



# The management of hepatitis B

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## Summary

**Chronic hepatitis B affects almost 1% of Australians, many of whom are born in endemic areas outside Australia. This infection can shorten lifespan, usually because of cirrhosis or hepatocellular carcinoma. Most patients acquire the infection perinatally or in childhood before migration. A small number of people acquire infection as adults via injecting drug use or sexual contact. Hepatitis B infection is usually asymptomatic, and screening using hepatitis B surface antigen should be considered for all patients from endemic countries and those with percutaneous or sexual risk factors. Improved laboratory testing for viral DNA can help identify the need for treatment and long-term risk of liver damage. Treatment is with nucleos(t)ide analogues (usually long-term) or pegylated interferon (for 12 months). This reduces inflammation, can improve liver injury and reduces progression to cirrhosis and hepatocellular carcinoma. Long-term monitoring is recommended to detect reactivation of infection and hepatocellular carcinoma.**

Key words: antiviral drugs, cirrhosis, hepatocellular carcinoma, liver.

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## Introduction

Although Australia has traditionally been regarded as having a low prevalence of chronic hepatitis B, recent estimates suggest that 160 000 people are infected.<sup>1,2</sup> The majority of these patients are born in an endemic area such as Asia, Africa, the Middle East, Central and South America, Eastern Europe (except Hungary), Mediterranean Europe (Greece, Italy, Malta, Portugal and Spain), the South Pacific and the Caribbean. High rates of infection also exist in indigenous populations.<sup>1</sup>

## Routes of transmission

Hepatitis B transmission can occur via a number of routes including percutaneous or parenteral, horizontal transmission through mucosal contact with infected blood or bodily

secretions, and during the perinatal period (see Table 1).

Transmission during the perinatal period is more common in patients born in endemic areas. Blood transfusions or organ transplantation are now extremely rare routes of transmission due to the rigorous screening protocols in Australia.

## Natural history of infection

Chronic hepatitis B shortens the lifespan in 45% of infected men and 15% of infected women usually due to the development of cirrhosis or hepatocellular carcinoma. Following exposure, acute hepatitis B infection has an incubation period of 6–12 weeks. Adults who acquire infection commonly develop symptoms of jaundice, anorexia, nausea, right upper quadrant discomfort and fatigue. In the perinatal setting asymptomatic subclinical hepatitis is common. While over 95% of people infected as adults will spontaneously clear the virus, this reduces to 30% in children, and 5% in infants.

## Diagnosis

It is important to distinguish between patients with newly acquired hepatitis B and those with chronic infection. This may be difficult because both groups may have the hepatitis B surface antigen (HBsAg) in their blood, and may be clinically well.

## Acute hepatitis B

Newly acquired infection is more likely if the patient has:

- recent risk factors
- negative HBsAg in last 1–2 years
- high levels of specific immunoglobulin (Ig) M antibody to hepatitis B core protein in the absence of previous evidence of infection.

Table 1

Routes of transmission of hepatitis B

Route	Example
Percutaneous	Injecting drug use Needlestick injury Tattooing/body piercing
Horizontal	Sexual contact with an infected individual (higher risk with anal intercourse) Child to child (usually through open sores of infected individual)
Perinatal	Mother to neonate at or around time of birth

## Chronic hepatitis B

Chronic infection is classically based on the detection of HBsAg on two occasions six months apart with no clinical or laboratory evidence of acute disease. IgG antibodies to hepatitis B core protein are present in chronic infection, and patients may be either positive or negative (depending on the phase of infection) for the hepatitis B e antigen (HBeAg).

In general practice, it is common to detect HBsAg in clinically well patients born in endemic areas. If there are no recent percutaneous or sexual risk factors for acquisition, these patients are likely to have chronic infection.

### Baseline evaluation

This should include a thorough history to identify the country of birth of the patient and their parents, family history of hepatitis B or hepatocellular carcinoma, cofactors for liver disease such as alcohol abuse, and risk factors for co-infection with hepatitis C virus or HIV. It is also important to get information about the patient's sexual contact(s), as well as their vaccination status. A physical examination should be carefully performed for evidence of chronic liver disease.

