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# B POSITIVE

## ALL YOU WANTED TO KNOW ABOUT HEPATITIS B
## A GUIDE FOR PRIMARY CARE PROVIDERS

SUPPORTING
THE HIV, VIRAL
HEPATITIS AND
SEXUAL HEALTH
WORKFORCE

**B POSITIVE – ALL YOU WANTED TO KNOW ABOUT HEPATITIS B:**
**A GUIDE FOR PRIMARY CARE PROVIDERS**

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# EXECUTIVE SUMMARY

Australia's second national strategy for hepatitis B (1) reiterates the key role of primary care practitioners in the diagnosis, care and management of people living with chronic hepatitis B (CHB). This document, *B positive – all you wanted to know about hepatitis B: a guide for primary care providers (second edition)*, provides a comprehensive summary of currently available knowledge and practice. Rather than being read from cover to cover, it is intended to be used as a desktop or online resource by practitioners who require information to direct management or answer questions from individuals living with CHB.

Practice profiles and the interests of primary care practitioners vary. This guide will be used in a variety of settings, including inner urban and remote rural settings, especially in clinics that serve Aboriginal and Torres Strait Islander people. The editorial team is therefore particularly grateful for input provided by a focus group of primary care practitioners with experience from a wide range of settings. We hope that this second edition of the guide covers the breadth of practice that is quality primary care.

In this revised edition of the guide the basic format of the original document (2) has been retained, but the layout has been improved to include more tables, summaries and highlighted information, to emphasise key practice points relevant to primary care practitioners. The hardcopy version includes a fold-out copy of the ASHM resource *Decision-making in HBV* (3), and sections of this useful two-page summary are referenced in the relevant chapters. The electronic version includes hyperlinks at the start of each chapter and throughout the text, which allow the reader to move easily between related topics. It also includes online and other related resources that may be helpful for providers involved in the assessment and management of hepatitis B positive patients, along with a patient fact sheet.

Updated information on the epidemiology of CHB is provided in **Chapter 1: Prevalence and epidemiology of hepatitis B**. In 2011, an estimated 218,000 Australians were living with CHB, representing 1% of the population. Most of those affected were born overseas, in the Asia and Pacific regions (particularly China and Vietnam); also disproportionally affected are Aboriginal and Torres Strait Islander people, who make up nearly 10% of people living with CHB. Liver cancer is the most rapidly increasing cause of cancer death and almost half of primary liver cancers diagnosed in Australia today arise in individuals born overseas. Understanding the epidemiology helps the primary care practitioner to target testing to individuals at greater risk of CHB in accordance with the newly released national testing policy (4), which recommends three tests for diagnostic testing: hepatitis B surface antigen (HBsAg), antibodies to core antigen (anti-HBc) and antibodies to surface antigen (anti-HBs) (**Chapter 3: Hepatitis B**

**virus testing and interpreting test results**). It also allows a focus on prevention, including vaccination of non-immune individuals at risk of infection (**Chapter 5: Primary prevention of hepatitis B virus infection**).

The understanding of the natural history of CHB is unchanged from the first edition of this guide, with four phases of infection characterised by the immune response to the virus. However, the effect of the treatment in reducing the risk of cancer by up to 75%, reversing severe fibrosis, is better understood (**Chapter 4: Natural history of chronic hepatitis B virus infection**). The primary care practitioner requires the patient's viral load, liver function tests and e antigen status to assess the disease phase and arrange appropriate monitoring and referral. In 2011, liver biopsy was removed as a requirement for initiation of antiviral therapy. Non-invasive alternatives to liver biopsy for the assessment of liver fibrosis – including transient elastography (Fibroscan®) – are now increasingly available, and offer a reliable and non-invasive means of fibrosis assessment. In areas where these tools are not available (particularly in remote areas), assessment of synthetic liver function may give an indication as to underlying cirrhosis (**Chapter 6: Clinical assessment of patients with hepatitis B virus infection**).

Emergence of resistance to older antiviral therapies (**Chapter 2: Virology, viral replication and drug resistance**) has left treating clinicians with three major therapeutic choices for treatment. Interferon-based therapy is still used in a select group of patients, but in most the mainstay is one of the oral treatments available on the Pharmaceutical Benefits Scheme (PBS), entecavir and tenofovir, which aim to suppress viral replication (**Chapter 7: Treatment of chronic hepatitis B virus infection**). These therapies are effective, well tolerated and have a barrier to resistance. Primary care practitioners may still see individuals on older combinations of drugs, especially in those who have started treatment overseas, where the cost of therapy limits drug choice.

All patients with advanced liver disease should be considered for antiviral therapy, and should receive shared care with a specialist unit, to prevent and manage complications of advanced disease and to consider whether transplantation is an option (**Chapter 8: Managing patients with advanced liver disease**).

Standardised incidence rates for primary liver cancer in people born overseas, in areas where hepatitis B virus (HBV) is highly endemic (China and Vietnam, Africa, the Mediterranean region, and the Asia and Pacific regions), are between two and 12 times greater than in the Australian-born population (**Chapter 9: Hepatitis B virus related hepatocellular carcinoma**). Liver cancer surveillance (6-monthly ultrasound and alpha-fetoprotein [AFP]) improves survival and is recommended in certain groups, based on evidence of cirrhosis, family history, age and country of birth. Aboriginal and Torres Strait Islander people living with CHB are recommended to start surveillance for liver cancer after the age of 50 years.

All pregnant women should be screened for CHB, and primary care practitioners are advised to order three tests (HBsAg, anti-HBc and anti-HBs) for women at risk of infection, rather than testing for HBsAg alone. All pregnant women with CHB need to have a viral load test during pregnancy; women with a viral load greater than 10,000,000 IU/mL should be considered for antiviral therapy during the third trimester, to further reduce the chance of transmission. All infants born to women with CHB should receive immunoglobulin within 12 hours, concurrently with birth dose hepatitis B vaccination (**Chapter 10: Managing hepatitis B virus in pregnancy and children**).

Transmission continues to occur in priority populations, including men who have sex with men and people living with human immunodeficiency virus (HIV) infection. Co-infection with hepatitis C virus, hepatitis D virus (HDV) and HIV needs special consideration and specialist management, because outcomes may be worse and management more complex in these patients. All patients undergoing significant immunosuppression, including chemotherapy (especially with biological agents), should be screened for infection and started on antiviral therapy if found to have CHB (**Chapter 11: Complex situations: Co-infection and immunosuppression**).

Universal precautions are the mainstay of infection control and should be understood and adhered to by all health practitioners. Vaccination of all health care professionals is recommended. People living with CHB are able to work in the health profession, but must not perform exposure prone procedures (**Chapter 12: Infection control and occupational health** and **Chapter 13: Privacy, confidentiality and other legal responsibilities**).

Irrespective of the stage of disease, many people living with HBV choose to use alternative or complementary medicines at some time during their infection. While there is no current evidence of benefit from complementary medicines in changing disease outcomes, there is evidence of harm with use of certain compounds. Thus, patients need sound advice to make good health choices (**Chapter 14: The role of complementary medicine in hepatitis B**).

The challenge presented by the need for what is often lifelong management of CHB cannot be overstated. Many people do not have a single health provider, so the key to effective care is not the enthusiasm of a single provider or clinic, but a health system that coordinates care and provides the best possible information for individuals to make informed choices. Community engagement and involvement in decision-making is vital to increasing the numbers diagnosed, and to appropriate management. Individuals living with hepatitis B need to receive clear and culturally appropriate information from primary care practitioners about their CHB.

Many uncertainties still exist, such as which patients will benefit from therapeutic intervention, the optimal time to initiate therapy, and the extent of virological suppression required to reduce disease progression. Our knowledge and understanding of this complex disease have been improved

by the greater number of effective agents and the availability of increasingly sensitive tests that monitor the natural history and the therapeutic response. Nevertheless, the appropriate identification, management and referral of people with HBV infection within the primary care setting is key to preventing a greater burden of CHB in Australia in the future.

As this edition goes to print, general practitioners can prescribe maintenance antiviral therapy under the Highly Specialised Drugs programme (under the direction of a treating specialist affiliated with a hospital; or, as part of s100 community prescriber programs in a number of jurisdictions). This is an area that may change in the future. Not all primary care practitioners will be confident in prescribing antiviral therapy; however, as with other models of chronic disease delivery, increased expertise (including prescribing) will be essential for decreasing the incidence of adverse outcomes, including liver cancer.

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## References

1. Australian Government Department of Health. National Hepatitis B Strategy 2014-2017. Canberra: Commonwealth of Australia, 2014.
2. Australasian Society for HIV Medicine (ASHM). B positive – all you wanted to know about hepatitis B: a guide for primary care providers (first edition). Darlinghurst NSW: ASHM, 2008.
3. Australasian Society for HIV Medicine (ASHM). Decision-making in HBV. Darlinghurst NSW: ASHM, 2013.
4. National HBV Testing Policy Expert Reference Committee. National hepatitis B testing policy. Darlinghurst NSW: Australasian Society for HIV Medicine (ASHM), 2012.

# CHAPTER 1 PREVALENCE AND EPIDEMIOLOGY OF HEPATITIS B


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**LINKS**

**Chapter 4:** Natural history of hepatitis B virus infection

**Chapter 5:** Primary prevention of hepatitis B virus infection

**Chapter 9:** Hepatitis B virus-related hepatocellular carcinoma


## KEY POINTS

- In 2011, there were an estimated 218,000 people living with chronic hepatitis B (CHB) infection in Australia, representing 1% of the population.
- Only 56% of people living with CHB in Australia are believed to have been diagnosed.
- Those born overseas and Aboriginal and Torres Strait Islander people comprise around two thirds of all Australians living with CHB.
- A higher prevalence of CHB infection is also observed in people who inject drugs and in men who have sex with men.
- Over 90% of new cases of CHB in Australia are attributable to migration and cannot be prevented through local vaccination initiatives.
- Deaths due to CHB result from complications of cirrhosis, liver failure and liver cancer (specifically, hepatocellular carcinoma) in up to one quarter of people living with CHB.

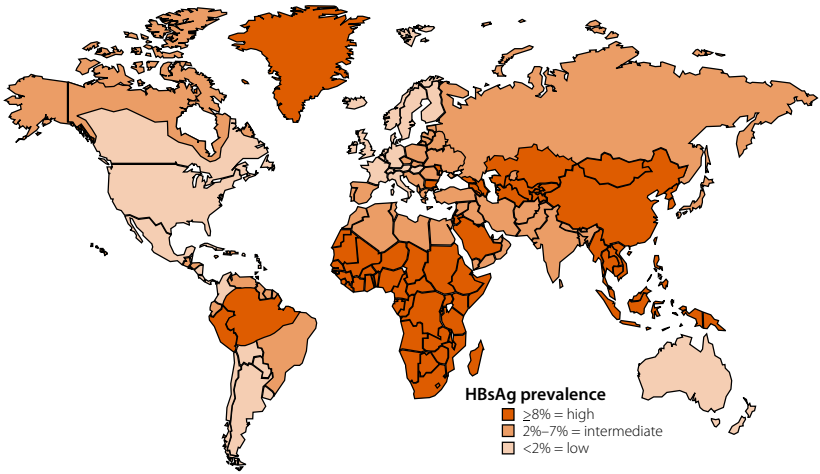
## Hepatitis B virus background and global epidemiology

The global burden of hepatitis B virus (HBV) infection is profound. Between 240 and 350 million people are estimated to be living with chronic hepatitis B (CHB) and over 2 billion have been infected (1, 2). CHB causes liver-related death in up to one quarter of people affected (1), making hepatitis B the second most important known human carcinogen after tobacco (3). HBV is the leading cause of liver cancer worldwide, with 70–85% of these liver cancers being hepatocellular carcinoma (HCC) (4). The Global Burden of Disease Study estimated that HBV infection was responsible for 786,000 deaths in 2010 (5).

Although the prevalence of CHB varies significantly by country, most people in the world live in an area endemic for hepatitis B (considered as >2% prevalence), and about 45% live in an area of high (>8%) prevalence (see Figure 1.1). HBV is transmitted through blood or infected bodily fluids; for example, by mother-to-child transmission, sexual contact or percutaneous exposures (1). HBV infection is not transmitted through sharing food or casual contact.

The epidemiology of CHB is predominantly determined by the age at exposure, with about 90% of infected infants progressing to chronic infection, compared with only 5% of immunocompetent adults (1) (see **Chapter 4**). This is why most people currently living with CHB in Australia acquired infection early in life (as is the case globally), and why universal infant vaccination is crucial for HBV control across

**Figure 1.1** Geographical distribution of hepatitis B virus (3)




* For multiple countries, estimates of prevalence of hepatitis B surface antigen (HBsAg), a marker of chronic HBV infection, are based on limited data and might not reflect current prevalence in countries that have implemented childhood hepatitis B vaccination. In addition, HBsAg prevalence might vary within countries by subpopulation and locality.

Adapted from: World Health Organisation, Introduction of hepatitis B vaccination into child immunization services. WHO. 2001. Available from: http://whqlibdoc.who.int/hq/2001/WHO_V&B_01.31.pdf. Accessed on: 01/07/2014.

populations. Although most countries have now implemented universal infant vaccination, the long delay between initial infection and the onset of complications, and the large number of existing chronic infections, means that the burden of disease attributable to CHB will remain high for several decades. Early diagnosis and appropriate management for those affected are essential for addressing the increasing morbidity and mortality associated with CHB.

## Epidemiology and burden of chronic hepatitis B in Australia

In 2011, an estimated 218,000 Australians (about 1% of the population) were living with CHB (6). The priority populations affected by CHB in Australia include those born overseas in endemic areas (particularly the Asia and Pacific regions) (Figure 1.2), Aboriginal and Torres Strait Islander people, people who inject drugs, and men who have sex with men (MSM); these groups make up over three quarters of those affected (Figure 1.3). Other Australian-born people at higher risk for CHB include those whose parents were born overseas in an endemic area, and those exposed to hepatitis B through sexual contact or medical transmission before routine blood donor screening.

The prevalence of CHB in Australia has increased over the past decade, predominantly related to the increases in migration from endemic areas such as the Asia and Pacific regions (7, 8) and sub-Saharan Africa. Other areas with an increased prevalence of CHB include parts of Southern and Eastern Europe, and the Middle East (see Figure 1.1).

**Figure 1.2** Top countries of birth for chronic hepatitis B in Australia (6)

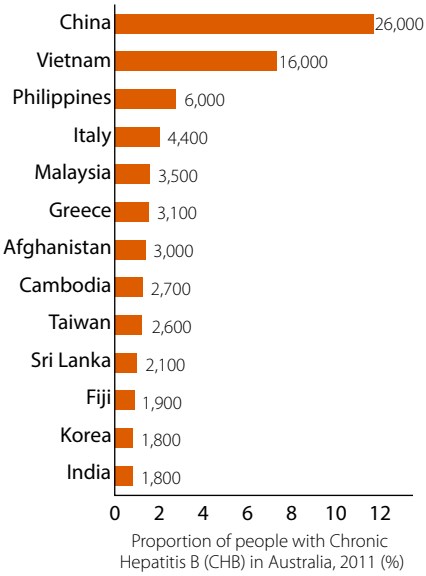
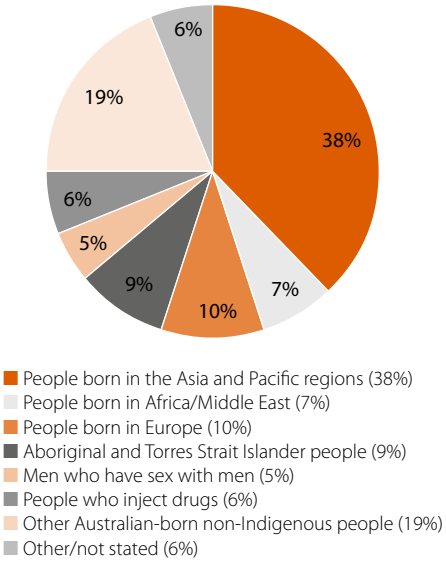



**Figure 1.3** Distribution of Australia's burden of chronic hepatitis B by priority population (6)



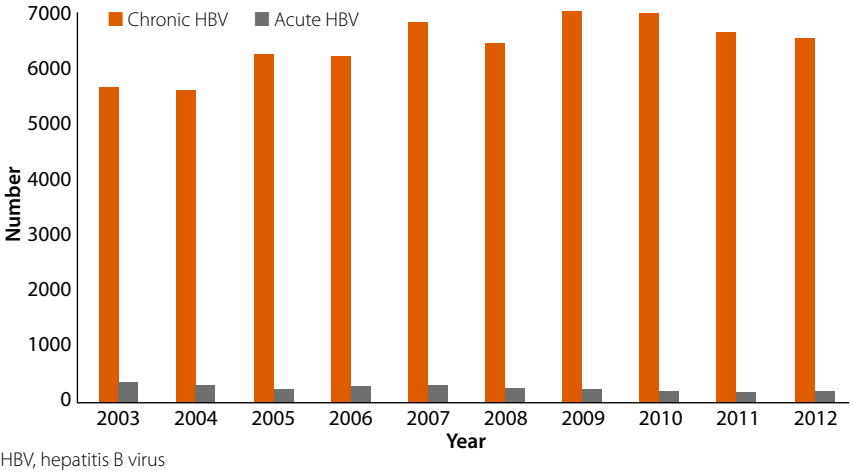
Australia implemented universal infant vaccination for hepatitis B in 2000 (9), as well as adolescent catch-up programs, which have been effective in reducing the number of people acquiring hepatitis B in adulthood (10) and will help prevent transmission to children born in Australia to mothers with CHB. However, given the large number of people already living with CHB and that most new CHB infections are entering the population through migration (6), vaccination programs are unlikely to have a substantial effect on morbidity and mortality associated with hepatitis B; instead, diagnosis and clinical management are the key components of an effective response (11).

Diagnosis of CHB requires notification to the relevant public health authority in all Australian states and territories. The rate of CHB diagnosis has remained relatively stable over the past decade, with about 7,000 new diagnoses annually (Figure 1.4); however, it is estimated that only about half of those living with CHB in Australia have been diagnosed (6). Newly acquired (acute) HBV infections represent about 5% of all notifications of hepatitis B. Notifications of newly acquired HBV infection fell over the course of the past decade, partly because of the impact of the universal infant and adolescent vaccination programs mentioned above.

This increasing prevalence and the large number of people living with undiagnosed infection is contributing to a rising burden of advanced liver disease, including HCC (6, 12-14). Liver cancer is now the ninth most common cause of cancer mortality in Australia, and mortality is increasing faster than for any other cause of cancer death (15, 16).

Most of the liver cancer in Australia is thought to be attributable to chronic viral hepatitis (B and C) (17), and the burden is greatest in Aboriginal and Torres Strait Islander people (18), and those born overseas (7, 19).

**Figure 1.4** Notifications of hepatitis B to Australia's National Notifiable Diseases Surveillance System, 2003–12




HBV, hepatitis B virus

## Chronic hepatitis B prevalence in specific populations

### Culturally and linguistically diverse communities

In the 2011 Census, about six million Australians (27%) were born overseas (20), with around 40% of these migrating from regions with a population CHB prevalence of 2% or more (20, 21). The prevalence of CHB in migrants generally reflects that of their country of origin (22, 23) and in Australia, particularly in urban areas, the prevalence of CHB by geographic area reflects the proportion of residents who were born overseas (8, 24).

When considering Australians born overseas living with CHB, the largest group consists of those born in the Asia and Pacific regions (38% of all Australians living with CHB). People born in Africa and the Middle East (7% of the total) and Europe (10% of the total) also make up a substantial proportion of people with CHB in Australia (6). This is reflected in the finding that Australians born overseas in HBV endemic areas have a much higher incidence of liver cancer than non-Indigenous Australian-born individuals, with those born in countries such as Cambodia, China, Korea and Vietnam up to 10 times more likely to be diagnosed with liver cancer than other Australians (7, 19).

### Aboriginal and Torres Strait Islander Australians

According to the 2011 Census, there were 517,000 Aboriginal and Torres Strait Islander Australians, representing 2.6% of the population (20). However, Aboriginal and Torres Strait Islander people are estimated to account for 10% of Australians living with CHB infection (6).

The prevalence of CHB in Aboriginal and Torres Strait Islander people has decreased over the past two decades, from an estimated 16% to 4%, but it remains four times higher than in non-Indigenous people (25). One explanation for this reduction in prevalence is the implementation of universal infant and adolescent vaccination programs. Despite these successes, there is evidence of gaps in the immunity of Aboriginal and Torres Strait Islander people. Several studies have demonstrated significant numbers of Aboriginal and Torres Strait Islander people lack markers of immunity to HBV infection (26, 27), and only 85.5% of children have been fully vaccinated (receiving three doses by 12 months of age), as compared to 92.1% of non-Indigenous children (28). Importantly, there is also evidence of vaccination failure even in children who were documented to have received a full course of vaccine (29). Further studies of the reasons for failure of vaccination policy in Aboriginal and Torres Strait Islander people are required (see **Chapter 5**).

The incidence of HCC has been demonstrated to be two to eight times higher in Aboriginal and Torres Strait Islander people compared with non-Indigenous Australians, in a number of areas of Australia (18). People living in remote areas of Australia often have limited access to primary health care and specialist services. A higher proportion of Aboriginal and Torres Strait Islander people compared with non-Indigenous Australians live in remote areas (25% compared to 2%) (30), with people living in remote areas often needing to travel great distances to access health services.

