Management of Hepatitis B

- Information for primary care providers

August 2019

Chronic hepatitis B (CHB) is often a lifelong condition. Not everyone with the condition needs anti-viral therapy. This document outlines the situations in which anti-viral therapy could be considered. At times the decision may be clear-cut, but at others careful discussion with the patient regarding the risks and benefits of commencing long term anti-viral therapy may be needed. Referral to a specialist (a gastroenterologist, hepatologist or infectious diseases physician) may also help in these incidences.

The decision to start anti-viral therapy is rarely an urgent one. Specialists at the Hepatitis Foundation are available for advice regarding non-urgent management discussions. For assistance with the urgent management of severe flares of CHB (or suspected acute infection), with associated hepatic impairment, please call your local on-call gastroenterology service.

What has changed?

Pharmac has recently announced the removal of special authority restrictions for the prescribing of anti-viral medications for CHB. This removes some of the barriers affecting patient access to treatment with entecavir and tenofovir. Non-specialist doctors can now prescribe these medications.

What has not changed?

The Hepatitis Foundation of New Zealand is a charitable trust funded by the Ministry of Health to provide a national monitoring programme for all New Zealanders affected by hepatitis B viral infection. People with CHB are at risk of liver failure and liver cancer.

Long-term regular blood test monitoring (and, in specific situations, abdominal ultrasounds), has been shown to reduce morbidity and mortality from CHB. We would recommend referring patients with CHB to our service.

We have a team of community nurses around NZ who can provide personalised education to patients and their families. We have two part-time specialists who review abnormal results on a case-by-case basis and can give you advice and support for the management of people with CHB.

About 25,000 people are enrolled in the Hepatitis Foundation's monitoring programme.

Natural history of chronic hepatitis B

In determining when to start anti-viral therapy, it is helpful to consider the natural history of CHB. Most are infected in infancy or early childhood and for many years the virus is present at very high titres (>10^8). The virus itself is not hepatotoxic and there is minimal damage occurring to the liver during this period. This is the immune-tolerant HBeAg-positive phase (fig1).

This may be followed, often in later childhood or early adulthood, by a period of active hepatitis when the immune system tries to destroy the virus by killing infected liver cells (known as HBeAg-positive chronic hepatitis or immune active CHB). A person may then become HBeAg-negative and move into a prolonged phase of normal liver function and a much lower viral load (HBeAg-negative chronic infection or inactive CHB).

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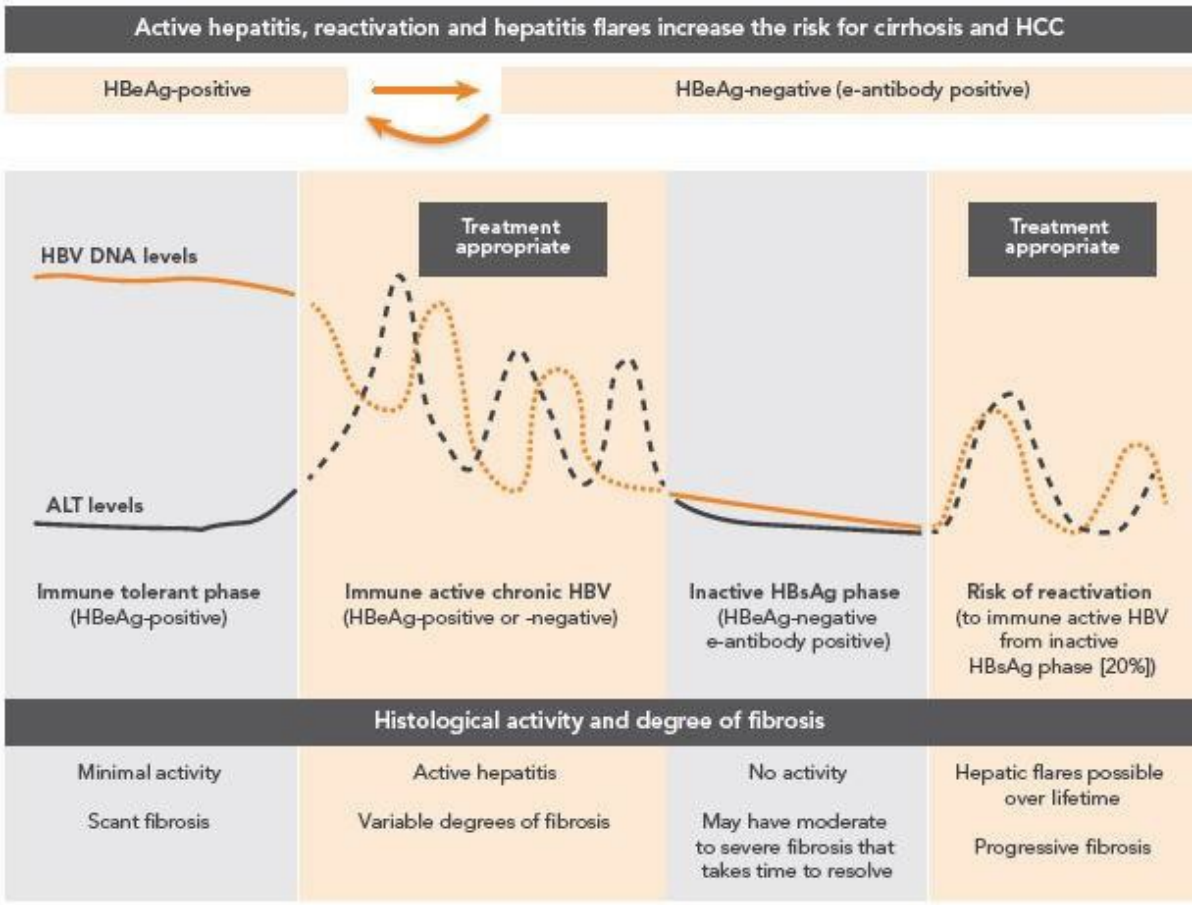
Fig 1: Natural history of chronic hepatitis B after infection in neonatal or childhood period