Initial blood tests should include liver function tests, full blood

examination, prothrombin time, as well as the presence of HBeAg and HBeAg-specific antibodies, viral DNA load, antibodies to hepatitis C, HIV antibody, hepatitis A-specific IgG, and alfa-fetoprotein. A baseline ultrasound of the liver should be performed to screen for hepatocellular carcinoma and identify any features of cirrhosis. If there is significant deterioration in liver function, testing for hepatitis D co-infection (by measuring hepatitis D antigen and antibody) should be considered as it can affect choice of therapy.

### Managing acute infection

Treatment of acute hepatitis B is supportive for most cases. However, acute liver failure can develop in up to 1%, and can be recognised clinically by the presence of encephalopathy, abnormal prothrombin time and renal impairment. These patients should be referred to a liver transplant unit.

### Managing the different phases of chronic infection

Patients with chronic hepatitis B can progress through up to four phases of disease (Table 2). Understanding these phases is critical to determining the risk of liver damage and need for treatment.

Table 2

Recognising and managing the phases of chronic hepatitis B infection

	Phase 1 Immune tolerance	Phase 2 Immune clearance	Phase 3 Immune control	Phase 4 Immune escape
HBeAg	Positive	Positive	Negative	Negative
Antibodies to HBeAg	Negative	Negative	Positive	Positive
Viral DNA (IU/mL)	>20 000	>20 000	<2 000	>2 000
Alanine aminotransferase	Persistently normal	Elevated (1–2 x) and fluctuating	Normal	Elevated or fluctuating
Liver histology	Normal or mild hepatitis	Moderate to severe hepatitis	Normal to mild hepatitis May have cirrhosis	Moderate to severe hepatitis May have cirrhosis
General recommendations	Monitor HBeAg and liver function annually	Liver biopsy Consider antiviral treatment Monitor liver function and viral load every 3 months if on drug treatment	Monitor liver function annually Check for signs of cirrhosis and biopsy if > 40 years of age	Liver biopsy Consider antiviral treatment Monitor liver function and viral load every 3 months if on drug treatment

HBeAg hepatitis B e antigen

### Phase 1 – immune tolerance

In this phase, which usually lasts for 20–40 years, the host immune system is 'tolerant' to the virus, resulting in high levels of viral replication and persistently normal alanine aminotransferase. Patients also have hepatitis B e antigen (HBeAg) (a protein which is secreted during viral replication), but no antibodies to this antigen.

#### Recommendation

During this phase there is minimal damage and so a liver biopsy and antiviral treatment are not required. However, the majority of patients will eventually progress to phase 2 and develop active disease. Patients should therefore be advised that periodic monitoring of liver function is important to detect a rise in alanine aminotransferase.

### Phase 2 – immune clearance

This phase is characterised by a more vigorous immune response resulting in liver damage with intermittently elevated alanine aminotransferase and elevated viral DNA. Repeated episodes of inflammation lead to fibrosis, and the duration and severity of this phase determines the degree of long-term liver damage. Approximately 30–40% of patients emerge from this phase with established cirrhosis.<sup>3</sup>

During this phase, approximately 5–10% of patients each year will spontaneously lose HBeAg and develop antibodies to HBeAg. This is called seroconversion and is usually associated with reduced viral replication. The median age for seroconversion is 30–32 years.

#### Recommendation

It is common practice to initially observe patients with high alanine aminotransferase concentrations (greater than 2–5 times upper limit of normal) for three months to assess whether spontaneous HBeAg seroconversion will occur.

All patients with a persistently abnormal alanine aminotransferase should therefore be referred to a hepatologist for consideration of a liver biopsy and treatment.

### Phase 3 – immune control

In this phase the immune response suppresses viral replication to low or undetectable levels. Inflammation reduces and serum alanine aminotransferase normalises. The establishment of immune control is associated with HBeAg seroconversion, and these patients are thought not to have ongoing damage. Once seroconversion occurs, patients may stay in this phase indefinitely.

#### Recommendation

Although most patients in this phase do not require antiviral treatment, a significant proportion will already have established cirrhosis and require regular careful assessment (Table 3).

Carefully performed ultrasound can reveal coarse echo texture suggestive of cirrhosis. Low albumin and elevated prothrombin time are markers of synthetic dysfunction seen in advanced disease, and low platelets ( $150 \times 10^9/L$ ) may be due to portal hypertension. If any of these features are detected, a liver biopsy should be considered, and treatment is recommended for patients with confirmed cirrhosis and detectable viral DNA.