This was highlighted in a study conducted in the Torres Strait Islands, which outlined a range of barriers for community members in accessing HBV testing, vaccination and ongoing management, together with numerous issues for clinical staff around workforce development, training and mentorship (31).

## People who inject drugs

A recent systematic review suggested that 4% of Australians who currently or recently injected drugs are living with CHB (32). Given that about 1.5% of the Australian population has injected drugs at some time (33), a conservative estimate of the number of people with a history of injecting drug use living with CHB is about 12,500, or 6% of all Australians living with CHB. Australian seroprevalence studies in people who inject drugs have shown that only about one quarter of participants had serological markers of immunity to HBV infection (34, 35), with a longer history of injecting and exposure to hepatitis C being independently associated with HBV infection.

## Men who have sex with men

The prevalence of CHB among MSM is around three times higher than the population prevalence in Australia, and MSM are estimated to comprise around 4% of all people living with CHB (6). Although the prevalence has declined among the MSM population since the 1980s, recent studies still indicate an increased risk in this community; for example, a sexual health clinic in Melbourne found a prevalence of 3% (36). Levels of immunity through both prior infection and immunisation have been demonstrated to be high, with studies involving men in Melbourne and Sydney showing that more than half had serological evidence of immunisation (37). Factors associated with increased risk of HBV infection among MSM include increased age, a higher number of sexual partners, and a history of sexually transmissible infections (36, 37).

**Table 1.1** People recommended for routine CHB screening in accordance with the National Hepatitis B Testing Policy (see testingportal.ashm.org.au/hbv)

| |
|---|
| People born overseas in areas with 2% HBV prevalence or greater (see Figure 1.1) |
| Aboriginal and Torres Strait Islander people |
| People who inject drugs |
| Men who have sex with men |
| People living with HIV and/or hepatitis C |
| Sex workers |
| People with haemophilia/history of blood transfusion in the pre-screening era |
| People with multiple sexual partners |
| Household and sexual contacts of people with CHB |
| People who are undergoing dialysis |
| People who have ever been in custodial settings |

## Other priority populations

A number of other population groups are identified as being at increased risk of HBV infection, including commercial sex workers (38), people in correctional facilities (39), people with haemophilia or a history of transfusion conducted before the implementation of screening in the late 1970s, and people born in Australia to mothers from endemic areas prior to commencement of universal infant vaccination in 2000. People living

with human immunodeficiency virus (HIV) or hepatitis C, or both, are at increased risk HBV infection, and of experiencing severe acute infection and (for HIV) progression to chronic infection. A comprehensive list of populations recommended for routine testing in Australia is given in Table 1.1.

## Putting epidemiology into practice: health-care service delivery to the populations affected by chronic hepatitis B

Understanding the epidemiology of CHB is crucial to identifying those at risk and guiding screening activities, but also for delivering appropriate and effective care to those groups disproportionately burdened.

Many people who belong to communities at greater risk for CHB have low awareness about hepatitis B, even when engaged with health-care services (40, 41). This situation highlights the need for improved targeting and engagement of high-risk groups by clinicians.

Those Australians born overseas, and Aboriginal and Torres Strait Islander people, often have lower rates of participation in preventive care services such as cancer screening (18, 42). This has significant implications for the clinical management of people from these populations living with CHB, with ultrasound-based screening for liver cancer a key part of management for those at risk (see **Chapter 9**).

In addition to general practices and other primary health-care services in Australia, there are over 150 Aboriginal Community Controlled Health Services (ACCHS), which provide culturally appropriate medical and allied health care to Aboriginal people.

Studies indicate that ACCHS are preferred primary health-care providers by Aboriginal and Torres Strait Islander people (43) and – with appropriate resourcing, training and support – have the potential to improve HBV testing uptake and vaccination coverage, plus provide ongoing monitoring and treatment for Aboriginal and Torres Strait Islander people living with CHB.

## Conclusion

In Australia, CHB disproportionately affects those from culturally and linguistically diverse backgrounds, with more than two thirds of those living with infection born overseas or being Aboriginal and Torres Strait Islander people. Most people currently living with CHB acquired it at birth or in early childhood. Despite CHB affecting more than 220,000 Australians, only just over half have been diagnosed, highlighting the importance of routine CHB screening in these groups. Given growing migration from endemic areas of the world such as Africa, the Asia and Pacific regions and the Middle East, targeted testing must intensify to increase detection rates and avert further increases in adverse outcomes of CHB, such as liver cancer, which has become the fastest growing cause of cancer death in Australia.

Knowledge of the Australian communities most affected by CHB is essential when planning and implementing clinical and public health responses aimed at addressing the increasing burden of disease, low levels of disease awareness and diagnosis, and low treatment uptake. Such an epidemiological understanding will help to ensure that any interventions are effective, understood and appropriate for the communities most affected.

## References


1. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat. 2004;11(2):97–107.
2. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B infection: New estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30:2212–9.
3. Previsani N, Lavanchy D. Hepatitis B. Geneva: Department of Communicable Diseases Surveillance and Response, World Health Organization, 2002.
4. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.
5. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.
6. MacLachlan JH, Allard N, Towell V, Cowie BC. The burden of chronic hepatitis B virus infection in Australia, 2011. Aust NZ J Public Health. 2013;37(5):416–22.
7. Supramaniam R, O'Connell D, Robotin M, Tracey E, Sitas F. Future cancer trends to be influenced by past and future migration. Aust N Z J Public Health. 2008;32(1):90–2.
8. MacLachlan JH, Cowie BC. Hepatitis B Mapping Project: Estimates of CHB prevalence and cultural and linguistic diversity by Medicare Local – National Report 2011. Darlinghurst: Australasian Society for HIV Medicine and Victorian Infectious Diseases Reference Laboratory, 2013.
9. The Australian immunisation handbook. 10th ed: ATAGI, NHMRC, Department of Health and Ageing, Australian Government; 2013.
10. HIV, viral hepatitis and sexually transmissible infections in Australia: Annual Surveillance Report 2013. Sydney: The Kirby Institute, The University of New South Wales, 2013.
11. Robotin MC, Kansil M, Howard K, George J, Tipper S, Dore GJ, et al. Antiviral therapy for hepatitis B-related liver cancer prevention is more cost-effective than cancer screening. J Hepatol. 2009;50(5):990–8.
12. Wong N, Haydon A, Kemp W, Wijeratne P, Roberts S. Improved survival trend of patients with hepatocellular carcinoma at an Australian tertiary hospital between 1995-2009. Internal Medicine Journal. 2013;43(2):197–203.
13. Cancer incidence projections: Australia, 2011 to 2020. Canberra: Australian Institute of Health and Welfare, 2012 Contract No.: Cat. no. CAN 62.
14. Nguyen VT, Amin J, Law MG, Dore GJ. Predictors and survival in hepatitis B-related hepatocellular carcinoma in New South Wales, Australia. J Gastroenterol Hepatol. 2009;24(3):436–42.
15. Cancer in Australia: in brief 2012. Canberra: Australian Institute of Health and Welfare, 2012.
16. MacLachlan JH, Cowie BC. Liver cancer is the fastest increasing cause of cancer death in Australians. Med J Aust. [Letter]. 2012;197(9):492–3.
17. Carville KS, Cowie BC. Recognising the role of infection: preventing liver cancer in special populations. Cancer Forum. 2012;36(1):21–4.
18. Cunningham J, Rumbold AR, Zhang X, Condon JR. Incidence, aetiology, and outcomes of cancer in Indigenous peoples in Australia. Lancet Oncol. 2008;9:585–95.
19. Amin J, O'Connell D, Bartlett M, Tracey E, Kaldor J, Law M, et al. Liver cancer and hepatitis B and C in New South Wales, 1990–2002: a linkage study. Aust N Z J Public Health. 2007;31(5):475–82.
20. 2011 Census of Population and Housing. Canberra: Australian Bureau of Statistics, Commonwealth of Australia, 2012.
21. Cowie BC. The linguistic demography of Australians living with chronic hepatitis B. Aust N Z J Public Health. 2011;35(1):12–5.
22. Kowdley KV, Wang CC, Welch S, Roberts H, Brosgart CL. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. Hepatology. 2012;56(2):422–33.
23. Turnour CE, Cretikos MA, Conaty SJ. Prevalence of chronic hepatitis B in South Western Sydney: evaluation of the country of birth method using maternal seroprevalence data. Aust N Z J Public Health. 2011;35(1):22–6.
24. Cowie B, Karapanagiotidis T, Enriquez A, Kelly H. Markers of hepatitis B virus infection and immunity in Victoria, Australia, 1995 to 2005. Aust N Z J Public Health. 2010;34(1):72–8.

25. Graham S, Guy RJ, Cowie B, Wand HC, Donovan B, Akre SP, et al. Chronic hepatitis B prevalence among Aboriginal and Torres Strait Islander Australians since universal vaccination: a systematic review and meta-analysis. BMC Infect Dis. 2013;13(1):403.

26. Harrod ME, Ward J, Couzos S, Dore G, Saunders M, Delaney-Thiele D, et al. Hepatitis B testing and positivity in four Aboriginal Community Controlled Health Services: data from the REACCH Collaboration. 8th Australasian Viral Hepatitis Conference; Auckland, New Zealand2012.

27. Carroll E, Page W, Davis JS. Screening for hepatitis B in East Arnhem Land: a high prevalence of chronic infection despite incomplete screening. Internal Medicine Journal. 2010;40(11):784–7.

28. Hull B, Dey A, Menzies R, McIntyre P. Annual immunisation coverage report, 2010. Commun Dis Intell Q Rep. 2013;37(1):E21–39.

29. Dent E, Selvey C, Bell A, Davis J, McDonald M. Incomplete protection against hepatitis B among remote Aboriginal adolescents despite full vaccination in infancy. Commun Dis Intell. 2010;34(4):435–9.

30. The health and welfare of Australia's Aboriginal and Torres Strait Islander peoples. Canberra: Australian Bureau of Statistics and the Australian Institute of Health and Welfare, 2008 Contract No.: ABS Cat. No. 4704.0; AIHW Cat. No. IHW 21.

31. Wallace J, Pitts M, McNally S, Ward J, Nakata Y, Fagan P. A Situational Analysis of Chronic Hepatitis B in the Torres Strait. Melbourne: La Trobe University, 2011 Contract No.: Monograph Number 82.

32. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011;378(9791):571–83.

33. 2010 National Drug Strategy Household Survey: Detailed Findings. Canberra: Australian Institute of Health and Welfare, 2011.

34. Miller ER, Hellard ME, Bowden S, Bharadwaj M, Aitken CK. Markers and risk factors for HCV, HBV and HIV in a network of injecting drug users in Melbourne, Australia. J Infect. 2009;58(5):375–82.

35. Day CA, White B, Dore GJ, van Beek I, Rodgers C, Cunningham P, et al. Hepatitis B virus among injecting drug users in Sydney, Australia: prevalence, vaccination and knowledge of status. Drug Alcohol Depend. 2010;108(1-2):134–7.

36. Gamagedara N, Weerakoon AP, Zou H, Fehler G, Chen MY, Read TR, et al. Cross-sectional study of hepatitis B immunity in MSM between 2002 and 2012. Sex Transm Infect. 2013.

37. Jin F, Prestage GP, Pell CM, Donovan B, Van de Ven PG, Kippax SC, et al. Hepatitis A and B infection and vaccination in a cohort of homosexual men in Sydney. Sex Health. 2004;1(4):227–37.

38. Seib C, Debattista J, Fischer J, Dunne M, Najman JM. Sexually transmissible infections among sex workers and their clients: variation in prevalence between sectors of the industry. Sex Health. 2009;6(1):45–50.

39. Butler T, Belcher JM, Champion U, Kenny D, Allerton M, Fasher M. The physical health status of young Australian offenders. Aust N Z J Public Health. 2008;32(1):73–80.

40. Caruana SR, Kelly HA, De Silva SL, Chea L, Nuon S, Saykao P, et al. Knowledge about hepatitis and previous exposure to hepatitis viruses in immigrants and refugees from the Mekong Region. Aust N Z J Public Health. 2005;29(1):64–8.

41. Wallace J, McNally S, Richmond J, Hajarizadeh B, Pitts M. Managing chronic hepatitis B: A qualitative study exploring the perspectives of people living with chronic hepatitis B in Australia. BMC Res Notes. 2011;4:45.

42. Anikeeva O, Bi P, Hiller JE, Ryan P, Roder D, Han G-S. The health status of migrants in Australia: a review. Asia-Pacific Journal of Public Health / Asia-Pacific Academic Consortium for Public Health. 2010;22(2):159–93.

43. Ward J, Bryant J, Worth H, Hull P, Solar S, Bailey S. Use of health services for sexually transmitted and blood-borne viral infections by young Aboriginal people in New South Wales. Aust J Prim Health. 2013;19(1):81–6.

# CHAPTER 2: VIROLOGY: VIRAL REPLICATION AND DRUG RESISTANCE

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**LINKS** **Chapter 7:** Treatment of chronic hepatitis B virus infection

## KEY POINTS

- The ability of hepatitis B virus (HBV) to cause persistent infection is due to the establishment of a covalently closed circular DNA (ccc DNA), which forms a stable minichromosome in the hepatocyte nucleus.
- In chronic hepatitis B, the ccc DNA is largely refractory to elimination by the immune response or by nucleos(t)ide analogue (NA) therapy. Upon immunosuppression or cessation of therapy, the ccc DNA can reinitiate virus replication, leading to reactivation of disease.
- HBV has an unusual replication strategy; it employs an error-prone reverse transcription step that allows mutations to be created.
- Under selection pressures (e.g. from vaccines or from NA therapy), escape mutants or variants conferring resistance can be readily selected.

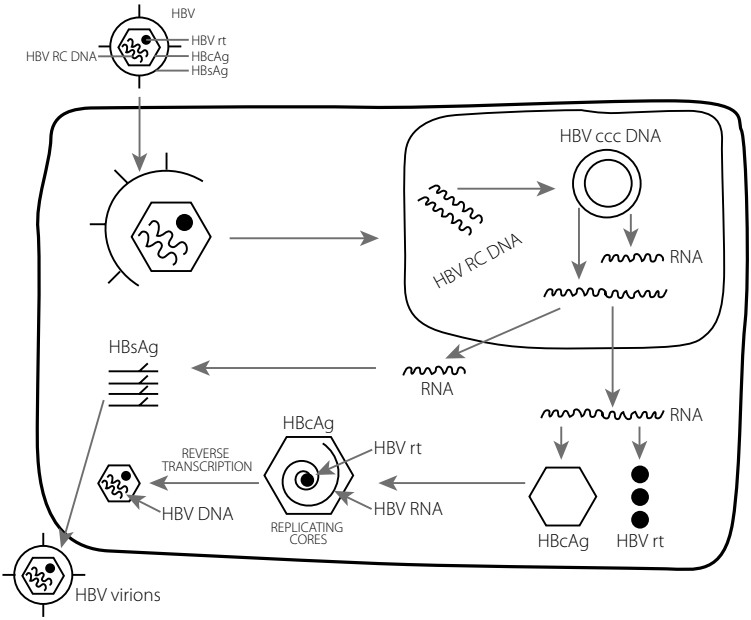
## Introduction and pathogenesis

Under normal circumstances, hepatitis B virus (HBV) infection is not cytopathic to liver cells. The liver damage associated with acute hepatitis B or with chronic hepatitis B (CHB) occurs mainly as a result of attempts by the host's immune response to clear HBV from infected hepatocytes (1).

HBV is a member of the family *Hepadnaviridae*. Novel features of hepadnavirus replication are a reverse transcription step and production of excess viral coat or envelope material – the hepatitis B surface antigen (HBsAg) that circulates in the blood, in titres that often exceed $10^{12}$ particles/mL.

The viral reverse transcriptase (rt) lacks a proofreading capacity; hence, it produces a population of closely related variants, known as a 'quasispecies'. This diversity ensures the survival of HBV because, when the virus is under pressure from the immune response or the introduction of an antiviral agent, a resistant viral sub-population will already be present in the infected person's pool of newly replicating virus. Therefore, whenever a new selection pressure is introduced, a number of immune or antiviral drug 'escape' (i.e. resistant) mutants of HBV can evolve to become the dominant population.

**Figure 2.1** Life cycle of the hepatitis B virus from entering the cell (at the top) to exiting the cell (shown at the bottom)

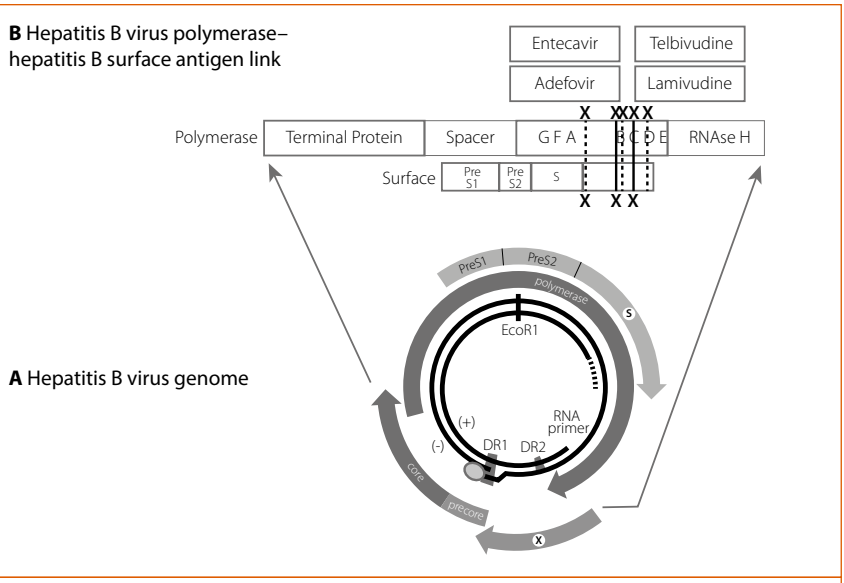



ccc, covalently closed circular DNA; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; RC, relaxed circular; rt, reverse transcriptase

## Hepatitis B virus replication: the virus and its life cycle

HBV is a DNA virus. The viral DNA genome is found inside the viral core structure (or hepatitis B core antigen [HBcAg]) along with the viral rt (a DNA polymerase). The core structure is surrounded by the viral envelope: HBsAg. The life cycle of HBV, shown in Figure 2.1, begins when its envelope protein attaches to the sodium taurocholate cotransporting polypeptide – the newly discovered receptor on the surface of the hepatocyte (2) – allowing the virus to enter the cell. Once inside the cell, the viral genomic DNA penetrates the nucleus and is converted into a covalently closed circular (ccc) DNA form. The HBV ccc DNA, the major transcriptional template of the virus, associates with cellular histone proteins and establishes itself as viral minichromosomes. After transcription from the ccc DNA, viral RNA is transported to the cytoplasm of the hepatocyte, where the viral structural proteins (HBcAg and HBsAg) and the replication enzyme are synthesised. The HBV rt then reverse transcribes the HBV pregenomic (pg)RNA into DNA, inside the core particle. The viral envelope proteins now coat the replicating core complexes, creating mature virions that are released from the cell to complete the life cycle. The only HBV enzyme identified to date is the viral rt, and this is the target for nucleos(t)ide analogue (NA) antiviral therapy.

**Figure 2.2** The hepatitis B virus genome and the virus polymerase-surface antigen link




A: Shows the circular arrangement of the four overlapping but frame-shifted open reading frames (ORFs)
B: Shows how the changes observed in the HBV Pol due to emergence of drug resistance affect the hepatitis B surface antigen (HBsAg) directly for all four nucleos(t)ide analogues approved for chronic hepatitis B treatment

The HBV genome encodes only four genes, but has evolved a remarkable replication strategy. It maximises its information content by using overlapping reading frames (ORFs), the longest of which (Pol ORF) encodes the viral rt/DNA polymerase. (This is shown in Figure 2.2[A]).

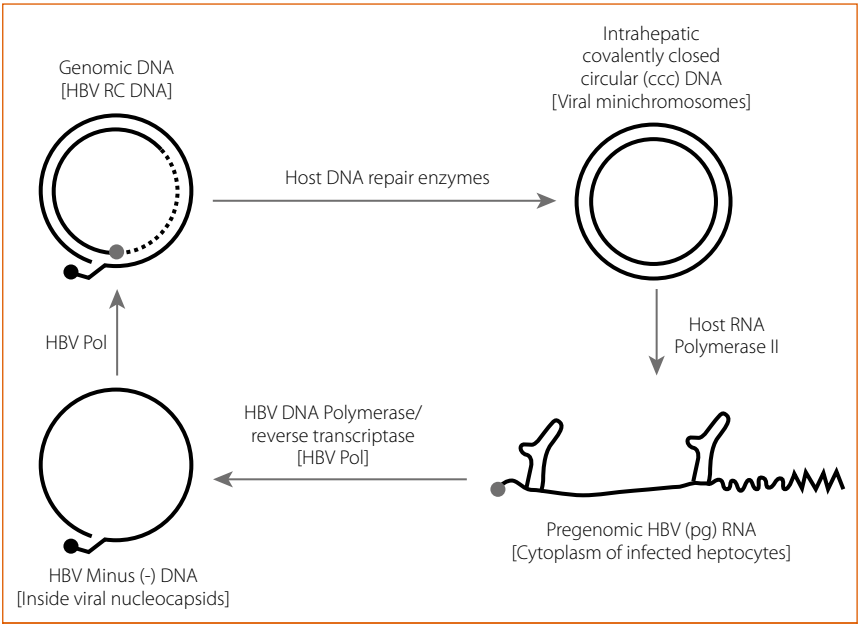
The envelope ORF is located within the Pol ORF, whereas the core (C) and the X ORFs overlap it. (This is shown in Figure 2.2[B]).