Subsequent viral mutation in some individuals can lead to partial escape of immune control and fluctuating or persistent chronic active hepatitis (HBeAg-negative chronic hepatitis or immune active chronic hepatitis B). During times of active hepatitis progressive liver damage and fibrosis can occur, leading ultimately to cirrhosis.

Hepatocellular carcinoma (HCC) can develop in anyone infected with CHB, but predominantly arises in those with established liver cirrhosis. The primary aim of treatment is to prevent progressive fibrosis and the subsequent complications of cirrhosis, liver failure and HCC.

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Nomenclature

Table 1: Serology and definitions

Test	Description
Hepatitis B surface antigen (HBsAg)	Shows whether the person has hepatitis B. In chronic HBV, HBsAg is always detected.
Hepatitis B surface antibody (HBsAb or anti-HBs)	Shows whether the person is developing immunity to HBV. It can be present while the person still has the virus (HBsAg-positive). If HBsAg is negative and HBsAb is positive, it means the person is immune from vaccination or past infection.
Hepatitis B e antigen (HBeAg)	Usually detected in the absence of anti-HBe. Shows the hepatitis virus is multiplying at a high rate and is therefore very infectious. The HbeAg-positive phase is the earliest stage of HBV and the most common one in children and young adults.
Hepatitis B e antibody (HBeAb or anti-HBe)	Usually detected in the absence of HBeAg. This later phase of HBV follows the development of the patient's immune response against HBeAg and is the most common phase of HBV infection found in middle-aged and elderly patients. This phase is usually associated with suppression of the virus and reduction in level of viral replication. However, HbeAg-negative patients are still infectious. They may still have active liver disease and could progress to cirrhosis.
Hepatitis B core antibody (HBcAb or anti-HBc)	Shows whether a person has ever been exposed to the hepatitis B virus. Is detected in patients with current infection and people with previous acute infection that has resolved. Is not detected in individuals who have immunity through vaccination.
Anti HBc IgM+	Always detected during acute infection and may be the only marker of acute infection in the 'window phase', when HBsAg has disappeared and anti-HBs levels are not yet high enough to be detected.
Hepatitis B virus DNA (HBV DNA)	Measures the amount of hepatitis B virus present in the blood (viral load). High HBV DNA levels are one of the criteria for commencing anti-viral therapy (along with high ALT or advanced fibrosis stage). The HBV DNA level is one of the most important prognostic factors for the development of complications of hepatitis B.

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Not all patients with CHB need treatment. The decision to treat depends on several factors including age, serial ALT and HBV DNA levels and severity of liver disease (degree of fibrosis). The three major international societies for the study of liver disease (APASL[1], EASL[2], AASLD[3]) have recently published updated guidelines on the management of hepatitis B. These vary in detail but broadly agree on the approach outlined in table 2. Patients with persistent active hepatitis (such as raised ALT with high viral load) should be offered treatment as well as all cases with cirrhosis. The degree of fibrosis (scar tissue) present is also an important factor in making treatment decisions in some scenarios.