Patients in this phase can reactivate at any time and should still undergo regular monitoring with at least annual liver function tests. Prophylactic treatment is recommended if patients require immunosuppressive therapy, for example cancer chemotherapy.

### Phase 4 – immune escape

In this phase the virus mutates and loses its ability to make the HBeAg protein. Despite this, it can still replicate, resulting in recurrence of active liver disease and progressive fibrosis. This phase is characterised by persistently elevated or fluctuating levels of alanine aminotransferase, HBeAg negativity, but elevated viral DNA. Patients in this phase are usually older than 40 years.

#### Recommendation

Patients in this phase are at high risk of cirrhosis (8–10% per year) and require long-term treatment to suppress viral replication.

### Referral

Drug treatment is primarily undertaken at a liver clinic under the supervision of specialist hepatologists. Non-urgent referrals should be directed to the liver clinic. Patients presenting with an alanine aminotransferase greater than 200 U/L, or decompensated liver disease (muscle wasting, ascites, jaundice, encephalopathy or bleeding) should be discussed with a specialist to expedite referral.

Table 3

#### Signs and symptoms of liver cirrhosis

Clinical	Fatigue Muscle wasting Dupuytren's contracture Palmar erythema Spider naevi Splenomegaly
Radiological	Coarse echotexture Features of portal hypertension - dilated portal vein - recanalisation of para-umbilical vein - varices
Laboratory	Synthetic dysfunction - low albumin - elevated prothrombin time Portal hypertension - thrombocytopenia

## Treatment options

Short-term treatment goals include suppression of viral replication, normalisation of serum alanine aminotransferase and improvement in liver histology. In HBeAg positive patients, seroconversion is a therapeutic end point because it is associated with an improved prognosis. The aim of long-term treatment is to prevent or delay the onset of complications including cirrhosis, hepatic decompensation and hepatocellular carcinoma.

The two major options for chronic hepatitis B are pegylated interferon or nucleos(t)ide analogue therapy. There are advantages and disadvantages with both treatments (Table 4).

### Interferons

Pegylated interferon therapy consists of weekly subcutaneous injections usually given for 12 months. This treatment stimulates the immune system to eradicate the virus from infected hepatocytes. The benefits of pegylated interferon can persist even after treatment, and relapse rates appear to be less than with non-pegylated interferon.<sup>4</sup>

Adverse effects include neutropenia and thrombocytopenia which require monthly blood monitoring, and dose reduction if

necessary. Fever after injection, fatigue, myalgia and headache are common in the first month and can be treated with standard dose paracetamol.

Interferons affect serotonin concentrations and can cause mood disturbance. It is therefore important to ensure that the patient is euthymic at the start of treatment and that their mood is monitored regularly. A past history of depression or anxiety, or antidepressant use is not a contraindication to interferon therapy. Mood disturbances respond to low-dose selective serotonin reuptake inhibitors and do not usually require interruption of interferon treatment.

### Nucleos(t)ide analogues<sup>4</sup>

Conversely, treatment with nucleos(t)ide analogue therapy is usually a once-daily oral treatment. While a number of different oral drugs are available, they all inhibit the viral polymerase enzyme to suppress viral replication. Unlike pegylated interferon, oral nucleos(t)ide analogues do not induce a strong immune response and thus often require long-term administration to prevent relapse.

Approximately 20% of HBeAg positive patients per year will achieve the therapeutic end point of HBeAg seroconversion on oral nucleos(t)ide analogue therapy. Consolidation treatment is recommended for 12 months after seroconversion. However, longer-term treatment may be needed if the patient does not seroconvert, has immune escape (HBeAg negative at the start of treatment) or is cirrhotic.

### Pregnancy

It is important to note that telbivudine is a category B1 drug whereas all the other nucleos(t)ide analogues are category B3. However, experience with drugs such as lamivudine is far greater than with telbivudine so many doctors would use lamivudine in pregnancy.

### Treatment initiation

In general, patients who are offered treatment have active viral replication and liver damage. Important considerations before treatment include:

- patient choice
- timing of pregnancy (oral drugs are not licensed for use in pregnancy)
- risk of progression without treatment (highest in those with high alanine aminotransferase, repeated flares or significant fibrosis already)
- potential need for indefinite therapy (immune escape/HBeAg negative disease and cirrhosis)
- risk of antiviral resistance with oral nucleos(t)ide analogues
- potential treatment-related adverse effects.