The life cycle of HBV involves two key processes, as shown in Figure 2.3:

- generation of HBV ccc DNA from genomic DNA to form a minichromosome, and subsequent processing of the minichromosome by host enzymes to produce viral RNA
- reverse transcription of the pregenomic (pg)RNA within the viral nucleocapsid to form HBV relaxed circular (RC) or genomic DNA, thereby completing the cycle (see Figure 2.1).

As discussed, HBV uses reverse transcription to copy its genome (i.e. from RNA to DNA). This viral enzyme lacks a proofreading or editing function; hence, many 'transcriptional mistakes' are introduced into the numerous newly replicated HBV DNA progeny molecules, resulting in substantial diversity in the viral genome.

**Figure 2.3** Major processes involved in hepatitis B virus (HBV) genome replication




Conversion of relaxed circular (RC) DNA into covalently closed circular (ccc) DNA; transcription of ccc DNA to produce pregenomic (pg)RNA; reverse transcription of pgRNA to make minus (–) HBV DNA; and HBV DNA polymerase activity to make the RC DNA, completing the cycle. The ccc DNA can only be found in the liver within the nucleus of infected hepatocytes and in the form of a viral minichromosome (3, 4)

This provides the virus with a strong survival advantage because, on a daily basis, every single nucleotide in the viral genome of 3,200 base pairs can be changed. Random mutations from copying errors can lead to phenotypic changes, which in turn may confer a selective advantage. Thus, single and double mutations associated with antiviral drug resistance are present before antiviral therapy is introduced. However, if three or four mutations in the HBV DNA were to be required to confer resistance to NA therapy, these would be unlikely to be found before therapy. This concept is the basis for the use of combination chemotherapy for chronic viral diseases such as human immunodeficiency virus (HIV) (e.g. combination anti-retroviral therapy – cART).

## Common mutants of HBV

### Mutations affecting hepatitis B e antigen

In addition to coding for HBcAg and HBsAg, the HBV genome encodes for hepatitis B e antigen (HBeAg). The HBeAg protein is thought to act as a tolerogen (5), and its production helps the virus avoid elimination by the host immunological response, especially during pregnancy or acute infection. Without HBeAg, it is unlikely that HBV could establish a chronic infection.

When put under the immunological pressure of HBeAg seroconversion, which is part of the natural history of CHB, the virus has a number of ways of 'escaping'. Two major groups of mutations have been identified that result in reduced or truncated HBeAg expression. The first group of mutations affect the basal core promoter (BCP), typically at nucleotide (nt)1762 and nt1764, resulting in a reduction in transcription of the precore mRNA (6). Mutations in the BCP, such as the change of an A to a T at nt1762 (designated A1762T), and of a G to an A at nt1764 (G1764A), may be found in isolation or in conjunction with precore mutations (discussed below). The double mutation of A1762T plus G1764A results in a significant decrease in HBeAg levels, but not its absolute absence, and this mutation has been associated with an increased viral load in patients. Importantly, these BCP mutations do not affect the transcription of HBV pgRNA or the translation of the core or polymerase protein. Instead, by removing the inhibitory effect of the precore protein on HBV replication, the BCP mutations appear to enhance viral replication by suppressing precore or core mRNA relative to pgRNA (6).

The second group of mutations introduce a translational stop codon mutation at nt1896 (codon 28: TGG; tryptophan) of the HBV precore gene (7). The single base substitution (G to A) at nt1896 (G1986A) gives rise to a translational stop codon (TGG to TAG; TAG = stop codon) in the second last codon (codon 28) of the precore gene that is located within the epsilon (ε) structure of pgRNA. The ntG1896A forms a base pair with ntT1858 at the base of the stem loop (7). Patients infected with precore mutant (G1896A) HBV are typically HBeAg negative. Other mutations in the precore gene can block HBeAg production; these include a mutation that abolishes the methionine initiation codon (8).

## Envelope gene mutations

During both HBeAg-positive and HBeAg-negative CHB, some patients have been found to be infected with HBV containing deletions, insertions and mutations in the viral envelope region that result in reduced or truncated viral secretion (9). Because the envelope region overlaps the polymerase region, envelope mutations can also produce a change in the overlapping polymerase, and vice versa (Figures 2.2[A] and 2.2[B]). Hence, substitutions in the HBsAg can result in changes in the polymerase that may confer antiviral resistance; conversely, changes induced by antiviral resistance may encode changes in the HBsAg, leading to potential vaccine escape mutants.

The current hepatitis B vaccine contains recombinant HBsAg. The subsequent immune response to the major hydrophilic region (MHR) of HBsAg, located from amino acid residues 99 to 170, induces protective immunity in the form of anti-HBs. Mutations within the MHR have been selected during vaccination (10), and following treatment of liver transplant recipients with hepatitis B immune globulin (HBIg) prophylaxis (11). Most vaccine-HBIg escape isolates have an amino acid change from glycine to arginine at residue 145 of HBsAg (sG145R), or aspartate to glutamic acid at residue 144 (sD144E). The sG145R mutation has been associated with vaccine failure (10); it has also been shown to be transmitted, establish persistent infection and cause disease.

## Polymerase mutations: antiviral drug resistance

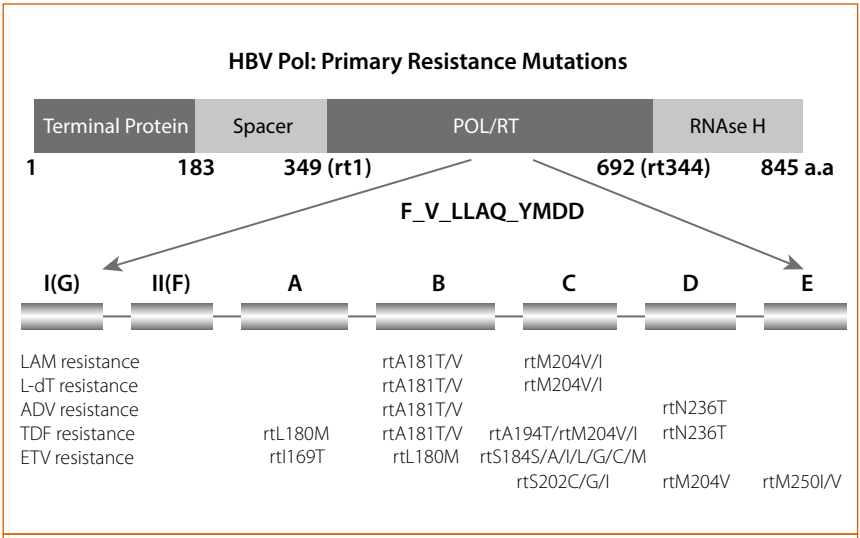
Antiviral drug resistance in clinical practice is discussed further in **Chapter 7**.

The treatment of CHB has advanced significantly during the past 15 years as a result of the development of safe and efficacious orally available antiviral NAs. Two synthetic NAs with an unnatural L-conformation – lamivudine and telbivudine – are widely available but are not commonly used in Australia. Adefovir is a prodrug for the acyclic dAMP analogue, adefovir. Adefovir gained approval in 2002, but has largely been replaced by its congener, tenofovir, which is now commonly used as a first-line agent. Tenofovir lacks the potential nephrotoxicity of adefovir; consequently, a higher dose can be used (300 mg/day vs. 10 mg/day for adefovir), which may explain its greater efficacy in vivo. The most potent anti-HBV drug discovered to date is the deoxyguanosine analogue, entecavir (12), which is now also widely used as a first-line agent for treating CHB.

### *Lamivudine and other L-nucleoside analogues*

Antiviral resistance to lamivudine is conferred by mutations that result in replacement of methionine at amino acid position 204 in the tyrosine-methionine-aspartate (YMDD) catalytic site motif (C-domain) of the rt by valine (rtM204V) or leucine (rtM204I) (Figure 2.4) (13). In a few cases, the B-domain change at rtA181T is also responsible for primary resistance to lamivudine. For other L-nucleosides such as telbivudine, the B-domain (rtA181T/V) and C-domain (rtM204I)

**Figure 2.4** Location of the major primary antiviral drug-resistant mutations associated with resistance in the major catalytic domains of the hepatitis B virus polymerase gene




ADV, adefovir; LdT, telbivudine; LAM, lamivudine; POL/RT, polymerase reverse transcriptase gene; rt, reverse transcriptase; TDF, tenofovir

changes are the main substitutions associated with the development of resistance (Figure 2.4).

Lamivudine resistance increases progressively during treatment at rates between 14% and 32% annually. At year four of therapy, rates of lamivudine resistance reach over 70% in HBV mono-infection, and exceed 90% in HBV–HIV co-infection (14, 15). Factors that increase the risk of development of resistance include high pretherapy serum HBV DNA and alanine transaminase (ALT) levels, and incomplete suppression of viral replication (14, 16). Lamivudine resistance does not usually confer cross-resistance to adefovir or tenofovir unless rtA181T is selected; however, the presence of rtM204I/V confers cross-resistance to the other L-nucleoside analogues, including telbivudine and, to a lesser extent, entecavir (Table 2.1).

**Table 2.1** Summary of cross-resistance profiles

| | LAM | ADV/ TDF | LdT | ETV |
|---|---|---|---|---|
| LAM-R | X | √ | X | Reduced |
| ADV-R | √ | X | √ | √ |
| LdT-R | X | √ | X | √ |
| ETV-R | X | √ | X | X |

ADV, adefovir; ETV, entecavir; LAM, lamivudine; LdT, telbivudine; R, resistant; TDF, tenofovir

X, resistant; √, sensitive

The rtM204I change can occur in isolation, but rtM204V is found only in association with other substitutions – predominantly with rtL180M, and occasionally with both rtL180M and rtV173L. These additional changes partly compensate for the loss of replication fitness that can be associated with the development of drug resistance (17).

High maternal viral loads have been shown to be a risk factor for neonatal immunoprophylaxis failure, and lamivudine has been used during the third trimester to reduce the risk of perinatal transmission. Recent evidence, obtained using next-generation sequencing, has shown that viral variants conferring lamivudine resistance are not only present at baseline, but (more importantly) are rapidly selected by the time of delivery (18). The presence of such variants could potentially complicate future clinical management; hence, alternative NAs (e.g. tenofovir) are usually recommended.

***Adefovir and tenofovir***

Resistance to adefovir has been associated with changes in the B (rtA181T/V) and D (N236T)-domains of the rt (19) (Figure 2.4). HBV resistance to adefovir occurs less frequently (about 2% after 2 years, 4% after 3 years and 18% after 4 years) than resistance to lamivudine. The rtN236T change does not significantly affect sensitivity to lamivudine (19), but the rtA181T/V change confers partial cross-resistance to lamivudine. Currently, there is little evidence for the occurrence of primary resistance to tenofovir; however, clinically, it has been shown that the presence of adefovir resistance impairs tenofovir efficacy (20).

***Entecavir***

Resistance to entecavir in patients naive to therapy is rare, and apparently occurs almost exclusively in patients who had already developed lamivudine-resistant HBV (21). Entecavir resistance appears to require the initial presence of rtM204V/I, followed by mutations that encode at least one additional entecavir 'signature' substitution at rtI169T or rtT184G (B-domain), rtS202I (C-domain) or rtM250V (E-domain) of HBV Pol (Figure 2.4).

***Multidrug resistance***

Multidrug-resistant (MDR) HBV has been reported in patients who received sequential treatment with different NA monotherapy, and rtA181T should be considered a MDR variant (21-26). The development of multidrug resistance will influence the efficacy of rescue therapy, as in the case of MDR HIV (27, 28). Successive evolution of different patterns of resistance mutations have been reported during long-term lamivudine monotherapy (29, 30). The isolates of HBV with these initial mutations appear to be associated with decreased replication fitness compared with wild-type HBV; however, additional mutations that can restore replication fitness are frequently detected as treatment is continued (31, 32).

***Public health issues: Pol-env overlap***

The polymerase gene overlaps with the envelope gene (see Figure 2.2[B]), and changes in the polymerase gene that confer antiviral resistance can cause concomitant changes to the ORFs of the envelope gene. Thus, the major resistance mutations associated with lamivudine, adefovir, entecavir and telbivudine failure also have the potential of altering the

C-terminal region of HBsAg. For example, changes associated with lamivudine and entecavir resistance, such as the rtM204V, result in a change at sI195M in the HBsAg. Similarly, the rtM204I change that is associated with lamivudine and telbivudine is linked to three possible HBsAg changes: sW196S, sW196L or a termination codon. The effect of the main lamivudine resistance mutations on the altered antigenicity of HBsAg have been examined in vitro (33), and animal models suggest that these findings have public health relevance (34). In particular, one of the common HBV quasispecies selected during lamivudine treatment is rtV173L + rtL180M + rtM204V, which results in change in the HBsAg at sE164D + sI195M, and thus has the potential to escape vaccine-induced anti-HBs. About 20% of people with HIV/HBV co-infection (15) and 10% of those with mono-infection treated with lamivudine encode this 'triple polymerase mutant' (31). In binding assays, HBsAg expressing these lamivudine-resistant associated residues had reduced anti-HBs binding (33). This reduction was similar to the classical vaccine escape mutant, sG145R, and has been confirmed as a significant variant by infecting vaccinated chimpanzees.

The adefovir resistance substitution rtN236T does not affect the envelope gene, and overlaps with the stop codon at the end of the region encoding the surface antigen. The rtA181T mutation selected by adefovir and lamivudine results in a stop codon mutation at sW172*. The adefovir resistant mutation at rtA181V results in a change at sL173F. HBV with mutations that result in a stop codon in the envelope gene, such as those for lamivudine and adefovir, would be present in association with a low percentage of wild-type HBV, to enable rescue for viral assembly and release.

The entecavir resistance-associated changes at rtI169T, rtS184G and rtS202I also affect HBsAg, and result in changes at sF161L, sL/V176G and sV194F. The rtM250V is located after the end of HBsAg. The sF161L is located within the region that was defined as the 'a' determinant or MHR, which includes amino acids 90–170 of the HBsAg (35). This region is a highly conformational epitope, characterised by multiple disulfide bonds formed from sets of cysteine residues at amino acids 107–138, 137–149 and 139–147 (35). Since distal substitutions such as sE164D strongly affect anti-HBs binding (33), the influence of other changes to HBsAg driven by NA resistance, such as sF161L, needs investigation in order to determine the effect on the envelope structure and subsequent anti-HBsAg binding.

Although evidence for the spread of transmission of antiviral-resistant HBV is limited, there has been at least one report of the transmission of lamivudine-resistant HBV to an HIV patient undergoing lamivudine as part of antiretroviral therapy (36). In addition, HBV encoding lamivudine-resistant mutations were also found in a cohort of dialysis patients with occult HBV (37). Both primary and compensatory antiviral-resistance mutations may result in associated changes to the viral envelope that could have substantial public health relevance (although, in the era of potent first-line therapies such as tenofovir and entecavir, this has yet to be demonstrated).

***Alternative antiviral therapy – interferon***

The development of longer-acting pegylated forms of interferon (IFN) has stimulated renewed interest in treating patients with immunomodulatory agents. However, the drawbacks of pegylated IFN (PEG-IFN) treatment are similar to that of conventional interferon, with low efficacy and high toxicity. One advantage of the pegylated form, however, is that treatment is finite: usually 48 weeks. Furthermore, IFN therapy is effective against NA-resistant HBV, and is not associated with any changes in the HBV polymerase region (38). Recent research has used the quantification of serum HBsAg as a clinical biomarker to identify the patient subgroup most likely to respond to PEG-IFN treatment (39, 40). This may allow the use of response guided therapy for CHB and provide higher rates of HBsAg seroclearance.

## Conclusion

Resistance may continue to be an important issue in the management of patients with CHB because long-term (probably life-long) therapy with NAs will be required in most patients. Moreover, in many countries with a high prevalence of CHB, the NAs most compromised by viral resistance (lamivudine, telbivudine) are cheap and commonly used. One of the important lessons learned from the HIV paradigm is that resistance is likely to occur if viral replication is present during treatment, as occurs with some existing monotherapy regimens that use L-nucleosides (41). Currently, however, first-line therapies with potent antivirals such as tenofovir or entecavir show little evidence of significant resistance development. It is not clear whether combination therapy for CHB – either as an initial strategy or in selected groups of patients with either MDR HBV or inadequate response to monotherapy – will be required in the future, and clinical trials are currently underway to investigate combination treatment strategies. Theoretically, combination therapy can reduce not only the viral load and quasispecies pool, but also the risk of selecting resistance, provided that the antiviral agents used do not select for mutual cross-resistance. Further, because of the overlap between the polymerase and envelope genes, the selection of drug-resistant HBV may have important clinical, diagnostic and public health implications. Envelope changes in HBV have been detected with lamivudine, adefovir, entecavir and telbivudine usage. The significance of these changes warrants further investigation to determine what effect they may have on the natural history of drug-resistant HBV and its possible transmissibility in the hepatitis B-vaccinated community at large.

## References


1. Chisari F, Ferrari C. Hepatitis B virus immunopathogenesis. Ann Rev Immunol. 1995;13:29–60.
2. Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z, et al. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. Elife. 2012;1:e00049.
3. Bock CT, Schranz P, Schroder CH, Zentgraf H. Hepatitis B virus genome is organized into nucleosomes in the nucleus of the infected cell. Virus Genes. 1994;8(3):215–29.
4. Newbold JE, Xin H, Tencza M, Sherman G, Dean J, Bowden S, et al. The covalently closed duplex form of the hepadnavirus genome exists in situ as a heterogeneous population of viral minochromosomes. Journal of Virology. 1995;69:3350–7.

5. Milich DR, Jones JE, Hughes JL, Price J, Raney AK, McLachlan A. Is a function of the secreted hepatitis B e antigen to induce immunologic tolerance in utero? Proc Natl Acad Sci U S A. 1990;87(17):6599–603.
6. Hunt CM, McGill JM, Allen MI, Condreay LD. Clinical relevance of hepatitis B viral mutations. Hepatology. 2000;31(5):1037–44.
7. Lok AS, Akarca U, Greene S. Mutations in the pre-core region of hepatitis B virus serve to enhance the stability of the secondary structure of the pre-genome encapsidation signal. Proc Natl Acad Sci U S A. 1994;91(9):4077–81.
8. Bartholomeusz A, Schaefer S. Hepatitis B virus genotypes: comparison of genotyping methods. Rev Med Virol. 2004;14(1):3–16.
9. Gunther S, Fischer L, Pult I, Sterneck M, Will H. Naturally occurring variants of hepatitis B virus. Adv Virus Res. 1999;52:25–137.
10. Carman WF, Zanetti AR, Karayiannis P, Waters J, Manzillo G, Tanzi E, et al. Vaccine-induced escape mutant of hepatitis B virus. Lancet. 1990;336(8711):325–9.
11. Carman WF, Trautwein C, van Deursen FJ, Colman K, Dornan E, McIntyre G, et al. Hepatitis B virus envelope variation after transplantation with and without hepatitis B immune globulin prophylaxis. Hepatology. 1996;24(3):489–93.
12. Shaw T, Locarnini S. Entecavir for the treatment of chronic hepatitis B. Expert Rev Anti Infect Ther. 2004;2(6):853–71.
13. Stuyver LJ, Locarnini SA, Lok A, Richman DD, Carman WF, Dienstag JL, et al. Nomenclature for antiviral-resistant human hepatitis B virus mutations in the polymerase region. Hepatology. 2001;33(3):751–7.
14. Lai CL, Dienstag J, Schiff E, Leung NW, Atkins M, Hunt C, et al. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. Clin Infect Dis. 2003;36(6):687–96.
15. Matthews GV, Bartholomeusz A, Locarnini S, Ayres A, Sasaduesz J, Seaberg E, et al. Characteristics of drug resistant HBV in an international collaborative study of HIV-HBV-infected individuals on extended lamivudine therapy. Aids. 2006;20(6):863–70.
16. Leung N. Clinical experience with lamivudine. Semin Liver Dis. 2002;22 Suppl 1:15–21.
17. Delaney WEt, Locarnini S, Shaw T. Resistance of hepatitis B virus to antiviral drugs: current aspects and directions for future investigation. Antivir Chem Chemother. 2001;12(1):1–35.
18. Ayres A, Yuen L, Jackson K, Manoharan S, Glass A, Maley M, et al. Short Duration of Lamivudine for Prevention of HBV Transmission in Pregnancy: Lack of Potency and Selection of Resistance Mutations. Journal of Viral Hepatitis. 2013;(in press).
19. Angus P, Vaughan R, Xiong S, Yang H, Delaney IV WE, Gibbs C, et al. Resistance to adefovir dipivoxil therapy associated with development of a novel mutation in the HBV polymerase. Gastroenterol. 2003;125:292–7.
20. van Bommel F, de Man RA, Wedemeyer H, Deterding K, Petersen J, Buggisch P, et al. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. Hepatology. [Multicenter Study Research Support, Non-U.S. Gov't]. 2010;51(1):73–80.
21. Tenney DJ, Levine SM, Rose RE, Walsh AW, Weinheimer SP, Discotto L, et al. Clinical emergence of entecavir-resistant hepatitis B virus requires additional substitutions in virus already resistant to Lamivudine. Antimicrob Agents Chemother. 2004;48(9):3498–507.
22. Brunelle MN, Jacquard AC, Pichoud C, Durantel D, Carrouee-Durantel S, Villeneuve JP, et al. Susceptibility to antivirals of a human HBV strain with mutations conferring resistance to both lamivudine and adefovir. Hepatology. 2005;41(6):1391–8.
23. Fung SK, Andreone P, Han SH, Rajender Reddy K, Regev A, Keeffe EB, et al. Adefovir-resistant hepatitis B can be associated with viral rebound and hepatic decompensation. J Hepatol. 2005;43(6):937–43.
24. Mutimer D, Pillay D, Cook P, Ratcliffe D, O'Donnell K, Dowling D, et al. Selection of multiresistant hepatitis B virus during sequential nucleoside-analogue therapy. J Infect Dis. 2000;181(2):713–6.
25. Villet S, Pichoud C, Aurelie O, Villeneuve JP, Trepo C, Zoulim F. Sequential Antiviral Therapy Leads to the Emergence of Multiple Drug Resistant Hepatitis B Virus. Hepatology. 2005;42 (Suppl. 1)(4):581A.

