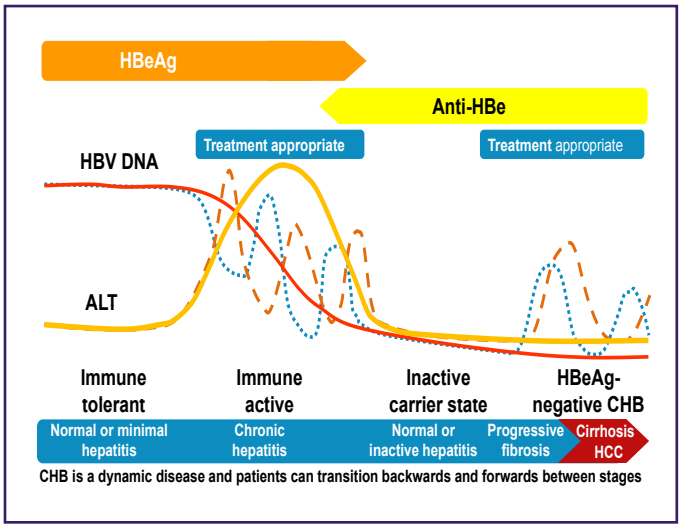

Figure 1. Chronic HBV infection has a dynamic disease course

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

The immune tolerant phase can last for many years, particularly in those infected in the perinatal period or during childhood. During this stage the immune system fails to recognize the presence of HBV and therefore does not mount a response against the infected cells. This phase is characterised by high serum HBV DNA levels but normal ALT levels, with minimal hepatic inflammation and fibrosis on biopsy.

During **the immune active stage**, a high viral load (HBV DNA level) elicits an immune response leading to destruction of the infected hepatocytes. This leads to elevated serum ALT levels and inflammation and fibrosis on biopsy. This stage is often cyclical, leading to periods of inflammation and repair. Treatment is warranted during this phase with the aim of reducing viral load, and promoting seroconversion from hepatitis B e antigen (HBeAg-) positive to hepatitis B e antibody (anti-HBe-) positive state.

In **the inactive carrier phase**, seroconversion to anti-HBe has occurred, either spontaneously or treatment-induced. HBV DNA levels fall to low or undetectable levels and serum ALT is persistently normal. This stage is associated with disease quiescence and fibrosis does not progress. However, patients remain at risk of hepatocellular carcinoma, particularly those with pre-existing cirrhosis. Furthermore, disease reactivation may occur and regular monitoring should continue.

Patients in the inactive carrier phase are not "cured", as HBV is never fully eradicated. Disease reactivation may occur during periods of immunosuppression and some individuals may develop **HBeAg-negative disease**. This occurs as a result of mutations in the precore or core promoter region of the HBV which enable the virus the host' immune C tly despite the absence of HBeAg and the presence of anti-HBe (similar to the inactive phase), the viral load (HBV DNA level) rises and inflammation and fibrosis occur. In patients with HBeAg-negative disease the serum HBV DNA level is often lower than in those in the immune active phase.

	Immune active (HBeAg-positive) disease	HBeAg-negative disease	Inactive carrier†
HBsAg positive	✓	✓	✓
HBeAg positive	✓		
HBeAg negative		✓	✓
Anti-HBe positive		✓ (rarely HBeAg-negative CHB may be anti-HBe negative)	✓
HBV DNA	>3–8 log IU/mL (5.26×10^3–5.26×10^8 copies/mL)	>3 log IU/mL (>5.26×10^3 copies/mL)*	<3 log IU/mL (<5.26×10^3 copies/mL)
ALT	Elevated	Intermittently elevated	Normal

*HBV DNA levels often fluctuate; †May reactivate
Based on a conversion factor of 1 IU/mL = 5.26 copies/mL

Figure 2. Differentiating immune active (HBeAg-positive) disease, HBeAg-negative disease, and the inactive carrier state

- Includes
  - individuals from all geographic regions *except* small towns of North America, Northern Europe
  - household and sexual contacts of HBV carriers
  - injection drug users
  - individuals having sex with multiple partners
  - individuals infected with a sexually transmitted disease, including HIV
  - inmates of correctional facilities
  - individuals with chronic liver disease
  - healthcare and public safety workers
  - patients undergoing renal dialysis
  - all pregnant women
- Important to consider and discuss with the patient, the potential impact of possible results before commencing screening

Table 1. Individuals at risk of HBV infection who should be considered for screening

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. 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.

Screening tests for HBV infection include serological and virological testing for hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis B core antibody (anti-HBc). Patients who are infected with HBV will be positive for HBsAg. Those who are anti-HBc negative and anti-HBs negative have never been infected and should undergo a course of vaccination.

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. 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. 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.

- **Initial screening tests**
  - **HBsAg:** Indicates current infection
  - **anti-HBs:** Indicates immunity (vaccination or past infection)
  - **IgG anti-HBc:** Indicates infection, either past or ongoing
- **If HBsAg positive, undertake the following investigations to better characterize stage of HBV infection**
  - **HBeAg**
  - **anti-Hbe**
  - **HBV DNA**
  - **ALT / AST**
  - **complete blood count**

Figure 3. Evaluating the person at risk for HBV infection

Many patients with chronic HBV infection are asymptomatic at the time of diagnosis. If symptoms are present, they may include epigastric pain, fatigue, flu-like symptoms, nausea, or stomach ache. Individuals may also report dark-yellow urine.

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. 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). 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.

Monitoring patients who do not currently require therapy

It is vitally important to monitor patients who are not currently eligible for therapy, even those classed as "inactive carriers". CHB infection is a dynamic disease and patients may switch between phases at any time. In addition, a significant degree of hepatic inflammation and fibrosis may occur before any signs or symptoms of liver damage are present.

In patients not currently requiring treatment, serum HBV DNA and ALT should be performed at 3–6 monthly intervals.

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.

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, overleaf). It is important to identify resistance to an agent as early as possible

(at viral breakthrough), as intervention (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

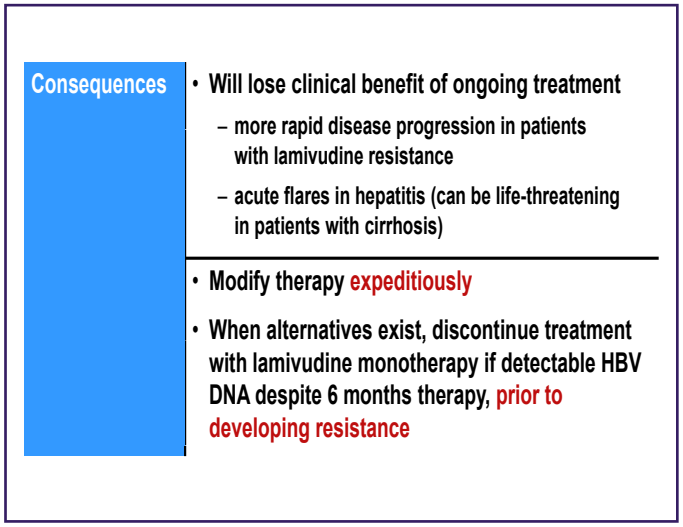

Figure 4. Manifestations of antiviral resistance

Adapted from Sherman et al, Can J Gastroenterol 2007; 21(Suppl C): 5C

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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