A general approach in treatment-naïve patients with chronic hepatitis B is outlined in Fig. 1.

Table 4

#### Pros and cons of drug treatments for hepatitis B

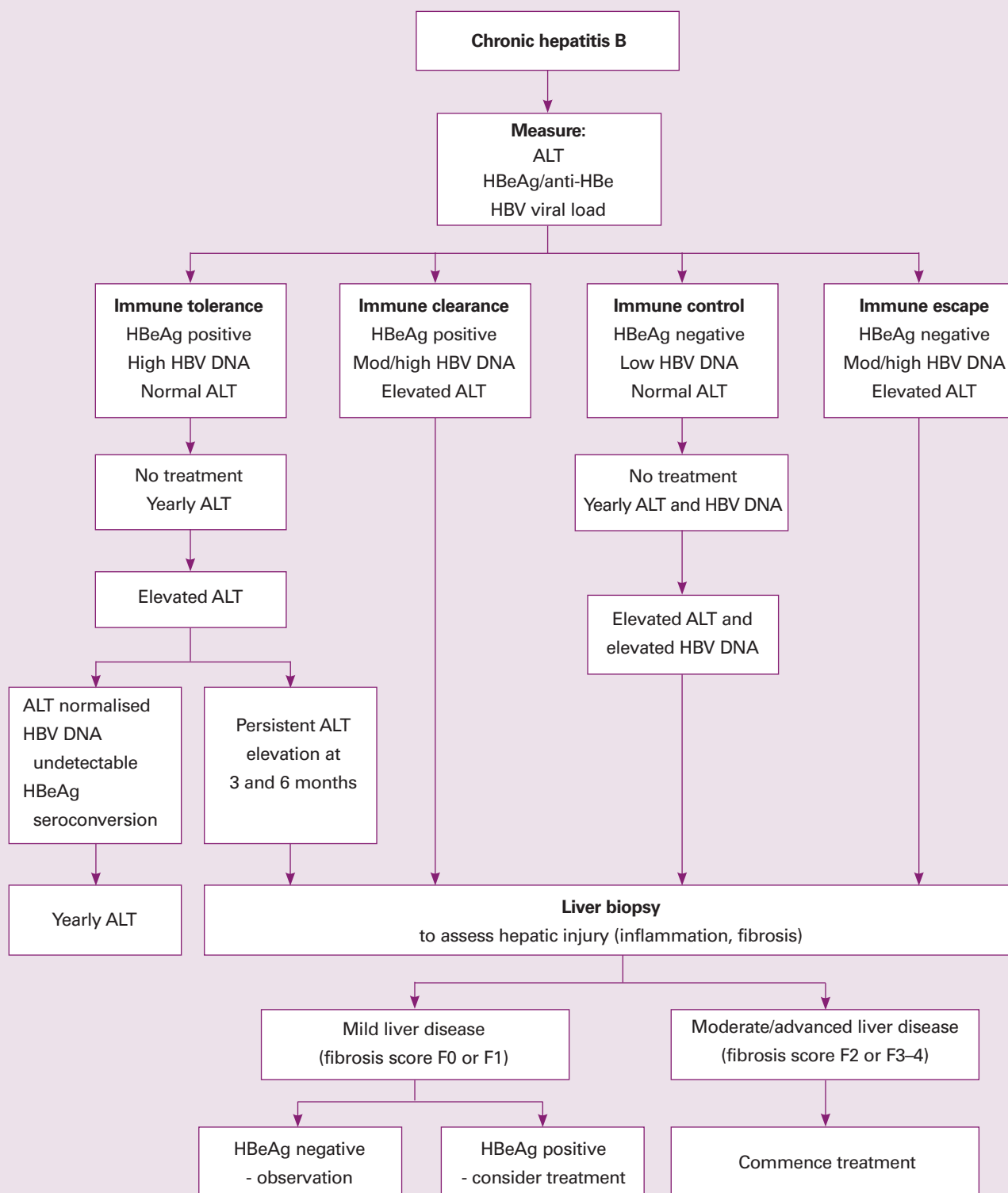
	Pegylated interferon	Nucleos(t)ide analogues
Example	Pegylated interferon alfa-2a	Entecavir – currently available Adefovir – second-line therapy Lamivudine – resistance problems Emtricitabine Telbivudine Tenofovir
Advantages	Defined treatment duration No antiviral resistance Durability of HBeAg seroconversion	Easy to administer and monitor Safe in cirrhosis and decompensated liver disease Well tolerated
Disadvantages	Subcutaneous injection Significant adverse effects Less effective than nucleos(t)ide analogues in patients with high HBV DNA and low alanine aminotransferase	Prolonged duration of therapy Risk of antiviral resistance with long-term use