26. Yim HJ, Hussain M, Liu Y, Wong SN, Fung SK, Lok AS. Evolution of multi-drug resistant hepatitis B virus during sequential therapy. Hepatology. 2006;44(3):703–12.

27. Gonzales MJ, Johnson E, Dupnik KM, Imamichi T, Shafer RW. Colinearity of reverse transcriptase inhibitor resistance mutations detected by population-based sequencing. J Acquir Immune Defic Syndr. 2003;34(4):398–402.

28. Shafer RW, Winters MA, Palmer S, Merigan TC. Multiple concurrent reverse transcriptase and protease mutations and multidrug resistance of HIV-1 isolates from heavily treated patients. Ann Intern Med. 1998;128(11):906–11.

29. Natsuizaka M, Hige S, Ono Y, Ogawa K, Nakanishi M, Chuma M, et al. Long-term follow-up of chronic hepatitis B after the emergence of mutations in the hepatitis B virus polymerase region. J Viral Hepat. 2005;12(2):154–9.

30. Yeh CT, Chien RN, Chu CM, Liaw YF. Clearance of the original hepatitis B virus YMDD-motif mutants with emergence of distinct lamivudine-resistant mutants during prolonged lamivudine therapy. Hepatology. 2000;31(6):1318–26.

31. Delaney IV WE, Yang H, Westland CE, Das K, Arnold E, Gibbs CS, et al. The hepatitis B virus polymerase mutation rtV173L is selected during lamivudine therapy and enhances viral replication in vitro. J Virol. 2003;77(21):11833–41.

32. Ono SK, Kato N, Shiratori Y, Kato J, Goto T, Schinazi RF, et al. The polymerase L528M mutation cooperates with nucleotide binding-site mutations, increasing hepatitis B virus replication and drug resistance. J Clin Invest. 2001;107(4):449–55.

33. Torresi J, Earnest-Silveira L, Deliyannis G, Edgtton K, Zhuang H, Locarnini SA, et al. Reduced antigenicity of the hepatitis B virus HBsAg protein arising as a consequence of sequence changes in the overlapping polymerase gene that are selected by lamivudine therapy. Virology. 2002;293(2):305–13.

34. Kamili S, Sozzi V, Thompson G, Campbell K, Walker CM, Locarnini S, et al. Efficacy of hepatitis B vaccine against antiviral drug-resistant hepatitis B virus mutants in the chimpanzee model. Hepatology. [Evaluation Studies]. 2009;49(5):1483–91.

35. Carman WF. The clinical significance of surface antigen variants of hepatitis B virus. J Viral Hepat. 1997;4(Suppl 1):11–20.

36. Thibault V, Aubron-Olivier C, Agut H, Katlama C. Primary infection with a lamivudine-resistant hepatitis B virus. Aids. 2002;16(1):131–3.

37. Besisik F, Karaca C, Akyuz F, Horosanli S, Onel D, Badur S, et al. Occult HBV infection and YMDD variants in hemodialysis patients with chronic HCV infection. J Hepatol. 2003;38(4):506–10.

38. Chen RY, Bowden S, Desmond PV, Dean J, Locarnini SA. Effects of interferon alpha therapy on the catalytic domains of the polymerase gene and basal core promoter, precore and core regions of hepatitis B virus. J Gastroenterol Hepatol. [Comparative Study]. 2003;18(6):630–7.

39. Brunetto MR, Moriconi F, Bonino F, Lau GK, Farci P, Yurdaydin C, et al. Hepatitis B virus surface antigen levels: a guide to sustained response to peginterferon alfa-2a in HBeAg-negative chronic hepatitis B. Hepatology. [Comparative Study]. 2009;49(4):1141–50.

40. Moucari R, Mackiewicz V, Lada O, Ripault MP, Castelnau C, Martinot-Peignoux M, et al. Early serum HBsAg drop: a strong predictor of sustained virological response to pegylated interferon alfa-2a in HBeAg-negative patients. Hepatology. 2009;49(4):1151–7.

41. Richman DD. The impact of drug resistance on the effectiveness of chemotherapy for chronic hepatitis B. Hepatology. 2000;32(4 Pt 1):866–7.

# CHAPTER 3: HEPATITIS B VIRUS TESTING AND INTERPRETING TEST RESULTS

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**LINKS**

**Chapter 2:** Virology: Viral replication and drug resistance
**Chapter 4:** Natural history of hepatitis B virus infection
**Chapter 5:** Primary prevention of hepatitis B virus infection
**Chapter 6:** Clinical assessment of patients with hepatitis B virus infection
**Chapter 13:** Privacy, confidentiality and other legal responsibilities

## KEY POINTS

- Opportunistic testing of people at risk of hepatitis B virus infection should be undertaken, particularly for people born in intermediate and high-prevalence countries, and Aboriginal and Torres Strait Islander people (1).
- Testing for hepatitis B in a patient from a hepatitis B priority population aligns with the screening provisions of the Medicare Benefits Schedule (2) and presents an opportunity to diagnose, intervene and prevent illness and death.
- Informed consent should be obtained before testing, and test results should be conveyed in a safe and culturally appropriate manner.
- When testing for hepatitis B, the tests to be ordered are: hepatitis B surface antigen (HBsAg), antibody to surface antigen (anti-HBs) and antibody to core antigen (anti-HBc). Positive HBsAg indicates current infection, positive anti-HBs indicates immunity (through vaccination or past infection), and positive anti-HBc indicates past or current infection (this test may occasionally give a false-positive result).

## Introduction

Hepatitis B is a complex disease that can be defined using biochemical, serological, virological and histological parameters. Management decisions are based on an accurate interpretation of these parameters. This chapter discusses who should be tested for hepatitis B virus (HBV) infection, and details the specific tests for HBV infection and the interpretation of test results.

## Who should be tested?

Guidelines from the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of Liver (EASL) and the Asian Pacific Association for the Study of Liver (APASL) recommend screening people born in high and intermediate-prevalence countries, including immigrants and adopted children (Table 3.1) (3-5). Other high-risk groups identified include household and sexual contacts of people positive for hepatitis B surface antigen (HBsAg), people with a history of injecting drug use, people with multiple sexual partners or any history of sexually transmitted infection, men who have sex with men, prison inmates, people with chronically elevated levels of alanine transaminase and aspartate aminotransferase (ALT/AST); people infected with human immunodeficiency virus (HIV) or hepatitis C virus (HCV), people undergoing haemodialysis and all pregnant women. In Australia, these recommendations should also

**Table 3.1** Priority populations for testing

| Who should be tested for hepatitis B? | Other patients whose HBV status should be determined include: |
|---|---|
| Opportunistic testing of people at risk, particularly<br>• **people born in intermediate and high prevalence countries and**<br>• **Aboriginal and Torres Strait Islander people,**<br>will reduce the number of people with CHB who are undiagnosed, and thus reduce the mortality and morbidity caused by hepatitis B. | • pregnant women (to prevent vertical transmission)<br>• adults at increased risk of transmission, including sexual and household contacts, and family members of people with hepatitis B, men who have sex with men, people who inject drugs, people with multiple sexual partners (including sex workers) and haemodialysis patients<br>• people living with hepatitis C or HIV infection (because of increased risk factors and the presence of co-infection that alters prognosis and treatment)<br>• patients about to commence chemotherapy or immunosuppressive therapy (because patients with past or present hepatitis B infection may develop a life-threatening flare of HBV on reconstitution of the immune system)<br>• people with clinical presentation of liver disease or elevated alanine transaminase (ALT) or alpha fetoprotein (AFP) of unknown aetiology<br>• health professionals who may be involved with exposure-prone procedures<br>• members of the armed forces. |
| Further details of people for whom opportunistic testing for HBV infection is recommended can be obtained at: www.testingportal.ashm.org.au/hbv | |

CHB, chronic hepatitis B; HBV, hepatitis B virus; HIV, human immunodeficiency virus

include Aboriginal and Torres Strait Islander people, who account for about 10% of the Australian HBV-infected population (6). High-risk patients undergoing treatment with immunosuppressive agents should also be screened for HBV. Seronegative people (who are susceptible to infection) should be vaccinated.

## Gaining informed consent for testing

Hepatitis B is a life-long disease for many patients. It is important to provide support and information about the testing process, to minimise the impact of a positive diagnosis on patients and their families, change high-risk health-related behaviour and reduce anxiety. Informed consent for testing means that the person agrees to be tested on the basis of understanding the testing procedures and the reasons for testing, and being able to assess the personal implications of a positive test result, including the need for further medical assessment.

The process of obtaining informed consent before testing needs to be conducted in a culturally appropriate and safe manner. It should acknowledge the patient's gender, cultural beliefs and practices, health literacy, behaviour and language; it should also consider local and cultural issues such as stigma, shame and concerns around confidentiality. This may be particularly relevant when dealing with patients from culturally and linguistically diverse (CALD) backgrounds, who may have low English proficiency, and Aboriginal and Torres Strait Islander people. The Good Medical Practice code of conduct recommends using qualified language or cultural interpreters to assist with communication (7), and providing information packs in the patient's first language (see **Appendix 2** for further information). Finally, it is important to address the implications of a positive, negative or indeterminate test result, the medical consequences of infection and the support mechanisms available, both while awaiting test results and in the event that the result is positive.

The Translating and Interpreting Service (TIS) is available 24 hours/7 days per week, and can be contacted via the Doctors' Priority Line on 1300 131 450.

## Diagnostic tests for hepatitis B

Serologic testing for HBV infection relies on immunoassay techniques for the detection of antigens and antibodies in patient serum. Current serological tests for hepatitis B are highly sensitive and specific. Initial testing should include HBsAg, antibody to surface antigen (anti-HBs) and antibody to core antigen (anti-HBc). Hepatitis serology tests are Medicare rebatable. However, to be able to order all three diagnostic tests (HBsAg, anti-HBc and anti-HBs) simultaneously, and retain Medicare eligibility, the requesting doctor should write '? chronic hepatitis B' or a similar clinical justification for testing on the request slip. Table 3.2 outlines the test results and their interpretation.

### Serological markers

#### *Hepatitis B surface antigen (HBsAg)*

The presence of HBsAg signifies HBV infection. HBs is an antigen on the envelope of the HBV virion, and is secreted as lipoprotein particles in

excess of virions by a ratio of greater than 1,000:1. In acute infection, HBsAg usually becomes detectable during weeks 4–10. Chronic hepatitis B (CHB) virus infection is defined by the persistence of HBsAg for more than 6 months .

### *Antibody to surface antigen (Anti-HBs)*

Anti-HBs is a protective antibody that develops with the resolution of acute infection, or following successful vaccination against HBV. Occasionally, anti-HBs and HBsAg can be found together; this situation has no known clinical significance. Rarely, there may be a window where both HBsAg and anti-HBs can be negative during the seroconversion and clearance of HBV.

### *Antibody to core antigen (Anti-HBc)*

HBV core antigen is not found as a discrete protein in the serum. During HBV replication, it is produced in the cytosol of the hepatocyte, surrounding the viral genome and the associated polymerase. It is then packaged within an envelope before being secreted from the hepatocyte. Anti-HBc is an antibody to a peptide of this core protein, which has been processed within an antigen-presenting cell. In acute infection, anti-HBc immunoglobulin M (IgM) is found in high concentrations, which gradually decline over 3–6 months, while there is a corresponding increase in anti-HBc immunoglobulin G (IgG). If acute hepatitis B is suspected (through recent risk or presentation, or both), a test for anti-HBc IgM can be ordered to support the clinical suspicion. Elevation (to a high titre) of anti-HBc IgM usually signifies acute infection, but low-grade elevations may also occur during reactivation or 'flares' of CHB. Anti-HBc IgG remains positive for life following exposure to HBV; however, unlike anti-HBs, anti-HBc is not a protective antibody. Most serological assays do not directly measure anti-HBc IgG; rather, they test for the total anti-HBc antibody.

**Table 3.2** Test results and their interpretation (8)

| Tests | Results | Interpretation |
|---|---|---|
| **HBsAg**<br>**anti-HBc**<br>**anti-HBs** | Negative<br>Negative<br>Negative | Susceptible to infection (if at risk, vaccination should be recommended) |
| **HBsAg**<br>**anti-HBc**<br>**anti-HBs** | Negative<br>Positive<br>Positive | Immune due to resolved infection |
| **HBsAg**<br>**anti-HBc**<br>**anti-HBs** | Negative<br>Negative<br>Positive | Immune due to hepatitis B vaccination |
| **HBsAg**<br>**anti-HBc**<br>**IgM anti-HBc***<br>**anti-HBs** | Positive<br>Positive<br>Positive<br>Negative | Acute HBV infection<br>*(high titre) |
| **HBsAg**<br>**anti-HBc**<br>**anti-HBs** | Positive<br>Positive<br>Negative | Chronic HBV infection |

HBsAg, hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; IgM anti-HBc, immunoglobulin M antibody to the hepatitis B core antigen; HBV, hepatitis B virus

An isolated elevation of anti-HBc occurs in four situations:

- previous infection with anti-HBs below the level of detection
- an occult infection, where the HBsAg level has fallen below the level of detection, but HBV DNA is detectable

- in the window after acute infection, when HBsAg has disappeared but anti-HBs has not yet developed (longitudinal testing is required in such cases)
- a false positive result (this is more likely in a stored specimen) (see Table 3.3).

**Table 3.3** What if the results are inconclusive?

| Tests | Results |
|---|---|
| **HBsAg** | Negative |
| **anti-HBc** | Positive |
| **anti-HBs** | Negative |
| **Interpretation possibilities include:**<br>• distant resolved HBV infection – the most common interpretation, particularly in people born in HBV-endemic areas<br>• false positive result – more common in people with a low risk of past HBV infection<br>• resolving acute HBV infection – in the period between HBsAg loss and development of detectable anti-HBs<br>• passive transfer of maternal anti-HBc – in children up to 3 years of age<br>• occult HBV infection – where HBV DNA is detectable in the absence of HBsAg; this can be determined by detecting HBV DNA in serum, but this test is not Medicare rebatable in the absence of HBsAg<br>• Confirmation via repeat serology should be considered. | |
| HBsAg, hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBV, hepatitis B virus | |

## Conveying a test result

The result of a test should be conveyed in a culturally appropriate and safe manner, using a qualified language interpreter (who is gender and dialect appropriate) for patients with a low proficiency in English. Results need to be given promptly and in person, in a setting where privacy is assured. It is important to avoid information overload, and it is often useful to provide written material that is culturally and language appropriate (taking literacy levels into account), and details of support services (for further information see http://testingportal.ashm.org.au/hbv/conveying-hepatitis-b-test-results).

### Conveying a hepatitis B test result: susceptible (non-immune)

A person is regarded as susceptible or non-immune when there is no documented history of completed vaccination, and the anti-HBs, anti-HBc and HBsAg results are all negative. This situation provides an opportunity to discuss hepatitis vaccination with the person, and to emphasise positive messages about safe behaviours (see **Chapter 5**).

### Conveying a hepatitis B test result: immune

A person is regarded as immune when the anti-HBs titre is positive in the setting of a previous completed vaccination, or the anti-HBc is positive (with or without anti-HBs being positive). Isolated anti-HBc positive results usually indicate distant resolved infection (with the anti-HBs titre having fallen below the threshold of the assay). However, the result is occasionally falsely positive and, rarely, isolated anti-HBc results can indicate a different hepatitis B status, as outlined in Table 3.3.

For patients who have become immune through natural infection or vaccination, this result should be conveyed to the patient

and clearly entered in their medical record, to avoid unnecessary repeat serologic testing or vaccination in the future.

Patients who have become immune through natural infection should be advised that they may be at risk in settings of immunosuppression.

### Conveying a hepatitis B test result: confirmed infection

A positive HBsAg test result can have a significant impact on the patient, and those close or important to them. It is important to focus on the person's immediate needs, and to provide support and allow adequate time for questions. It is essential to use a language interpreter (who is gender and dialect appropriate) for patients with a low proficiency in English. The process of conveying a positive result should include:

- giving the test result in person, and in a confidential manner that is sensitive and appropriate to the gender, culture, behaviour, language and literacy level of the person who has been tested
- informing the patient about how hepatitis B is and is not transmitted, and how onward transmission may be prevented, including discussion about hepatitis B vaccination for partners, household contacts and other close contacts
- discussing strategies for disclosure to the patient's partner and family members, including discussion of the following (depending on whether the person has acute or chronic disease):
  - disclosure to children
  - whether current and future household and sexual contacts should be tested for hepatitis B, and subsequently vaccinated if they are found to be susceptible
- providing information about the legal considerations around disclosure of hepatitis B status (see **Chapter 13**).
- providing information about (and referral to) available support services.

## Considerations

### Considerations for acute hepatitis B

Information should be provided about the natural history of hepatitis B, and the importance of clinical monitoring to identify resolution of acute infection (which will occur in 95% of adults) or the possibility of going on to have CHB.

### Considerations for chronic hepatitis B

Information should be provided about the natural history of CHB, and the need for regular, ongoing clinical monitoring to detect progression of liver disease, determine the need for treatment and prevent liver cancer (see **Chapter 6**). Health maintenance strategies should be identified; such strategies could include alcohol minimisation, weight loss, smoking cessation and harm-reduction strategies, as appropriate. Discussion should also cover the availability, efficacy and timing of treatment options, including the fact that antiviral therapy may not be needed. It may be necessary to cover these issues over a period of time rather than

in a single session; hence, a subsequent consultation should be arranged at the time of diagnosis.

## Markers of hepatitis B virus infection

The parameters used to define and characterise CHB include HBV antigens and host antibodies; HBV DNA and genotype; biochemical markers such as alanine transaminase (ALT); and the degree of hepatic fibrosis and inflammation. The definition and characterisation of the phases of CHB infection (Figure 3.1) are discussed in more detail in **Chapter 4**. Information on which tests to order during initial assessment or ongoing management of CHB are discussed in more detail in **Chapter 6**.

### Antigens

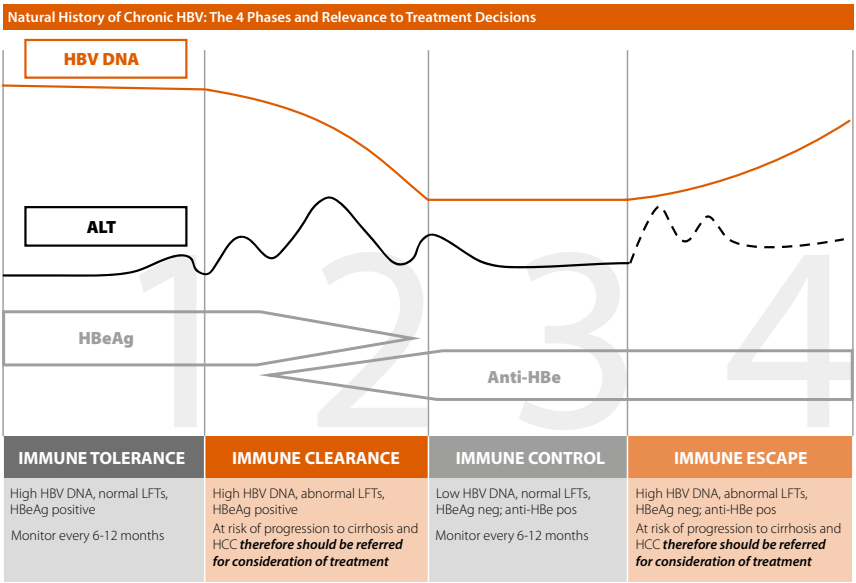
#### *Hepatitis B e antigen*

HBeAg is an accessory protein from the precore region of the HBV genome that is not necessary for viral infection or replication (9). It is, however, produced during active viral replication, and may act as an immunogen or a tolerogen, promoting persistent infection.

#### *Antibody to e antigen*

Anti-HBe is not a protective antibody; however, its appearance usually coincides with a significant immunological change

**Figure 3.1** The four phases of chronic hepatitis B




ALT, alanine transaminase; anti-HBe, antibody to e antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LFT, liver function test

associated with better virological control and lower HBV DNA replication (<2,000 IU/mL). The loss of HBeAg and the development of anti-HBe is termed 'HBeAg seroconversion', and it has been used as an end-point for treatment in HBeAg-positive people, because seroconversion is associated with a lower risk of progression to liver disease (10).