In most cases this can be obtained non-invasively with a fibroscan. In a small number of cases a liver biopsy may be useful.

Because the decision to treat is rarely urgent, a persistent pattern of elevated LFTs (at least three measurements three months apart) should be established prior to commencing treatment. If there are no features of advanced fibrosis or cirrhosis monitoring should continue six-monthly. Entecavir and tenofovir (*hyperlink*) are the main medications used to treat CHB. These are single, daily-dose tablets. Both are renally excreted and require dose reduction in renal failure. Both also effectively suppress viral replication but do not eliminate the virus, therefore the duration of therapy is long-term.

Table 2: Management of chronic hepatitis B - summary of international guidelines

TREAT:

- All cases with cirrhosis or severe liver disease with any detectable HBV DNA
- HBeAg positive patients with persistent ALT>2x upper limit normal*
- HBeAg negative patients with persistent ALT>2x upper limit normal* and HBVDNA>2000 IU/ml

MONITOR

- HBeAg positive <35yrs with normal ALT
- HBeAg negative with normal ALT and HBVDNA<2000 IU/ml

FURTHER ASSESS**

- HBeAg positive patients >35yrs
- HBeAg negative with ALT<2x upper limit normal and HBVDNA>2000 IU/ml
- HBeAg negative with raised ALT and HBVDNA<2000 IU/ml
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*70 U/L males, 50 U/L females

** Should consider other possible causes of liver damage, fibrosis staging, and risk factors such as age and family history.

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HBeAg-positive

People under 40 who are HBeAg-positive with ALT elevation > 2x ULN may be in the process of HBeAg seroconversion. This can be monitored for a period of time. If persistent, their degree of liver fibrosis should be assessed and treatment commenced.

In select individuals, especially young patients (such as females prior to pregnancy), with HBeAg-positive hepatitis, a 48-week trial of weekly interferon injections under specialist care may be an option.

Approximately a third of HBeAg-positive patients on treatment will HbeAg-seroconvert to an inactive HBeAg-negative hepatitis status. Treatment can be discontinued after a further 12 months of persistent HBeAg loss and development of anti-HBe. However, there is a risk of viral reactivation and subsequent liver injury, especially in people who had moderate or advanced fibrosis when they started anti-viral therapy. Close monitoring is required for 12 months following drug discontinuation.

HBeAg-negative

Anti-viral medication is continued in HBeAg-negative patients until loss of HBsAg, which occurs in a small proportion of patients. The patient must be counselled regarding the likely need for treatment to be lifelong. Periods of non-adherence can lead to rapid viral rebound and associated severe and sometimes life-threatening liver injury.

What monitoring is needed?

All patients with CHB should have six-monthly liver function tests (AFP, HBsAg, HbeAg), as is requested by the Hepatitis Foundation. An annual full blood count is recommended to look for thrombocytopaenia as a marker of portal hypertension and cirrhosis. When a patient is on anti-viral treatment, in addition to the standard bloods, they should have an annual HBV DNA and, if on Tenofovir, calcium, phosphate and creatinine. If the ALT rises it may indicate poor adherence or rarely viral resistance. An HBV DNA can be done.

Those with cirrhosis, a first-degree relative with HCC or those with additional risk factors (after specialist review) should have six-monthly liver ultrasounds for HCC surveillance.

Special situations

- Pregnancy
  - Pregnant women occasionally need treatment for themselves because of evidence of active hepatitis.
  - All babies born to mothers who are HBsAg positive should receive HBIG and first dose vaccine given on the day of birth. This reduces the risk of vertical transmission of hepatitis B to the infant by 95 percent.
  - Women who are HBeAg-positive or negative with a viral load >200,000 IU/ml are at higher risk of transmitting the virus and therefore should also be given Tenofovir for the last 8-12 weeks of pregnancy and one-month post-partum. Tenofovir has the most evidence of safety during pregnancy.

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- Immune suppression
  Patients on potent immunosuppression, e.g. for malignant or autoimmune diseases should be considered for prophylactic anti-viral therapy to prevent viral flares and liver inflammation. Please refer to a local specialist.

- Delta virus
  Pacific Islanders (especially those from Samoa, Niue and Kiribati) with hepatitis B may have super-infection with hepatitis Delta (HDV). If the ALT is high this should be tested for. Treatment is difficult and needs specialist management.

- Co-infection with hepatitis C or HIV
  Such individuals have higher risks of complications and more complex management needs and should be referred to a specialist.

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