HBeAg hepatitis B e antigen

HBV hepatitis B virus

Fig. 1

**General approach to treatment-naïve patients with chronic hepatitis B infection**



ALT alanine aminotransferase

HBeAg hepatitis B e antigen

HBe hepatitis B e

HBV hepatitis B virus



## Follow-up

Ongoing monitoring is recommended even in patients for whom antiviral treatment is not currently indicated. Patients in the immune tolerant phase should have yearly liver function tests and those in the immune control phase should also have yearly tests for viral DNA. All patients with an abnormal alanine aminotransferase should be referred to a specialist or hepatology clinic for consideration of therapy.

Surveillance for hepatocellular carcinoma is recommended in high-risk patient groups and consists of an abdominal ultrasound and serum alpha-fetoprotein every six months. High-risk groups include patients with cirrhosis, family history of hepatocellular carcinoma, Asians older than 35 years (if infected early in life) and Africans older than 20 years.

## Conclusion

Chronic hepatitis B is a common health problem in Australia. Treatment options include either oral nucleos(t)ide analogue drugs or pegylated interferon. Therapy reduces inflammation, can improve liver injury and reduces progression to cirrhosis and hepatocellular carcinoma. Long-term monitoring is recommended even in patients not currently on antiviral therapy. Patients at increased risk of hepatocellular carcinoma should undergo surveillance with six-monthly liver ultrasound and serum alpha-fetoprotein tests.

## References

1. Dore G, Wallace J, Locarnini S, Desmond P, Gane E, Crawford D. Hepatitis B in Australia: responding to a diverse epidemic. 2006. [http://alliance.hepatitis.org.au/uploads/ACT\\_HBV.pdf](http://alliance.hepatitis.org.au/uploads/ACT_HBV.pdf) [cited 2009 Jul 14]
2. O'Sullivan BG, Gidding HF, Law M, Kaldor JM, Gilbert GL, Dore GJ. Estimates of chronic hepatitis B virus infection in Australia, 2000. *Aust N Z J Public Health* 2004;28:212-6.
3. Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. *Hepatology* 2001;34:617-24.
4. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007;45:507-39.

*Conflict of interest: Dr Bell is on an advisory board for Bristol-Myers Squibb (makers of entecavir) and is a speaker for Gilead (makers of tenofovir) and Roche (makers of pegylated interferon).*

## Self-test questions

*The following statements are either true or false (answers on page 115)*

5. The hepatitis B virus can develop resistance to nucleos(t)ide analogues.
6. Pegylated interferon is usually the best treatment for patients with high levels of hepatitis B virus DNA.



## NPS RADAR update

The latest issue of *NPS RADAR* reviews rivaroxaban listed on the Pharmaceutical Benefits Scheme on 1 August 2009. Rivaroxaban is the first of a new class of oral anticoagulants for preventing venous thromboembolism after elective hip or knee replacement surgery. The 10 mg tablet should be taken once daily for 35 days after hip surgery and for 14 days after knee surgery. Neither monitoring of prothrombin time nor dose adjustment is required but, as with other drugs for this

indication, managing the risk of bleeding is a primary concern.

Also included in *NPS RADAR* are *In Brief* items covering:

- oxybutynin patches as an alternative for patients with overactive bladder who cannot tolerate or swallow oral oxybutynin. Dry mouth and constipation are less likely with transdermal oxybutynin than oral formulations, but application site reactions are common
- praziquantel for people with schistosomiasis.

For more information about rivaroxaban, oxybutynin patches and praziquantel, see the *NPS RADAR* website ([www.npsradar.org.au](http://www.npsradar.org.au)) or your mailed copy from 1 August.

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