## Virological markers

### *Hepatitis B virus DNA*

With the advent of molecular amplification technology such as polymerase chain reaction (PCR), it has become possible to directly quantify the level of HBV replication. This is now an integral part of HBV management, especially with the development of effective antiviral treatments. PCR-based assays (target amplification assays) involve lysing the virion and purifying the DNA, which is then amplified and quantified. Alternatively, signal amplification assays can quantify the level of HBV DNA from serum, and require no purification step. Currently, the PCR-based assays for HBV DNA detection have the best range of quantification, now being standardised to IU/mL (11). The introduction of real-time PCR has allowed for sensitivities ranging from about 5–10 IU/mL to about 8–9 $\log_{10}$ IU/mL (12). The level of 20,000 IU/mL has been arbitrarily selected as the level below which there is a relatively low likelihood of hepatic damage, although damage can still occur (13).

The serum level of HBV DNA is a dynamic parameter in CHB. The level of circulating HBV is the strongest predictor of the development of cirrhosis and hepatocellular carcinoma (HCC) (14, 15). In a large, prospective Taiwanese cohort (n=3,653) followed over 11 years, the incidence of cirrhosis and HCC ranged from 4.5% and 1.3%, respectively, in those with low HBV DNA (<50 IU/mL), to 36.2% and 14.9%, respectively, in those with high HBV DNA ($>2 \times 10^5$ IU/mL). The incidence of both cirrhosis and HCC had dose-response relationships with HBV DNA levels, independent of HBeAg status and ALT level. Importantly, the risk of HCC and cirrhosis increased significantly at $10^4$ IU/mL. Effective suppression of HBV replication with antiviral therapy may reduce the incidence of significant fibrosis and HCC.

HBV DNA testing is now a vital part of the pretreatment evaluation and assessment of the efficacy of antiviral treatment. Before the introduction of HBV DNA testing, HBeAg was used as the biomarker of HBV replication. However, it is now clear that there is a population with HBV infection with active replication (high-level HBV DNA) who are HBeAg negative. This is termed 'e antigen negative chronic HBV'. This state occurs as a result of a mutation in the precore or basal core promoter region of the HBV genome (see **Chapter 2**). A major problem with the use of some antiviral therapies is the development of drug resistance, defined as a rise of ≥1 log IU/mL in the HBV DNA level while on therapy (4, 16). The development of treatment resistance has important management implications. Many patients treated with nucloes(t)ide analogues are negative for HBV DNA, but remain positive for HBeAg, which probably represents the

lack of effect of the drugs on the integrated HBV DNA in the hepatocytes. Based on increasing evidence of the importance of HBV DNA testing, the Medical Services Advisory Committee, of the then Australian Government Department of Health and Ageing, approved HBV DNA testing. The committee recommended one pretreatment assay for monitoring of patients not on antiviral therapy, and up to four assays over 12 months for those on antiviral therapy (17).

### *Hepatitis B virus genotyping*

Genotyping is determined by sequencing the HBV genome. It is defined as at least 4% divergence in the s antigen and at least 8% divergence in the entire nucleotide sequence. There are 10 currently recognised genotypes (A–J), which vary geographically, with the four most common genotypes being A–D. The most prominent genotypes in the Asia and Pacific regions are B and C. Genotype may have an important influence on disease progression and treatment response (18). Although the reasons are unclear, it appears that, in Asian populations, genotype B has increased rates of HBeAg seroconversion, and is associated with less aggressive liver disease and lower rates of HCC than genotype C (19). Furthermore, genotypes A and B have better response rates to interferon when compared to genotypes C and D (20). Currently, genotyping is a research tool and is not routinely performed for HBV in Australia. However, it may become a relevant test in future clinical practice, to identify patients at greater risk for disease progression.

## Biochemical markers

### *Alanine transaminase (ALT)*

The main biochemical marker in viral hepatitis is the serum ALT level, which is used as a surrogate marker for necroinflammation in the liver. An elevated ALT is also associated with better serological response to treatment with pegylated interferon. However, some studies have suggested that significant liver fibrosis can occur in the context of a normal ALT level. Recent data show that 12–43% of patients with chronic HBV with normal ALT levels have significant hepatic fibrosis (stage 2 fibrosis or greater) (21, 22). In part, this may relate to what is currently considered a normal ALT. It is likely that the original data to determine normal reference ranges for ALT levels included people with subclinical liver disease, which led to an overestimation of what should be considered a normal ALT level. A large study of healthy blood donors revealed the upper limit of normal for serum ALT was 30 IU/L for men and 19 IU/L for women (Figure 3.2), significantly lower than the current range (23).

**Figure 3.2** Alanine transaminase (ALT) upper limit of normal

Beware of what the laboratory lists as a **'normal'** ALT.

**Elevated ALT levels are:**

>30 U/L in men

>19 U/L in women

## Conclusion

Testing people at risk of HBV infection provides an opportunity to diagnose, intervene, and prevent illness and death. It is essential that informed consent is gained prior to testing, and that test results are conveyed in a safe and culturally appropriate manner. Requesting all three serological tests – HBsAg, anti-HBc and anti-HBs – in a patient at risk of hepatitis B infection allows systematic interpretation of results to determine a patient's hepatitis B status, either as susceptible (to infection), immune through vaccination or resolved infection, or chronically infected with hepatitis B. This avoids missed diagnoses, unnecessary vaccination and recalling patients or adding tests for diagnosis. The parameters used to define and characterise CHB infection include HBeAg and anti-HBe, HBV DNA, ALT and the degree of hepatic fibrosis and inflammation. Subsequent management and treatment decisions based on these results are discussed in detail in **Chapters 4** and **6**.

## References


1. National HBV Testing Policy Expert Reference Committee. National hepatitis B testing policy. Darlinghurst NSW: Australasian Society for HIV Medicine (ASHM), 2012.
2. Medicare Benefits Schedule (MBS). MBS – Note G13.1. 2012.
3. Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. 2008;2(3):263–83.
4. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology (Baltimore, Md). 2007;45(2):507–39.
5. EASL Clinical Practice Guidelines: management of chronic hepatitis B. Journal of Hepatology. 2009;50(2):227–42.
6. MacLachlan JH, Allard N, Towell V, Cowie BC. The burden of chronic hepatitis B virus infection in Australia, 2011. Aust NZ J Public Health. 2013;37(5):416–22.
7. Medical Board of Australia (MBA). Good Medical Practice: A Code of Conduct for Doctors in Australia: MBA, 2010. http://www.amc.org.au/index.php/about/good-medical-practice; 28/5/2014.
8. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part 1: Immunization of infants, children, and adolescents. MMWR. 2005;54(16).
9. Milich D, Liang TJ. Exploring the biological basis of hepatitis B e antigen in hepatitis B virus infection. Hepatology (Baltimore, Md). 2003;38(5):1075–86.
10. Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. The New England Journal of Medicine. 1996;334(22):1422–7.
11. Lindh M, Hannoun C. Dynamic range and reproducibility of hepatitis B virus (HBV) DNA detection and quantification by Cobas Taqman HBV, a real-time semiautomated assay. Journal of Clinical Microbiology. 2005;43(8):4251–4.
12. Weiss J, Wu H, Farrenkopf B, Schultz T, Song G, Shah S, et al. Real time TaqMan PCR detection and quantitation of HBV genotypes A-G with the use of an internal quantitation standard. Journal of Clinical Virology. 2004;30(1):86–93.
13. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000 – summary of a workshop. Gastroenterology. 2001;120(7):1828–53.
14. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006;130(3):678–86.

15. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. Journal of the American Medical Association. 2006;295(1):65–73.

16. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology (Baltimore, Md). 2009;50(3):661–2.

17. Medical Services Advisory Committee. Australian Government Department of Health and Ageing, 2007.

18. Fung SK, Lok AS. Hepatitis B virus genotypes: do they play a role in the outcome of HBV infection? Hepatology (Baltimore, Md). 2004;40(4):790–2.

19. Kao JH, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. Gastroenterology. 2000;118(3):554–9.

20. Buster EH, Hansen BE, Lau GK, Piratvisuth T, Zeuzem S, Steyerberg EW, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. Gastroenterology. 2009;137(6):2002–9.

21. Wang C, Shuhart M, Manansala J, Corey L, Kowdley K. High prevalence of significant fibrosis in patients with immunotolerance to chronic hepatitis B infection. Hepatology (Baltimore, Md). 2005;42:573A.

22. Lai MD, Hyatt B, Afdal N. Role of liver biopsy in patients with normal ALT and high HBV DAN. Hepatology (Baltimore, Md). 2005;42:720A.

23. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Annals of Internal Medicine. 2002;137(1):1–10.

# CHAPTER 4: NATURAL HISTORY OF HEPATITIS B VIRUS INFECTION

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**LINKS**

**Chapter 2:** Virology: viral replication and drug resistance
**Chapter 7:** Treatment of chronic hepatitis B virus infection
**Chapter 11:** Complex situations: co-infection and immunosuppression

## KEY POINTS

- Birth in highly endemic regions such as sub-Saharan Africa and East Asia is a risk factor for developing chronic hepatitis B (CHB) infection (1). The primary mode of transmission in such cases is vertical (i.e. mother to child).
- The risk of developing CHB is highest in those who acquire hepatitis B virus (HBV) infection perinatally and lowest in those who acquire the infection in adulthood.
- The natural history of HBV infection depends on complex interactions between host, virus and environment.
- There are four phases of CHB, and the host immune response in each phase determines the outcome of infection and the severity of liver injury.
- Liver damage is caused by the host immune response rather than the HBV itself.
- Complications of CHB include cirrhosis with hepatocellular failure and hepatocellular carcinoma. All complications can be minimised with effective antiviral therapy.

## Transmission of hepatitis B

Hepatitis B virus (HBV) is transmitted through infected blood or bodily fluids (semen and vaginal fluids). The virus enters the bloodstream either through a break in the skin or through mucous membranes (eyes, nose and mouth). The modes of transmission are summarised in Table 4.1

## Acute hepatitis B virus infection (7)

Acute HBV infection, as with other acute viral hepatitis infections, is asymptomatic in most individuals. Symptoms are more likely to occur in adults acquiring the infection, and will usually be mild, comprising arthralgia and nausea with or without right upper quadrant abdominal pain preceding any overt jaundice. HBV infection can be associated with a range of extrahepatic manifestations, more common in chronic hepatitis B (CHB). Those who acquire HBV perinatally or in infancy are likely to progress from acute to chronic infection. The acute illness can be described as having four stages.

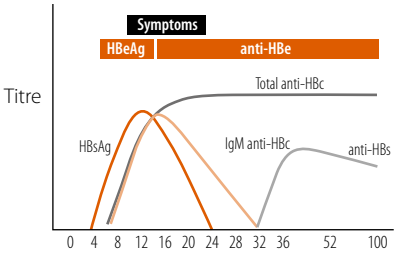
**Table 4.1** Modes of transmission of hepatitis B virus

| | |
|---|---|
| **Vertically –** from mother to child during childbirth | This is the most common way the virus spreads in high-prevalence countries.<br>Breastfeeding does not appear to increase the risk of HBV transmission to the infant, and it should not be discouraged if vaccination and HBIG are administered at birth.<br>Most guidelines do not recommend caesarean section as an intervention to reduce vertical transmission (2). |
| **Horizontally** | From a person with hepatitis B to other household contacts who are unvaccinated (e.g. through sharing toothbrushes, razors, nail files or other personal items that may lead to exchange of body fluids).<br>Infection acquired in early childhood after delivery is well recognised and has been attributed to parent-to-child contact (3-5), sibling contact (5, 6) and medical procedures such as intramuscular injections (6). |
| **Sexually** | Through unprotected vaginal, anal or oral sex with a person who has hepatitis B. |
| **Percutaneously** | Through the sharing or re-use of injecting equipment, tattooing, body piercing, acupuncture, cupping and some other cultural practices. |
| **Medically acquired** | There are still countries where blood transfusions, organ transplants and other medical interventions pose an extreme risk because donors are not screened for HBV. In most countries where screening is in place, the risk of infection is low.<br>Medical procedures – including dentistry, surgery, dialysis and alternative health-care procedures – pose a risk if appropriate infection control procedures are not adhered to.<br>Needlestick injury or splashing of infected blood or body fluids are a particular concern for health-care workers and emergency services providers. |

HBIG, hepatitis B immune globulin; HBV, hepatitis B virus

1. **Incubation:**
   The incubation period of acute HBV infection can last up to 12 weeks.
2. **Symptomatic hepatitis:**
   Acute hepatitis develops after the incubation period, and is characterised by elevated alanine transaminase (ALT) levels lasting 4–12 weeks. Symptoms and signs include anorexia, dark urine, jaundice and right upper quadrant abdominal discomfort. Acute symptoms are common in adults but not in infants and children.
3. **Recovery:**
   A recovery period follows with normalisation of the levels of ALT.
4. **Viral clearance and immunity:**
   Hepatitis B surface antigen (HBsAg) clearance in the serum follows after a few months, coinciding with the development of hepatitis B surface antibodies (anti-HBs). Hepatitis B core antibodies (anti-HBc) appear much earlier than anti-HBs and, in those who clear the infection, hepatitis B e antigen (HBeAg) appears and is cleared before the appearance of anti-HBs (Figure 4.1).

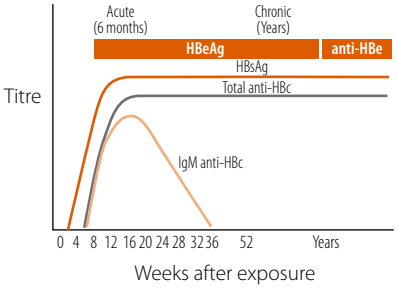
**Figure 4.1** Acute hepatitis B virus infection with clearance




anti-HBc, antibody to core antigen; anti-HBe, antibody to e antigen; anti-HBs, antibody to surface antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgM, immunoglobulin M

Adapted from: Centers for Disease Control and Prevention. Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection. MMWR 2008;57(No. RR-8):1-10.

**Figure 4.2** Progression to chronic hepatitis B virus infection




anti-HBc, antibody to core antigen; anti-HBe, antibody to e antigen; anti-HBs, antibody to surface antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgM, immunoglobulin M

Adapted from: Centers for Disease Control and Prevention. Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection. MMWR 2008;57(No. RR-8):1-10.

## Progression from acute to chronic hepatitis B virus infection

The transition from acute to chronic infection (Figure 4.2) signifies a failure of the immune response to eradicate the virus. Progression from acute to CHB infection is influenced by the age at which the subject acquires the virus. The overall risk of chronic infection is highest in those who acquire the virus perinatally (80–90%) (8). This is related to the inability of the immune system to recognise the virus and the high level of viral replication; it results in immunological tolerance. In adults, a cell-mediated response to foreign HBV proteins results in acute hepatitis, which may be asymptomatic;

**Table 4.2** Risk of progression, by age at infection (11)

| | Perinatal | Childhood | Adult |
|---|---|---|---|
| Risk of development of chronic infection (%) | 80–90 | 30 | <5 |
| Risk of advanced liver disease (% exposed to HBV) | 20–30 | 5–10 | 1–2 |
| Risk of advanced liver disease (% of those with chronic liver disease) | 20–30 | 20–30 | 20–30 |
| Length of immune tolerance phase | Prolonged | Variable | Short |

HBV, hepatitis B virus

the response leads to clearance of the infection in all but 1–5% of patients (9).

In those who acquire the infection in childhood, the risk of chronic hepatitis is 30% (10) (Table 4.2).

## Chronic infection – definition and preferred terminology

The American Association for the Study of Liver Diseases (AASLD) practice guidelines define CHB as a chronic necroinflammatory disease of the liver caused by persistent infection with HBV. CHB is defined serologically as HBsAg positivity for more than 6 months (12).

The terminology used to describe the different phases in the natural history of CHB infection varies considerably, and has been the subject of much debate and confusion. In particular, the immune control phase has been incorrectly referred to as the 'healthy carrier' state, the 'inactive carrier' state or the 'non-replicative' state of CHB. There is no such thing as a 'healthy carrier' – the term fails to reflect the fluctuating nature of CHB virus infection over time. The terms used in Table 4.3 to describe the phases of CHB reflect the importance of the immune system in controlling this infection.

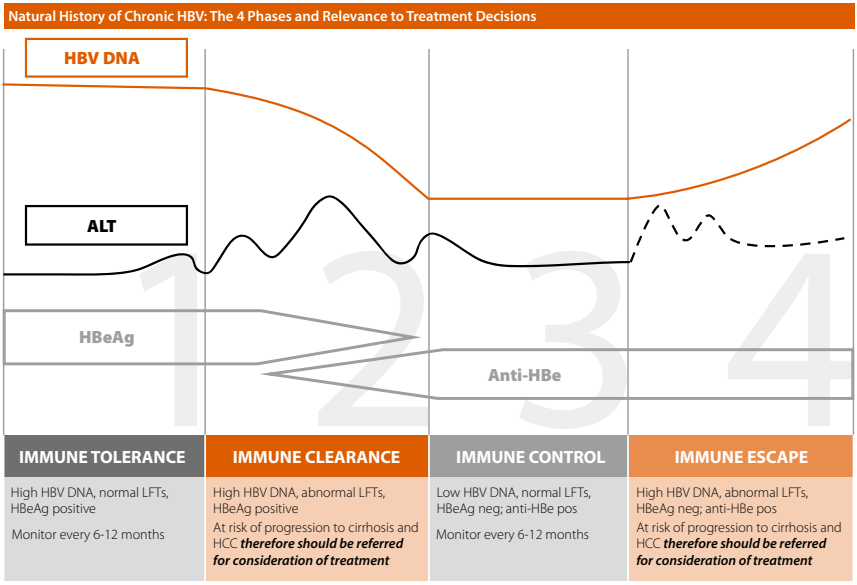
**Table 4.3** Terminology of chronic hepatitis B

| Preferred term | Numerical | Also known as |
|---|---|---|
| Immune tolerance | Phase I | Immunotolerant phase<br>Replicative state |
| Immune clearance | Phase II | Immune competence phase<br>Immunoactive phase |
| Immune control | Phase III | Non-replicative state |
| Immune escape | Phase IV | HBeAg-negative CHB<br>Precore mutant disease<br>Reactivation phase |

CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen

The four phases outlined in Table 4.3 are dependent on the complex interaction between host immune responses and

**Figure 4.3** The four phases and relevance to treatment decisions




ALAT, alanine aminotransferase; anti-HBe, antibody to e antigen; HBeAg, hepatitis B e antigen
HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LFT, liver function test

viral and environmental factors. These factors determine the outcome of infection and the severity of liver injury at any particular point in time in the natural history of HBV infection, as shown in Figure 4.3.

## Immune tolerance phase

The immune tolerance phase is characterised by hepatitis B e antigen (HBeAg) positivity, high HBV DNA levels (>20,000 IU/mL, and commonly over 1 million IU/mL), normal ALT levels and minimal level liver injury. During this phase, which may persist for decades, liver inflammation or fibrosis is either absent or minimal. This phase is associated with a low risk of progression to advanced liver disease, and it is thought to occur most commonly in those who acquire the infection vertically from HBeAg-positive mothers (13).

## Immune clearance phase

The immune clearance phase is also called the 'immune competent' or 'active' phase. The liver injury in HBV is determined by the immune response to the virus. The host's immune system recognises the HBV as foreign, and mounts a cytotoxic response to infected hepatocytes. This phase is characterised by fluctuating HBV DNA and ALT levels. Recurrent bouts of active inflammation and, eventually, fibrosis can occur in the liver following these repeated immune-mediated

attacks. An important outcome of this phase is the seroconversion of HBeAg to HBe antibody (anti-HBe), which is associated with a lower level of viraemia. The observed rate of clearance of HBeAg in those with or without elevated ALT levels averages 8%–12% per year (14). However, a number of people will still develop active liver disease after HBeAg seroconversion, generally owing to immune escape; that is, emergence of HBV mutant variants, particularly the core or precore mutation that renders the virus unable to encode for HBeAg (15) (see **Chapter 2**).

### Immune control phase

Patients in the immune control phase have previously been described as 'inactive carriers' of the infection. Liver inflammation is minimal, HBV DNA is undetectable or at a low level (<2,000 IU/mL), and liver function tests (LFTs) are usually normal (minor fluctuations of ALT may occur in relation to intercurrent infections, medication reactions and, possibly, early attempts to clear the virus). These patients are at low risk of developing advanced liver disease and its related complications (16). In a study assessing the long-term outcomes for HBsAg-positive individuals who had normal LFTs and normal or minimal changes on liver biopsy, liver histology and ALT remained unchanged over a 12-year follow-up period.

About 10–20% of patients who are anti-HBe positive may develop subsequent reactivation of HBV, with immune escape, after many years (17). This is associated with flares of hepatitis with HBV reactivation and ALT elevation (3). In addition, some patients may enter the control phase with already moderate to severe fibrosis. Therefore, all patients should be followed up indefinitely with 6-monthly ALT and annual measurement of HBV DNA, to monitor whether they remain in the immune control phase.

In addition, there is now emerging evidence that, in patients with an HBV DNA level of less than 2,000 IU/mL who were thought to have a comparable risk of hepatocellular carcinoma (HCC), an HBsAg level greater than 1,000 IU/mL is an independent risk factor for HCC development (18). However, it is currently not routine practice to measure HBsAg titres, and the role of measuring this antigen in clinical practice is an area for further studies.

### Immune escape phase

The immune escape phase of CHB is characterised by negative HBeAg, positive anti-HBe and detectable viral load (HBV DNA >2,000 IU/mL). It is often termed 'precore mutant HBV', because a mutation in the precore region of the DNA results in a lack of HBeAg production.

HBeAg-negative CHB is more common in Asian and Mediterranean countries. It occurs due to the selection of a mutant HBV that does not produce HBeAg but is still able to replicate. This immune selection process is likely to occur late in the natural history of CHB.

Patients who are HBeAg negative tend to be older and have more advanced liver disease. The natural course of patients with HBeAg-negative disease is characterised by fluctuations in clinical status, and in biochemical and viral load parameters,

caused by recurrent hepatic flares. About 70% of those with eAg-negative CHB have a fluctuating course characterised by periods of apparent inactivity (19). Although patients with HBeAg-negative disease tend to have lower HBV viral load than those with HBeAg-positive infection (<20,000 IU/mL vs >20,000 IU/mL), they display more hepatic inflammation on liver biopsy (20). Consequently, the annual incidence of cirrhosis is significantly higher (8–10%) in HBeAg-negative CHB patients than in those with HBeAg-positive CHB (2–5%) (21).

## Reactivation of hepatitis B virus following immunosuppression

Low levels of HBV DNA remain in hepatocytes after recovery from acute hepatitis B. Patients who have been exposed to HBV are at risk of reactivation of hepatitis B in the context of immunosuppression (22). Reactivation of HBV can occur in those who are HBsAg positive, and even in those who are both HBsAg negative and anti-HBc positive, if there is potent immunosuppression. Reactivation may be characterised by positive anti-HBc immunoglobulin M (IgM), but at lower titres than acute infection. Current AASLD guidelines suggest that patients who are at high risk of HBV infection should undergo testing for HBsAg and anti-HBc before chemotherapy or immunosuppressive therapy. Reactivation has been reported in 20–50% of those who are HBsAg positive and who undergo immunosuppressive treatment; the reactivation may result in hepatic decompensation and death (23). Thus, it is important for people with HBV infection undergoing immunosuppressive therapy to be carefully monitored, and managed appropriately with prophylaxis as indicated (see **Chapter 11**).

## Occult hepatitis B virus

Occult hepatitis B infection refers to the presence of the HBV DNA in the blood or liver, in the absence of HBsAg in the serum. With the emergence of highly sensitive HBV DNA polymerase chain reaction (PCR) assays, a population of patients has been identified with occult HBV infection. Its presence may be related to the persistence of HBV DNA within hepatocytes, in the form of covalently closed circular DNA (ccc DNA), which remains present even in people who are HBsAg negative (24). The reactivation of hepatitis B following immunosuppression has been described in patients with occult infection. Occult hepatitis B infection may contribute to the development of HCC, and there is evidence that it may also accelerate the progression of liver disease in the context of hepatitis C virus (HCV) co-infection (25).

## Complications of hepatitis B virus infection

Sequelae of HBV infection range from asymptomatic disease, to decompensated liver failure, to extrahepatic manifestations. Cirrhosis and HCC are major causes of morbidity and mortality. It is estimated that 600,000 patients worldwide die annually from HBV-related liver disease (26). The cumulative 5-year survival rate once decompensated cirrhosis ensues is 35% (27). The development of cirrhosis is influenced by several factors, most of which are virus and host related (Table 4.4).

**Table 4.4** Factors influencing progression to cirrhosis and hepatocellular carcinoma

| Risk factor | Reference |
|---|---|
| Active HBV DNA replication / viral load | Chen CJ et al (2006) (28) |
| HBV genotype C | Yang et al (2002) (29) |
| HBeAg-negative core promoter mutation | Yang et al (2002) (29) |
| Cirrhosis | Schiff et al (2006) (30) |
| Male sex | Bosch (1999) (31) |
| Asian/African/Aboriginal and Torres Strait Islander ethnicity | Fattovich (2003) (32)<br>Parker (2014) (33) |
| Coexisting non-alcoholic fatty liver disease and diabetes | El-Serag (2001) (34) |
| Smoking, alcohol, obesity | Marrero (2005) (35) |
| Positive family history 1st degree relative | Loomba (2013) (36) |

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus

Studies provide strong evidence that the risk of HCC in HBV is linked to levels of serum HBV DNA. In HBV-related HCC, 30–40% of HCC cases develop in the absence of cirrhosis (37).

HBV has the ability to integrate its genome into the host's hepatocyte DNA. Over many decades, especially during the immune tolerance phase, persistently high levels of HBV DNA lead to an accumulation of multiple sites of integration, thus increasing the risk of HCC even in the absence of active inflammation and fibrosis (38).

## Impact of antiviral therapy on the natural course of chronic hepatitis B virus infection

The importance of HBV viral replication to the natural history of the infection has been reported in the REVEAL HBV study (28, 39). The study showed that serum HBV DNA level was an independent risk factor for the development of cirrhosis and HCC after adjusting for other risk factors (e.g. male gender, alcohol use, cigarette smoking and older age).

There is ample data to suggest that patients who achieve long-term HBV DNA suppression through antiviral medications have reduced incidence of both HCC (40) and cirrhosis (41).

Newer, more potent agents such as entecavir and tenofovir have replaced lamivudine and adefovir as first-line antiviral medication for CHB (4) (see **Chapter 7**).

## Conclusion

The outcome of HBV infection and progression to chronicity is determined particularly by age at acquisition. The natural history of CHB virus infection is

characterised by four distinct phases that depend on complex interactions between host, virus and environment. In each phase, it is the host's immune response that determines the outcome of infection and the severity of liver injury. Sequelae of HBV infection range from asymptomatic carrier status to decompensated liver failure and HCC (42). Effective antiviral therapy can alter the natural course of HBV infection and reduce long-term complications related to the disease.

## References


1. World Health Organization (WHO). Global policy report on the prevention and control of viral hepatitis. Geneva: WHO, 2013.
2. Australasian Society for HIV Medicine (ASHM). Antenatal testing and blood-borne viruses (BBVs), 2011.
3. Takegoshi K, Zhang W. Hepatitis B virus infections in families in which the mothers are negative but the fathers are positive for HBsAg. Hepatology Research. 2006;36(2):75–7.
4. Tajiri H, Tanaka Y, Kagimoto S, Murakami J, Tokuhara D, Mizokami M. Molecular evidence of father-to-child transmission of hepatitis B virus. Journal of Medical Virology. 2007;79(7):922–6.
5. Komatsu H, Inui A, Sogo T, Hiejima E, Kudo N, Fujisawa T. Source of transmission in children with chronic hepatitis B infection after the implementation of a strategy for prevention in those at high risk. Hepatology Research. 2009;39(6):569–76.
6. Ko YC, Li SC, Yen YY, Yeh SM, Hsieh CC. Horizontal transmission of hepatitis B virus from siblings and intramuscular injection among preschool children in a familial cohort. American Journal of Epidemiology. 1991;133(10):1015–23.
7. Villeneuve JP. The natural history of chronic hepatitis B virus infection. Journal of Clinical Virology. 2005;34:S139–S42.
8. Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC. The influence of age on the development of the hepatitis B carrier state. Proceedings Biological Sciences. 1993;253(1337):197–201.
9. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009;50(3):661–2.
10. Beasley RP, Hwang LY, Lin CC, Leu ML, Stevens CE, Szmuness W, et al. Incidence of hepatitis B virus infections in preschool children in Taiwan. The Journal of Infectious Diseases. 1982;146(2):198–204.
11. Edith Cowan University. Hepatitis Education Project. 2014; Available from: http://hepatitis.ecu.edu.au/.
12. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2007;45(2):507–39.
13. Livingston SE, Simonetti JP, Bulkow LR, Homan CE, Snowball MM, Cagle HH, et al. Clearance of hepatitis B e antigen in patients with chronic hepatitis B and genotypes A, B, C, D, and F. Gastroenterology. 2007;133(5):1452–7.
14. McMahon BJ, Holck P, Bulkow L, Snowball M. Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. Annals of Internal Medicine. 2001;135(9):759–68.
15. Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. Hepatology. 2001;34(4 Pt 1):617–24.
16. Manno M, Camma C, Schepis F, Bassi F, Gelmini R, Giannini F, et al. Natural history of chronic HBV carriers in northern Italy: morbidity and mortality after 30 years. Gastroenterology. 2004;127(3):756–63.
17. Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology. 2002;35(6):1522–7.
18. Tseng TC, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. Gastroenterology. 2012;142(5):1140–9.
19. Chu CJ, Hussain M, Lok AS. Quantitative serum HBV DNA levels during different stages of chronic hepatitis B infection. Hepatology. 2002;36(6):1408–15.
20. Yuen MF, Tanaka Y, Ng IO, Mizokami M, Yuen JC, Wong DK, et al. Hepatic necroinflammation and fibrosis in patients with genotypes Ba and C, core-promoter and precore mutations. Journal of Viral Hepatitis. 2005;12(5):513–8.
21. Fattovich G. Natural history of hepatitis B. Journal of Hepatology. 2003;39:S50–S8.

22. Gupta S, Govindarajan S, Fong TL, Redeker AG. Spontaneous reactivation in chronic hepatitis B: patterns and natural history. Journal of Clinical Gastroenterology. 1990;12(5):562–8.

23. Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology. 2006;43(2):209–20.

24. Raimondo G, Caccamo G, Filomia R, Pollicino T. Occult HBV infection. Seminars in Immunopathology. 2013;35(1):39–52.

25. Raimondo G, Pollicino T, Cacciola I, Squadrito G. Occult hepatitis B virus infection. Journal of Hepatology. 2007;46(1):160–70.

26. World Health Organization (WHO). Hepatitis B fact sheet. Geneva: WHO, 2012.

27. Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, et al. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. 1995;21(1):77–82.

28. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. Journal of the American Medical Association. 2006;295(1):65–73.

29. Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med. 2002;347(3):168–74.

30. Schiff ER. Prevention of mortality from hepatitis B and hepatitis C. Lancet. 2006;368(9539):896–7.

31. Bosch FX, Ribes J, Borras J. Epidemiology of primary liver cancer. Semin Liver Dis. 1999;19(3):271–85.

32. Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis. 2003;23(1):47–58.

33. Parker C, Tong S, Dempsey K, Condon J, Sharma S, Chen J, et al. Hepatocellular carcinoma in Australia's Northern Territory – high incidence and poor outcomes. MJA. 2014;Accepted January 2014.

34. El-Serag HB, Richardson PA, Everhart JE. The role of diabetes in hepatocellular carcinoma: a case-control study among United States Veterans. Am J Gastroenterol. 2001;96(8):2462–7.

35. Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. J Hepatol. 2005;42(2):218–24.

36. Loomba R, Liu J, Yang HI, Lee MH, Lu SN, Wang LY, et al. Synergistic effects of family history of hepatocellular carcinoma and hepatitis B virus infection on risk for incident hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2013.

37. Bosch FX, Ribes J, Cleries R, Diaz M. Epidemiology of hepatocellular carcinoma. Clinics in Liver Disease. 2005;9(2):191–211, v.

38. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology (Baltimore, Md). 2009;49(5):S45–S55.

39. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006;130(3):678–86.

40. Sung JJ, Tsoi KK, Wong VW, Li KC, Chan HL. Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. Alimentary Pharmacology & Therapeutics. 2008;28(9):1067–77.

41. Kim CH, Um SH, Seo YS, Jung JY, Kim JD, Yim HJ, et al. Prognosis of hepatitis B-related liver cirrhosis in the era of oral nucleos(t)ide analog antiviral agents. Journal of Gastroenterology and Hepatology. 2012;27(10):1589–95.

42. Raimondo G, Pollicino T, Squadrito G. What is the clinical impact of occult hepatitis B virus infection? Lancet. 2005;365(9460):638–40.

# CHAPTER 5: PRIMARY PREVENTION OF HEPATITIS B VIRUS INFECTION


| | |
|---|---|
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**LINKS**

**Chapter 3:** Hepatitis B virus testing and interpreting test results
**Chapter 10**: Managing hepatitis B virus infection in pregnancy and children
**Chapter 12:** Infection control and occupational health

## KEY POINTS

- Universal vaccination programs for hepatitis B have had a profound impact on reducing the incidence of hepatitis B virus (HBV) infection.
- All infants should receive hepatitis B vaccination, with the first dose given at birth.
- Infants born to mothers positive for hepatitis B surface antigen (HBsAg) should receive both hepatitis B immunoglobulin and the first dose of hepatitis B vaccine, administered concomitantly, within 12 hours of birth.
- For HBsAg-positive women with high viral loads (>7 log IU/mL), consider use of antiviral therapy to further reduce the risk of perinatal transmission.
- It is recommended that adolescents not vaccinated in childhood receive hepatitis B vaccines.
- Individuals at risk of exposure should be vaccinated.

## Introduction

Primary prevention of hepatitis B virus (HBV) infection includes:

- vaccination of non-immune individuals at risk of infection
- prevention of mother-to-child transmission, including routine antenatal testing of all women, universal infant immunisation, and appropriate management and follow-up of both hepatitis B surface antigen (HBsAg)-positive women during pregnancy and their infants (see **Chapter 10**)
- universal precautions to prevent exposure and post-exposure prophylaxis for individuals exposed to potentially infectious body fluids (see **Chapter 12**).

## Aims of vaccination

Hepatitis B vaccination aims to prevent HBV infection and its complications, which include fulminant hepatitis, cirrhosis, liver failure and hepatocellular carcinoma (HCC). In acute cases, fulminant hepatitis occurs rarely, but it is associated with significant mortality, especially in infants (1).

The World Health Organization (WHO) strategy for the control of HBV infection aims to provide universal infant hepatitis B immunisation, with the first dose given at birth (2). By the end of 2011, global coverage for hepatitis B vaccine in routine childhood vaccination schedules reached 180 countries (93%) (3). The vaccine induces antibodies to hepatitis B surface antigen (anti-HBs), and a titre of 10 mIU/mL or more is considered to be protective against HBV infection. With the introduction of universal infant vaccination programs in countries with a high prevalence of hepatitis B (e.g. Taiwan), universal hepatitis B vaccination programs have had a profound impact on reducing the incidence of chronic infection, dropping the HBsAg prevalence rate in children from 10% to 1% (4), and halving the incidence of HCC in children aged 6–14 years (5, 6).

## Target groups for vaccination in Australia

Target groups for adult vaccination in Australia are essentially the same groups in whom testing for evidence of chronic infection should be considered (see **Chapter 3**) (7). High-priority groups include:

- household, close and sexual contacts of people with chronic hepatitis B (CHB)
- Aboriginal and Torres Strait Islander people
- people from countries that have a high or intermediate prevalence of hepatitis B.

Other priority groups that should be offered testing and vaccination include men who have sex with men, people living with hepatitis C or human immunodeficiency virus (HIV), people who inject drugs, people in custodial settings and people in at-risk professions. A complete list of the groups that should be considered for vaccination is given in Table 5.1.

Transmission of HBV through blood transfusion and organ transplant has been almost entirely eliminated through the screening of blood and organ donors

**Table 5.1** Groups at risk of exposure or significant morbidity from exposure to HBV infection that should be targeted for vaccination

| The Australian National Immunisation program | People at higher risk of hepatitis B virus infection | People prone to exposure or at risk of significant morbidity from exposure | People at risk of occupational exposure |
|---|---|---|---|
| **1.** Infants – recommended as part of routine childhood immunisation and funded for children under the Immunise Australia Program. The first dose is given at birth, followed by another three doses at 2, 4 and 6 months of age<br>**2.** Adolescents – recommended for adolescents who have not yet received a primary course of hepatitis B vaccine | 1. Household, family and other close contacts of people with acute or chronic hepatitis B<br>2. Sexual contacts of people with hepatitis B<br>3. Migrants from hepatitis B-endemic countries<br>4. Men who have sex with men<br>5. Commercial sex workers<br>6. Aboriginal and Torres Strait Islander people<br>7. People who inject drugs<br>8. Inmates or staff of correctional facilities<br>9. People adopting a child from a country with high prevalence rates<br>10. Travellers to hepatitis B -endemic areas, either long-term or frequent travellers, and those likely to undertake exposure-prone activities<br>11. Vulnerable populations including the homeless and people with mental health issues | 1. Haemodialysis patients<br>2. People with clotting disorders and others who may need multiple blood or blood-product transfusions, especially if given overseas<br>3. HIV-positive and other immunosuppressed people<br>4. Transplant recipients<br>5. People with chronic liver disease or hepatitis C<br>6. Clients and staff of facilities for the intellectually disabled | 1. Health-care workers<br>2. People who have had accidental exposure (e.g. tattooists, body piercers, dentists)<br>3. People playing contact sport<br>4. Child-care workers<br>5. Embalmers<br>6. People working in accident and emergency services (e.g. paramedics, police, state emergency service, volunteer first aid givers – Red Cross, St John Ambulance) |
| As there are state and territory differences, primary care providers should check with their local health departments for information on which of these groups may be entitled to funded vaccination. | | | |
| See *The Australian Immunisation Handbook* for further information http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home | | | |

in Australia. However, there remains a small risk of exposure to HBV for patients with clotting disorders who receive blood-product concentrates.

The modes of transmission still relevant in Australia include:

- perinatal
- household contact
- sexual contact
- re-use of injecting or tattooing equipment
- occupational exposure.

In addition to screening blood donors, organ donors and health-care workers for HBV, the strategy to control HBV infection in Australia includes universal hepatitis B vaccination of neonates and the administration of hepatitis B immunoglobulin (HBIG) at birth to neonates born to HBsAg-positive mothers. In the Northern Territory, the hepatitis B vaccine has been routinely administered to Aboriginal and Torres Strait Islander newborns since 1988, and to all newborns since August 1990. The universal infant program began in 2000, with the first dose given at birth. Hepatitis B vaccination for all adolescents commenced in 1997 in some Australian states and territories, but has now been phased out because those immunised for hepatitis B in the infant program have reached adolescence. Non-immune adolescents should still be considered for vaccination, especially those aged 10–13 years who might have fallen through the gap between the introduction of universal infant and the adolescent programs, and susceptible teenage migrants.

**Table 5.2** Prevalence of chronic hepatitis B in Australia by risk group (8)

| Group | HBsAg prevalence in risk group (%) | Proportion of CHB in Australia (%) |
|---|---|---|
| People born in high or intermediate-prevalence countries | 2.4 (average)<br>3.6 (Asia and Pacific regions)<br>2.7 (Africa/Middle East)<br>1.0 (Europe) | 56 |
| Aboriginal and Torres Strait Islander people | 3.7 | 9 |
| People who inject drugs | 4 | 6 |
| Men who have sex with men | 3 | 4 |
| Non-indigenous Australian-born individuals* | 0.3 | 19 |
| Other or not stated | 1.0 | 6 |

*excluding those belonging to the other priority populations listed above
CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen

**Table 5.3** Vaccines available in Australia

| **Monovalent vaccines** | |
|---|---|
| **Trade name (formulation)** | **Dose of HBsAg protein and volume** |
| Engerix-B (adult formulation) | 20 µg in 1 mL |
| Engerix-B (paediatric formulation) | 10 µg in 0.5 mL |
| H-B-VAX II (adult formulation) | 10 µg in 1 mL |
| H-B-VAX II (paediatric formulation) | 5 µg in 0.5 mL |
| H-B-VAX II (dialysis formulation) | 40 µg in 1 mL |
| **Combinations containing hepatitis A vaccine** | |
| Twinrix Junior (360/10) | 10 µg in 0.5 mL |
| Twinrix (720/20) | 20 in 1 mL |
| **Combination vaccines used in infant vaccination or catch-up schedules** | |
| **Trade name (formulation)** | **Type of combination** |
| Infanrix HepB (paediatric) | diphtheria-tetanus-acellular pertussis-hepatitis B |
| Infanrix Hexa (paediatric) | diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine-*Haemophilus influenzae* type b |
| Infanrix Penta (paediatric) | diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine |
| HBsAg, hepatitis B surface antigen | |

## Recommendations for vaccination

The national recommendations for vaccinations are given in the latest edition of the *Australian Immunisation Handbook* (9). Table 5.3 summarises the vaccines available in Australia.

### Infants

It is recommended that all newborns receive hepatitis B vaccine within 24 hours of birth, followed by three further doses in infancy, at 2, 4 and 6 months of age. The first dose can be given at 6 weeks of age. If an infant did not receive the birth dose within 7 days of birth, no catch up of that dose is necessary; these infants only require a three-dose course of a hepatitis B-containing combination vaccine, given at 2, 4 and 6 months of age. There should be an interval of at least 8 weeks between doses two and three. The minimum age for administration of dose three is 24 weeks. The type of hepatitis B vaccine used differs between states and territories.

### Premature infants

Preterm babies do not respond as well as term babies to hepatitis B vaccine (10). For babies under 32 weeks gestation or less than 2,000 g birth weight, it is recommended to give the vaccine at 0 (within 24 hours of birth), and 2, 4 and 6 months of age and do one of the following:

- measure anti-HBs at 7 months of age and, if antibody titre is less than 10 mIU/mL, give a booster at 12 months of age
- give a booster at 12 months of age without measuring the antibody titre (9).

### Infants born to mothers positive for hepatitis B surface antigen with chronic hepatitis B

Infants born to HBsAg-positive mothers should be given HBIG (100 IU), preferably within 12 hours (or at most 48 hours) of birth, in addition to the birth dose of monovalent hepatitis B vaccine (9) (see **Chapter 10**). The doses should be given at the same time but in separate sites. Monovalent vaccine alone has been shown to be protective and should not be delayed; it is most effective given within 24 hours of birth. In all infants, HBsAg and anti-HBs should be measured at 9–12 months of age (i.e. 3–12 months after completing the course of primary vaccination). If the anti-HBs level is less than 10 mIU/mL, further testing for evidence of HBV infection is advised.

### Adolescents

It is recommended that adolescents not vaccinated in childhood receive hepatitis B vaccines (9). Two regimens are available:

- Three-dose regimen for adolescents aged up to 20 years: hepatitis B (paediatric formulation) – three doses of 0.5 mL. The optimal interval is 1 month between the first and second dose, and a third dose 5 months after the second dose.
- Two-dose regimen for adolescents aged 11–15 years: H-B-Vax II 10 µg (adult formulation) or Engerix-B 20 µg (adult formulation) at 0 and 4–6 months.

State and territory health authorities can provide further information on hepatitis B vaccine for this age group (see **Appendix 2**).

### Adults aged 20 years or over

Groups recommended for vaccination (after testing) are listed in Table 5.1.

Monovalent hepatitis B vaccine is usually given in a three-dose schedule, at 0, 1 and 6 month or 0, 2 and 4 month intervals. The minimum interval is 1 month between the first and second doses, 2 months between the second and third doses, and 4 months between the first and third doses. Special consideration is needed for immunocompromised individuals, who may require alternative dosing regimens.

### Accelerated vaccination schedules

Two products, Engerix-B (paediatric and adult) and Twinrix (720/20), are registered for use in accelerated schedules, which consist of four doses in total. Accelerated schedules should only be used if there is limited time before departure to endemic regions (Table 5.4).

**Table 5.4** Accelerated hepatitis B vaccination schedules

| Vaccine | Age | Dose (HBsAg protein) | Volume | Schedule |
|---|---|---|---|---|
| Engerix-B (paediatric) | Up to 20 years | 10 µg | 0.5 mL | 0, 1, 2 months; booster at 12 months |
| Engerix-B (adult)* | >20 years | 20 µg | 1.0 mL | 0, 7, 21 days; booster at 12 months or<br>0, 1, 2 months; booster at 12 months (preferred schedule) |
| Twinrix (720/20)* | >15 years | 20 µg | 1.0 mL | 0, 7, 21 days; booster at 12 months |

*If time permits, it is recommended that the 0, 1, 2 month schedule be used, because higher seroprotective rates are observed following this schedule than with a 0, 7, 21 day schedule; a booster dose at 12 months is recommended for long-term protection.

## Booster doses

Although vaccine-induced antibody levels decline with time and may eventually become undetectable, booster doses are not recommended in immunocompetent people after a primary course, because there is good evidence that a completed primary course of hepatitis B vaccination provides long-lasting protection. This recommendation includes health-care workers. Booster doses are recommended, however, for people who are immuno-compromised (e.g. those with HIV infection or renal failure).

## Hepatitis B testing before vaccination

Testing before vaccination is recommended for those at increased risk of infection (see **Chapter 3** and Table 5.2), including people born overseas in high or intermediate-prevalence countries, Aboriginal and Torres Strait Islander people, men who have sex with men, people who inject drugs, sex industry workers, immunocompromised people and people in custodial settings, or those who have been in such settings.

## Hepatitis B testing post vaccination

Infants born to HBsAg-positive mothers should be tested 3–12 months after the primary course of vaccination is completed. Testing for post-vaccination response 4 weeks after the primary course is also recommended for:

- health-care workers involved with exposure-prone procedures (see **Chapter 12**)
- those at risk of severe or complicated disease (e.g. immunosuppressed patients and patients with chronic liver disease)
- those expected to have a poor response to hepatitis B vaccine (e.g. haemodialysis patients)

- those at high risk of acquiring hepatitis B (e.g. contacts of those with CHB, people who inject drugs, sex industry workers, and those living in communities with high prevalence of hepatitis B).

## Adverse events following hepatitis B vaccination

Adverse events that can occur following hepatitis B vaccination include:

- soreness at the injection site (5%), fever (usually low grade, 2–3%), nausea, dizziness, malaise, myalgias and arthralgias. Fever can be expected in some neonates (0.6–3.7%).
- anaphylaxis has been reported in adults, but only rarely
- although various adverse events (e.g. demyelinating diseases, multiple sclerosis, Guillain-Barré syndrome and arthritis) have been reported, there is no evidence of a causal relationship with these events and hepatitis B vaccination (11, 12).

## Hepatitis B immunoglobulin

HBIG is prepared from pooled plasma from the blood bank, with samples selected on the basis of high levels of anti-HBs. Its use is recommended in infants born to HBsAg-positive mothers and to non-immune people exposed to blood of people with CHB infection.

HBIG should be given to the newborn within 12 hours of birth, or to adults not previously vaccinated within 72 hours of exposure, because efficacy diminishes with time from 48 hours after exposure.

The hepatitis B vaccine can be given at the same time as HBIG or within 7 days of exposure. Previous vaccination in the exposed adult should be verified by evidence of detectable anti-HBs. If the anti-HBs is undetectable, HBIG dose should be as follows:

- 100 IU children (<30 kg weight)
- 400 IU (>30 kg weight).

## Non-response or vaccination failure

A non-responder is a person who has a documented history of an age-appropriate primary course of hepatitis B vaccine, but has never achieved an anti-HBs level of over 10 mIU/mL. In such cases, HBsAg carriage should first be excluded as a cause of failure in vaccine non-responders. For those subjects who have not achieved adequate anti-HBs levels (≥10 mIU/mL) after the third dose of vaccine, a single booster dose (fourth dose) can be given, and anti-HBs checked 4 weeks later. If the anti-HBs level is over 10 mIU/mL the person can be regarded as immune. People who are non-responders after the fourth booster dose should be given two further doses at monthly intervals, followed by testing for response 4 weeks later. A few small studies have reported success with administration of high-dose formulations of double-dose administration for the fourth or subsequent doses. Persistent non-responders should be informed about the need for HBIG within 72 hours of parenteral exposure to HBV. The efficacy of intradermal routes of vaccine administration in non-responders remains unconvincing.

Vaccination failure may occur in people exposed to HBV variants with mutations

in the HBV surface gene (vaccine-induced escape mutant). Current hepatitis B vaccines are not effective in preventing infection with these mutants. Most such vaccine-induced escape mutants were initially reported in neonates through vertical transmission and in transplant recipients. These vaccine-induced escape mutants were responsible for most of the 3.4% vaccine failure rate reported in the Chinese adult population undergoing a hepatitis B vaccination program (13).

## Hepatitis B vaccination during pregnancy and breastfeeding

Hepatitis B vaccination during pregnancy is not routinely recommended. The vaccine can be given to susceptible pregnant women for whom it would otherwise be recommended, including for post-exposure prophylaxis in non-immune women exposed to a HBsAg-positive source (9). Vaccination is not contraindicated in breastfeeding, and breastfeeding in the vaccinated infant to a HBsAg-positive mother poses no additional risk of viral transmission, despite evidence of HBV in breast milk (14).

For further information about these recommendations, please refer to the latest edition of *The Australian Immunisation Handbook* (9).

## References


1. Kao JH, Hsu HM, Shau WY, Chang MH, Chen DS. Universal hepatitis B vaccination and the decreased mortality from fulminant hepatitis in infants in Taiwan. The Journal of Pediatrics. 2001;139(3):349–52.
2. Goldstein ST, Fiore AE. Toward the global elimination of hepatitis B virus transmission. The Journal of Pediatrics. 2001;139(3):343–5.
3. World Health Organization (WHO). Global routine vaccination coverage, 2011. Geneva: WHO, 2012.
4. Ni YH, Huang LM, Chang MH, Yen CJ, Lu CY, You SL, et al. Two decades of universal hepatitis B vaccination in taiwan: impact and implication for future strategies. Gastroenterology. 2007;132(4):1287–93.
5. O'Sullivan BG, Gidding HF, Law M, Kaldor JM, Gilbert GL, Dore GJ. Estimates of chronic hepatitis B virus infection in Australia, 2000. Australian and New Zealand Journal of Public Health. 2004;28(3):212–6.
6. Williams A. Reduction in the hepatitis B related burden of disease--measuring the success of universal immunisation programs. Communicable Diseases Intelligence. 2002;26(3):458–60.
7. National HBV Testing Policy Expert Reference Committee. National hepatitis B testing policy. Darlinghurst NSW: Australasian Society for HIV Medicine (ASHM), 2012.
8. MacLachlan JH, Allard N, Towell V, Cowie BC. The burden of chronic hepatitis B virus infection in Australia, 2011. Aust NZ J Public Health. 2013;37(5):416–22.
9. The Australian Immunisation Handbook. 10th ed: ATAGI, NHMRC, Department of Health and Ageing, Australian Government; 2013.
10. Saari TN, American Academy of Pediatrics Committee on Infectious D. Immunization of preterm and low birth weight infants. Pediatrics. 2003;112(1 Pt 1):193–8.
11. World Health Organization (WHO). The Global Advisory Committee on Vaccine Safety rejects association between hepatitis B vaccination and multiple sclerosis (MS), 2002.
12. Duclos P. Safety of immunisation and adverse events following vaccination against hepatitis B. Expert Opinion on Drug Safety. 2003;2(3):225–31.
13. He C, Nomura F, Itoga S, Isobe K, Nakai T. Prevalence of vaccine-induced escape mutants of hepatitis B virus in the adult population in China: a prospective study in 176 restaurant employees. Journal of Gastroenterology and Hepatology. 2001;16(12):1373–7.
14. Zheng Y, Lu Y, Ye Q, Xia Y, Zhou Y, Yao Q, et al. Should chronic hepatitis B mothers breastfeed? a meta analysis. BMC Public Health. 2011;11(1):502.

# CHAPTER 6: CLINICAL ASSESSMENT OF PATIENTS WITH HEPATITIS B VIRUS INFECTION


| | |
|---|---|
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**LINKS**

**Chapter 3:** Hepatitis B virus diagnosis and interpreting test results
**Chapter 4:** Natural history of hepatitis B virus infection
**Chapter 5:** Primary prevention of hepatitis B virus infection
**Chapter 7:** Treatment of chronic hepatitis B virus infection
**Chapter 9:** Hepatitis B related hepatocellular carcinoma
**Chapter 11:** Complex situations: Co-infection and immunosuppression

## KEY POINTS

- Determining the phase of hepatitis B virus (HBV) infection is essential to the clinical assessment of the patient with HBV.
- HBV DNA, liver function testing and fibrosis assessment (non-invasive liver imaging +/– biopsy) are all key components of this assessment.
- HBV DNA is an important parameter in informing treatment decision. Testing is Medicare rebatable for one test annually for monitoring and up to four tests annually for those on treatment.
- All patients should be evaluated for possible fibrosis. Non-invasive methods of assessing hepatic fibrosis, such as transient elastography (FibroScan®), are increasingly becoming available and being used.
- Normal alanine aminotransferase (ALT) ranges are being revised downwards (<19 for females and <30 for males), and normal liver function tests do not rule out significant hepatic disease.
- Transmission risks, lifestyle modification, cultural factors and long-term complications associated with chronic hepatitis B (CHB) infection are important components of patient education.
- When a person is diagnosed with hepatitis B, testing and assessment should be offered to their household and sexual contacts.
- All patients with CHB require regular monitoring for liver damage and disease progression.

## Initial assessment of patients with chronic hepatitis B virus infection

For a summary on acute hepatitis B virus (HBV) infection, see Figure 6.4 (at the end of this chapter).

### History and physical examination

The assessment of patients with chronic hepatitis B (CHB) should commence with a thorough clinical history and physical examination. Language interpreters are required when patients are not proficient in English. Aspects of the history that deserve close attention are:

- any risk factors for the acquisition of CHB; for example, ethnic background, family history of CHB and family history of hepatocellular carcinoma (HCC)
- host or viral factors that are associated with an increased risk of cirrhosis; for example, older age (longer duration of infection), heavy alcohol consumption, cigarette smoking, and co-infection with other viruses such as hepatitis C virus (HCV), hepatitis D virus (HDV) and human immunodeficiency virus (HIV).

The severity of the underlying liver disease should be clinically evaluated by examining for peripheral signs of chronic liver disease, hepatic encephalopathy, splenomegaly, ascites and peripheral oedema (1, 2).

Extrahepatic manifestations of CHB occur in 10–20% of patients, and effective antiviral therapy is pivotal in such patients. An example of such a manifestation is polyarteritis nodosa involving multiple organ systems, including the gastrointestinal tract (colitis), kidney (glomerulonephritis), neurological (neuropathy) and dermatological (vasculitic skin rashes, palpable purpura) systems. Conversely, about 50% of patients with polyarteritis nodosa are positive for hepatitis B surface antigen (HBsAg). Hepatitis B virus infection-associated glomerulonephritis usually presents with nephrotic range proteinuria, which may progress to renal failure in the absence of effective antiviral therapy (3).

### Laboratory investigations

Complete HBV serology – HBsAg, antibody to surface antigen (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), hepatitis B e antigen (HBeAg), antibody to hepatitis B e antigen (anti-HBe) (Table 6.1) – and measurement of HBV DNA level should be performed initially to evaluate HBV replication status (1). HBsAg is the first serological marker to appear, and its presence for more than 6 months indicates CHB infection. HBsAg appears in serum 4–10 weeks after exposure, preceding the onset of symptoms of acute hepatitis and alanine aminotransferase (ALT) elevation. HBsAg will become undetectable 4–6 months after acute exposure in those patients who achieve successful immune clearance (see **Chapter 3**) (1, 2, 4).

Anti-HBs indicates immunity to HBV when the antibody emerges following the disappearance of HBsAg. Anti-HBs usually persists for life, conferring long-term immunity (1, 2, 4).

HBcAg is only expressed in liver tissue and is therefore not used in routine clinical practice. Anti-HBc is a marker of exposure. Anti-HBc immunoglobulin M (IgM) is seen in high titres in acute HBV infection, and at lower levels in patients with CHB undergoing a flare in disease activity.

**Table 6.1** Tests used in the initial assessment of patients with chronic hepatitis B

| Test | Why the result is important |
|---|---|
| HBeAg / anti-HBe<br>HBV DNA | Quantify replication, identify phase of infection and consider treatment |
| HAV, HCV, HDV, +HIV serology | Ascertain co-infection, evidence of immunity to hepatitis A (need to offer vaccination) |
| LFTs | Necroinflammatory activity, synthetic function |
| FBC | Thrombocytopenia may indicate cirrhosis |
| PT, INR | Assessing the liver's synthetic function |
| Alpha fetoprotein | HCC |

anti-HBe, antibodies to envelope antigen; FBC, full blood count; HAV, hepatitis A virus; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; INR, international normalisation ratio; LFT, liver function test; PT, prothrombin time

HBeAg is considered a marker of HBV replication and infectivity. Seroconversion (i.e. loss of HBeAg and development of anti-HBe) often signals transition from an active phase (immune clearance) of the disease to an immune control phase (HBeAg negative, anti-HBe positive, low HBV DNA level). Patients can fluctuate between the active (HBeAg positive, anti-HBe negative, high HBV DNA level) and immune control phases of the disease over time. The absence of HBeAg, however, does not necessarily preclude active viral replication, since specific mutations in the HBV genome can prevent HBeAg synthesis – the so-called precore and core promoter mutants. Patients with these HBV mutants have elevated HBV DNA and ALT despite the absence of HBeAg (HBeAg-negative CHB). In Australia, the frequency of HBeAg-negative CHB is increasing, representing 20–40% of CHB infection (5).

HBV DNA level is a measure of viral replication, used as a criterion for commencing antiviral therapy in patients with CHB in conjunction with evidence of ongoing liver damage. In population studies, a HBV DNA level greater than 2,000 IU/mL was found to be a strong predictor of increased risk of cirrhosis and HCC (6). Results of HBV DNA levels were previously expressed as copies/mL, but the current standard is to convert them to international units (IU)/mL. The conversion factor ranges from 5.2 to 5.8, depending on the laboratory. Currently, most HBV DNA assays are based on real-time polymerase chain reaction (PCR), which provides increased sensitivity and greater dynamic range quantification than hybridisation assays. An earlier version of the hybridisation assay, used commonly until a few years ago, has a threshold of detection greater than 20,000 IU/mL (>141,500 copies/mL). Hence, the clinical status for some patients may need to be

reinterpreted using the results obtained with the newer assays. In particular, patients with HBeAg-negative CHB might be erroneously diagnosed as 'inactive' or being in the immune control phase, because of the inability of older assays to demonstrate viraemia below the assay detection threshold.

The threshold of HBV DNA level associated with liver disease is unknown. However, treatment is usually considered in HBeAg-positive patients with HBV DNA level of at least 20,000 IU/mL, and in HBeAg-negative patients with HBV DNA of at least 2,000 IU/mL (1, 2, 4). HBV DNA levels may fluctuate widely in CHB. More accurate assessment of the patient's clinical status requires serial measurements of HBV DNA.

Laboratory evaluation should also include an assessment of liver enzymes, hepatic synthetic function (including coagulation profile), and liver ultrasound and alpha fetoprotein estimation. A complete laboratory screen for other causes of liver dysfunction and testing for co-infection with other viruses (e.g. hepatitis C and D) is also recommended (1, 2, 4).

## Fibrosis assessment

### Liver biopsy

Liver biopsy should only be performed on the recommendation of a specialist clinician. It provides an accurate assessment of the degree of necroinflammatory activity and extent of hepatic fibrosis, and excludes other liver diseases. Such information can be vital in informing the need for antiviral therapy. The two histological features of liver biopsy used in the assessment of HBV are fibrosis (stage of disease) and necroinflammation (grade of disease). Liver fibrosis is usually graded from 0 to 4 (1=limited portal fibrosis; 2=periportal fibrosis; 3=septal fibrosis linking portal tracts or central vein; and 4=cirrhosis with development of nodules and thick fibrous septa). Liver biopsy may be performed percutaneously or – in those with ascites or significant coagulopathy – via the transjugular route. It has been the gold-standard investigation for determining the stage of fibrosis or liver disease. A number of different scoring systems have been developed to stage fibrosis and grade inflammation. Prominent among these are the Scheuer Score, Histological Activity Index (HAI), the Ishak modified HAI and the METAVIR system, which is used mainly for hepatitis C (7-9).

The development of significant fibrosis (stage 2 or greater) implies progressive disease and the need for treatment. Inflammation is graded using necroinflammatory scores.

Liver biopsy has a number of disadvantages. It is an invasive, uncomfortable, costly and time-consuming procedure that carries a small but significant risk of complications. For these reasons, some patients are unwilling to undergo the procedure. Liver biopsy also suffers from sampling bias, because scarring and necroinflammation may be heterogeneously distributed in the liver. The absolute requirement for a biopsy before commencing treatment was removed by the Pharmaceutical Benefits Advisory Committee (PBAC) in November 2011. However, in some patients, biopsy remains the best investigation

for determining the true nature of the liver disease, especially in patients with co-morbidities associated with liver injury (e.g. obesity, alcohol use disorders and iron storage disorders). The unique value of biopsy needs to be carefully explained to patients.

### Non-invasive assessment of hepatic fibrosis

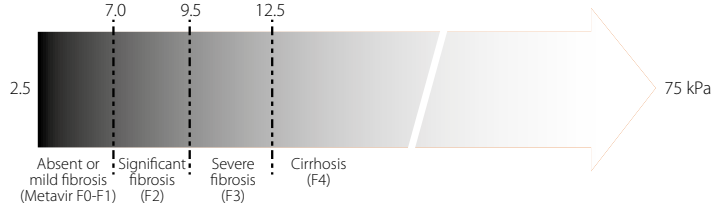
Non-invasive measures of hepatic fibrosis are increasingly becoming available; the most commonly used being transient elastography (TE) or FibroScan®. This uses ultrasound elastography to measure liver stiffness. Shear waves are generated and measured in kPa, which correlate with fibrosis score as determined by biopsy. Cut-offs are given that can accurately place the patient in different stages of fibrosis (Figure 6.1). A meta-analysis of the use of TE in CHB found that it performed well in detecting cirrhosis (sensitivity 85% and specificity 82%), but was less specific at detecting severe fibrosis (sensitivity 74% and specificity 64%). (10). Some international consensus guidelines have begun to include TE as an acceptable alternative to biopsy for fibrosis staging (11). Currently, FibroScan® is available through liver and hepatitis clinics, but its availability in other settings is likely to increase. There is no Medicare rebate for these services, and access is usually offered as part of a specialist review.

A number of other means of assessing fibrosis non-invasively have been reported; they include acoustic radiation force impulse, magnetic resonance imaging (MRI)-based elastography and serum blood algorithms, such as those used to derive the Fibrotest and hepascore results. These methods are not routinely available in Australia at present. Further research into non-invasive assessment of hepatic fibrosis is required.

## Determining the need for treatment

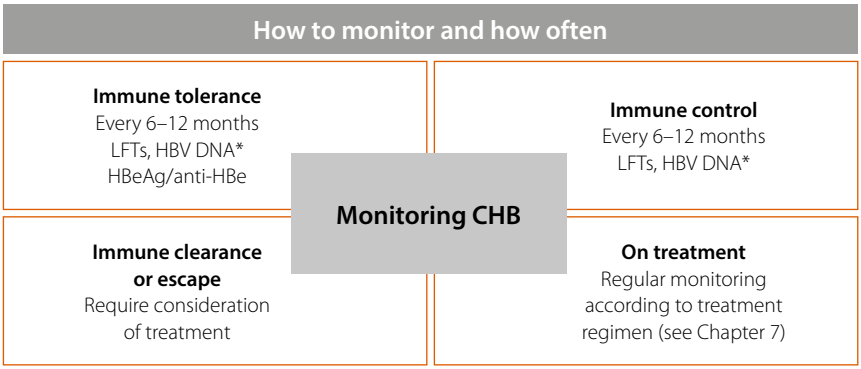
The need for treatment is based on assessment of HBV DNA and liver function tests (to determine the phase of infection), and assessment of fibrosis. Candidates for treatment are those in the immune clearance and escape phases, and all patients with cirrhosis. Pharmaceutical Benefits Scheme (PBS) criteria for initiating therapy are given in Table 7.2 (**Chapter 7**). All patients with CHB require some form of monitoring, the frequency of which is determined by their clinical state (Figure 6.2).

**Figure 6.1** FibroScan® suggested cut-off




Adapted with permission from: Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. Journal of Hepatology. 2008;48(50):835-847.

**Figure 6.2** Monitoring patients with CHB




*HBV DNA only Medicare rebatable once/year in patients not on treatment, 4 times/year on antiviral treatment

anti-HBe, antibodies to envelope antigen; CHB, chronic hepatitis B; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; LFT, liver function test

Monitoring for those not on treatment consists of liver function tests 6-monthly and HBV DNA annually (Medicare rebatable once per 12 months). The monitoring is needed to determine if and when the disease phase has changed and when treatment may be indicated.

## Management of patients with chronic hepatitis B virus infection

CHB can be a life-long disease, and it is important to counsel patients as carefully as possible about the disease, the risks of transmission, and the role of therapy and its limitations. The epidemiology of CHB indicates that most patients will come from culturally and linguistically diverse (CALD) backgrounds. Aboriginal and Torres Strait Islander people also have a high prevalence of CHB. It is important to ensure that counselling patients about CHB is done in a culturally appropriate and safe manner. Health practitioners need to be sensitive about the cultural beliefs of specific patient groups, and aware of the implications of a diagnosis of CHB in various patient populations. When there are language barriers, an accredited interpreter is essential to ensure that information is properly understood and that the patient has an opportunity to ask questions. Family members can be of great support to the patient, but should never be used in place of a qualified interpreter. The Translating and Interpreting Service (TIS) has a number of services, including the Doctors' Priority Line 1300 131 450 (which is freely available, 24 hours/7 days). For more information on TIS, and links to HBV information packages in other languages, see **Appendix 2**.

Various lifestyle issues need to be addressed: alcohol consumption should be avoided or minimised, and cigarette smokers or cannabis users should be strongly encouraged to quit. Weight reduction should be encouraged for those who are overweight or obese

(based on body mass index), and sound nutritional advice should be provided. Vaccination and transmission issues should be addressed (see **Chapter 5**).

All patients should understand the aims of treatment (with the assistance of language interpreters where necessary), namely:

- to achieve prolonged suppression of HBV replication
- to arrest (or reverse) the progression of liver damage, with the ultimate goal of preventing cirrhosis, HCC and liver failure.

Patients need to have an understanding of the key factors, including the role of liver biopsy, that influence the decision to commence treatment. Figure 6.3 provides some examples of when to seek urgent advice or referral.

**Figure 6.3** Critical situations and the need for referral

**Severe acute exacerbation (or acute HBV)**

- Potential for fulminant disease – how to recognise/react
- Read more on natural history of ACUTE HBV in Chapter 4.

**Reactivation during immunosuppression/chemotherapy**

- One situation where urgent antiviral therapy required
- Read more on immunosuppression in Chapter 11.

**Cirrhosis (especially where suggestion of decompensation)**

- Needs immediate discussion, triage prioritisation with specialist service

**Possible HCC found on surveillance**

- Read more on hepatocellular carcinoma in Chapter 9.

This list provides some examples of when to seek urgent advice and/or referral.

**Identifying a patient with cirrhosis**

The following may be indicators of advanced disease, and referral should be considered:

- low or borderline-low albumin level for age and gender
- low platelet count
- reversed ratio of ALT and aspartate aminotransferase (AST)
- elevated prothrombin time
- reverse portal flow on ultrasound
- firm nodular liver edge
- splenomegaly
- stigmata of chronic liver disease (e.g. spider naevi, caput medusae, Dupuytren's contractures).

Remember, patients with advanced disease may have normal liver function test results.

## Screening for hepatocellular carcinoma

An important element in the assessment of a patient with CHB is HCC screening; this is recommended for patients with CHB who are at high risk of HCC (Table 6.2). Screening is recommended every 6 months, using ultrasound and alpha fetoprotein estimation (1, 2, 4, 12).

The incidence of HCC is lower in patients receiving nucleos(t)ide analogues (based mainly on data from treatment with lamivudine or adefovir) or interferon than in untreated patients, even in those without cirrhosis (5, 6). However, screening for HCC needs to continue, regardless of treatment outcome, because the risk is not completely eliminated.

**Table 6.2** Recommended screening for hepatocellular carcinoma (HCC) screening in patients with chronic hepatitis B

| **Ongoing surveillance, including 6-monthly ultrasound (US) tests and alpha fetoprotein (AFP) level tests, is recommended for the following patients with CHB.** |
|---|
| • Any patient with cirrhosis |
| • Asian men over 40 years of age |
| • Asian women over 50 years of age |
| • African people over 20 years of age |
| • Aboriginal and Torres Strait Islander people over 50 years of age |
| • those with a family history of HCC. |

**Figure 6.4** Acute hepatitis B virus (HBV) infection

The incidence of acute HBV infection has been decreasing in Western countries for a number of years, due to widespread vaccination and routine blood testing. Acute HBV infection is characterised by the onset of symptoms 1–4 months after exposure. A serum sickness-like syndrome may occur, followed by an illness characterised by anorexia, nausea, jaundice and right upper quadrant pain. Symptoms usually disappear after 1–3 months, but some patients have prolonged fatigue even after liver function tests have normalised.

Elevated ALT/AST with values up to 1,000–2,000 IU/L are characteristic of acute HBV. Prothrombin time is the best guide to prognosis. In the early phase of infection, HBsAg, anti-HBc IgM and HBeAg are all positive. The disappearance of HBsAg is usually followed by the appearance of anti-HBs. However, the appearance of this antibody may be delayed, creating a window period where the diagnosis of recent HBV infection can only be made by the detection of anti-HBc IgM.

A small proportion of patients (0.1–0.5%) will develop fulminant hepatic failure, believed to be caused by massive immune-mediated lysis of infected hepatocytes. Such patients may have no evidence of active viral replication at the time of presentation.

The management of acute HBV is symptomatic care. Bed rest and nutritional support are central. Anti-nausea medications may be of benefit, and limited doses of paracetamol (<2 g/day) or codeine may be cautiously administered for abdominal pain or fevers. Since most patients recover, antiviral therapy is not generally recommended. However, case reports and results from a small series of patients suggest some benefits of early therapy. Current recommendations support the use of nucleos(t)ide analogues at the first sign of severe liver injury or impending hepatic failure. Patients should be monitored regularly with laboratory tests during the acute phase of their illness, and referred for specialist review if they have a prolonged prothrombin time, elevated serum bilirubin concentration, and signs of encephalopathy, or if the illness is uncharacteristically lengthy. Continued serological assessment following recovery from the icteric illness is important to identify the small proportion of patients who develop CHB.

ALT, alanine aminotransferase; anti-HBc, antibodies to core antigen; anti-HBs, antibodies to surface antigen; AST, aspartate aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IgM, immunoglobulin; IU, international units

## Conclusion

The assessment of patients with CHB infection is complex because it requires an intimate knowledge of the natural history of the disease. Current understanding of CHB has improved dramatically, and new therapeutic agents have altered the management of patients in recent years. Treatment paradigms of CHB are constantly changing. Primary-care doctors will need to keep abreast of these developments to properly advise their patients of the most appropriate management plan. Imparting current knowledge is particularly relevant because the current migration patterns suggest that the prevalence of disease in Australia will continue to increase.

## References


1. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009;50(3):661–2.
2. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. Journal of Hepatology. 2012;57(1):167–85.
3. Yi Z, Jie YW, Nan Z. The efficacy of anti-viral therapy on hepatitis B virus-associated glomerulonephritis: A systematic review and meta-analysis. Annals of Hepatology. 2011;10(2):165–73.
4. GESA. Clinical Update: Chronic Hepatitis B (CHB) Recommendations – Summary and Algorithm: Gastroenterological Society of Australia, 2010.
5. McMahon BJ. Epidemiology and natural history of hepatitis B. Seminars in Liver Disease. 2005;25:3–8.
6. Sung JJ, Tsoi KK, Wong VW, Li KC, Chan HL. Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. Alimentary Pharmacology & Therapeutics. 2008;28(9):1067–77.
7. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. Journal of Hepatology. 1995;22(6):696–9.
8. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. Hepatology. 1996;24(2):289–93.
9. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The Lancet. 1997;349(9055):825–32.
10. Chon YE, Choi EH, Song KJ, Park JY, Kim do Y, Han KH, et al. Performance of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B: a meta-analysis. PLoS One. 2012;7(9):e44930.
11. Liaw YF, Omata M. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatol Int. 2012;Hepatol Int(6):531–61.
12. Wong GL, Chan HL, Tse YK, Chan HY, Tse CH, Lo AO, et al. On-treatment alpha-fetoprotein is a specific tumor marker for hepatocellular carcinoma in patients with chronic hepatitis B receiving entecavir. Hepatology. 2014;59(3):986–95.

# CHAPTER 7: TREATMENT OF CHRONIC HEPATITIS B INFECTION


| | |
|---|---|
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**LINKS**

**Chapter 4:** Natural history of chronic hepatitis B virus infection
**Chapter 6:** Clinical assessment of patients with hepatitis B virus infection
**Chapter 8:** Managing patients with advanced liver disease
**Chapter 10:** Managing hepatitis B virus infection in pregnancy and children

## KEY POINTS

- Patients in the immune clearance and immune-escape phase of infection should be considered for antiviral therapy. Treatment is indicated for those with any of the following:
  - high hepatitis B virus (HBV) DNA
  - elevated alanine aminotransferase levels or evidence of inflammation
  - fibrosis on liver biopsy or marked fibrosis on FibroScan®.
- All patients with cirrhosis are candidates for treatment.
- Patient and doctor attention to the issue of adherence by patient is critical for the success of therapy.
- Entecavir and tenofovir are first-line treatment options for oral antiviral therapy.
- Pegylated interferon is an alternative option in some patients.

## Goals of therapy

The goal of therapy is to prevent, halt or even reverse the progression of liver injury towards cirrhosis, liver decomposition and liver cancer, which are the major causes of death in older patients with hepatitis B virus (HBV) infection (1). This is achieved by controlling viral replication, either with direct acting anti-viral therapy or indirectly using interferon (IFN) to stimulate immune control. Control of viral replication reverses decompensated liver disease and reduces the risk of hepatocellular cancer (2, 3). The challenge for the clinician is to determine the phase of infection and anticipated natural history for an individual patient, so that therapy can be tailored to those likely to benefit. The phase of infection can be determined using the standard narrative (see **Chapter 4**). In communicating information to patients about their treatment choices for hepatitis B, language, literacy and culture are important considerations. Patient resources are available to aid communication; for example, the *hepatitis B bear*, or the *Hepatitis B story* (see **Appendix 1** and **Appendix 2** for patient factsheets and other resources).

**Aims of treatment**

- Limit liver damage due to immune-mediated inflammation and fibrosis.
- Achieve sustained suppression of viral replication.
- Achieve clearance (hepatitis B surface antigen [HBsAg] seroconversion) – rare.
- Reduce risk of progression to cirrhosis and hepatocellular carcinoma.
- Reduce morbidity and mortality.
- Minimise toxicity, minimise resistance, maximise adherence.

## Indications for antiviral therapy

The decision to commence antiviral therapy is based on a number of factors, including the patient's age, serum HBV DNA concentration, extent of hepatic fibrosis, alanine transaminase (ALT) levels, hepatitis B e antigen (HBeAg) status and the risk of hepatocellular carcinoma (HCC). Barriers to treatment adherence need to be considered (Table 7.1), because liver damage can be worsened by stopping and starting treatment. Many guidelines are available on this subject, but there are no absolute rules (4). A recent review summarises the variance in international consensus guidelines for treatment initiation and the art of decision making in the clinic (5). Previously, a liver biopsy demonstrating necroinflammation consistent with chronic hepatitis B (CHB) was a necessary prerequisite for reimbursed access to antiviral therapy in Australia. A liver biopsy is no longer mandatory for reimbursement; however, in some settings, it may still have a role in decision making. Non-invasive techniques to indirectly measure the extent of liver fibrosis may be used to assist decision making in the absence of liver biopsy (6, 7) (see **Chapter 6**).

There are two main classes of therapy for CHB:

- direct antiviral agents, which inhibit the function of the viral polymerase and thus prevent viral replication
- the IFNs, which are synthetic cytokines that act via multiple different intracellular biological pathways to eradicate viral infection.

**Table 7.1** Potential barriers to treatment adherence (8, 9)

| | |
|---|---|
| **The patient** | Understanding of disease or reason for antiviral treatment<br>Cultural health beliefs, literacy or health literacy<br>Competing priorities (e.g. health, employment and family issues)<br>Other social issues (e.g. substance use, poverty and housing)<br>Distance, time and cost to attend appointments (including lost work time) |
| **Doctor–patient interaction** | Poor communication, including inadequate use of culturally appropriate resources or interpretation services (or both) when needed<br>Failure to appreciate barriers to adherence, and to employ strategies and appropriate one-to-one education |
| **Health system** | Geographical and system barriers to treatment access, including specialist availability, local availability of antiviral therapy for ongoing supply, hospital outpatient waiting lists and outpatient appointment waiting time |
| **Nature of disease** | Hepatitis B is asymptomatic<br>People feel well, so may discontinue treatment<br>Long-term therapy leads to treatment fatigue |

In practical terms, once the decision to commence antiviral therapy has been made, the physician should choose one of the three agents that are currently approved by the Australian Government's Therapeutic Goods Administration (TGA) and reimbursed under the Pharmaceutical Benefits Scheme (PBS) for the initial treatment of CHB in Australia. These agents are pegylated IFN (PEG-IFN) alfa-2a (180 µg/week), tenofovir (300 mg/day) and entecavir (0.5 mg/day) (Table 7.2). Several other oral agents – including lamivudine, adefovir and telbivudine – have been registered for the treatment of CHB, but are not preferred due to inferior potency or inferior barrier to resistance.

When choosing the most appropriate anti-HBV therapy, it is important to consider the advantages and disadvantages of each treatment option. The choice of therapy must take into account the drug's efficacy, safety, chance of achieving desired endpoints, anticipated duration of therapy and the likelihood of developing resistance.

## Who should be considered for therapy?

### Hepatitis B e antigen (HBeAg) positive patients

Patients who are positive for HBeAg should be considered for antiviral therapy if they also have elevated serum ALT (i.e. >30 IU/L for males and >19 IU/L for females) that is persistent (i.e. 3–6 months without an alternative cause), and a serum HBV DNA level of greater than 20,000 IU/mL (10). In contrast, those with a persistently normal ALT level are often in the immune tolerance phase of their illness, and treatment is usually not of benefit.

**Table 7.2** Treatment indications and recommended antiviral agents for patients with chronic hepatitis B

| Patients to be considered for therapy | PBS-listed indications *CHB in a patient who has:* | First-line therapies | PBS streamlined codes[a] |
|---|---|---|---|
| **HBeAg-positive patients**<br>• Persistent (at least 3–6 months) elevated ALT‡<br>• HBV DNA >20,000 IU/mL | Elevated HBV DNA levels[(1)] and evidence of chronic liver injury[(2)] | **Tenofovir** Tablet 300 mg **OR** **Entecavir** Tablet 0.5 mg | 4489 |
| **HBeAg-negative patients**<br>• HBV DNA >2,000 IU/mL WITH<br>• Persistent (at least 3–6 months) elevated ALT‡<br>or<br>• evidence of accumulated liver damage (e.g. fibrosis, or moderate to severe inflammation) | | | 3961 |
| **Patients with advanced fibrosis or cirrhosis**, irrespective of ALT (e.g. Schueur score of 3) or 4 on biopsy, or FibroScan >~10k Pa | Cirrhosis and detectable HBV DNA | **Tenofovir** Tablet 300 mg **OR** **Entecavir** Tablet 0.5 mg | 4476 |
| | | | 3962 |
| | Failed HBV therapy and has cirrhosis and detectable HBV DNA | **Tenofovir** Tablet 300 mg | 4510 |
| | Failed HBV therapy and has evidence of treatment failure[(3)] | | 4490 |
| | Failed lamivudine and has cirrhosis and detectable HBV DNA | **Entecavir** Tablet 1.0 mg | 3966 |
| | Failed lamivudine and has evidence of treatment failure[(3)] | | 3964 |

‡ **Note: Elevated ALT**

'Elevated' serum ALT varies between guidelines, but would usually be considered as >2 × ULN ALT ULN for men >30 ALT ULN for women >19

(1) >20,000 IU/mL (100,000 copies/mL) if HBeAg positive, or >2,000 IU/mL (10,000 copies/mL) if HBeAg negative

(2) As determined by: (a) confirmed elevated serum ALT; or (b) liver biopsy

(3) (a) Repeatedly elevated serum ALT levels while on concurrent antihepadnaviral therapy of ≥6 months duration in conjunction with documented chronic hepatitis B infection; or (b) Repeatedly elevated HBV DNA levels one log greater than the nadir value or failure to achieve a 1 log reduction in HBV DNA within 3 months, while on previous antihepadnaviral therapy except in patients with evidence of poor compliance.

All persons with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin <30 g/L, bilirubin >30 µmol/L) should have their treatment discussed with a transplant unit before therapy is started.

[a] **PBS Streamlined codes – GP HBV s100 prescribers accredited to prescribe by their state or territory through the public hospital system can use streamlined codes.** The streamlined authority process is designed to reduce the administrative burden on prescribers, because it removes the need for prior telephone or written approval from the DHS or the DVA to prescribe some PBS Authority required items. To prescribe a streamlined authority item, a prescriber is required to include a 'streamlined authority code' on the authority prescription. Streamlined codes may be updated from time to time, see www.pbs.gov.au/info/browse/publications. For information on general practitioner prescribing see www.ashm.org.au

ALT, alanine aminotransferase; CHB, chronic hepatitis B; DHS, Australian Government Department of Human Services; DVA, Australian Government Department of Veterans' Affairs; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IU, international unit; PBS, Pharmaceutical Benefits Scheme; ULN, upper limit of normal

Patients in the immune tolerance phase should be monitored every 6 months, to identify when they shift from the immune tolerance phase to the immune clearance phase of the disease, at which point treatment would be considered.

Older patients with significant viraemia but only mildly elevated ALT levels may have significant liver injury from a prior phase of CHB (11). A liver biopsy or other assessment of liver fibrosis (e.g. transient elastography) will assist in determining the need for therapy. Patients with advanced fibrosis or cirrhosis, irrespective of ALT (e.g. a Schueur score of 3 or 4 on biopsy, or a FibroScan® of >~10 kPa or equivalent) should be considered for antiviral therapy (see **Chapter 8**).

### Hepatitis B e antigen (HBeAg) negative patients

Patients who are HBeAg negative and are thus in the immune escape phase of infection are often older, with ALT levels and serum HBV DNA levels lower than in patients with HBeAg-positive CHB. Nevertheless, the former are at greater risk of liver injury and worse outcomes than younger patients with HBeAg-positive disease. It is therefore recommended that the threshold serum HBV DNA level for initiating antiviral therapy should be 2,000 IU/mL, in combination with either an elevated ALT, or evidence of accumulated significant liver damage (e.g. fibrosis, or moderate or severe inflammation), or both (12). Assessment by an invasive technique (liver biopsy) or a non-invasive technique (elastography) can greatly assist decision making. In general, other recommendations for therapy in HBeAg-negative patients are similar to those for HBeAg-positive disease.

### Women of child-bearing age

Female patients interested in starting a family should consider the safety profile of various treatment options, and restricted access to treatment under PBS Section 100 criteria. Management decisions for patients initiated on treatment who later fall pregnant must be individualised. The abundant safety data for lamivudine and tenofovir in HIV-treated patients may facilitate a discussion on the risks and benefits of treatment; this discussion should also include the possibility of a flare of disease activity during pregnancy, and the likelihood of vertical transmission despite immunoprophylaxis in pregnant women with a viral load of more than 7 log10 IU/mL (11). There is limited data on the safety of entecavir in pregnancy, and its use is not recommended. Initiating a patient prior to family planning with PEG-IFN could be an alternative option because this treatment is limited to a defined duration.

## Therapeutic options

### Interferons

The use of conventional IFN has been supplanted by the use of PEG-IFN, which has the advantage of weekly dosing and (probably) of improved efficacy. The recommended standard dosing of PEG-IFN alfa-2a is 180 µg, given weekly for 48 weeks. The side effects are similar to conventional IFN (e.g. influenza-like symptoms, fatigue, leukopenia, irritability, sleep disturbance and depression), but are neither universal nor easy to predict. In HBeAg-positive patients, HBe seroconversion occurred in 32% of patients up to 6 months after the end of treatment. Baseline predictors of

response include genotype A infection, lower HBV DNA (<9 log copies/mL) and higher ALT levels (>2 × ULN). A small but significant proportion of patients treated with IFN also achieve hepatitis B surface antigen (HBsAg) seroconversion. This is seen particularly in genotype A, and is uncommon in Asian patients. Genotype D HBV patients have the lowest response rates to PEG-IFN therapy. Given the expense and side-effect profile of IFNs, it would be helpful to identify non-responders early, although rules for stopping IFN have not been clearly established. Failure to suppress the virus by 6 months is usually indicative of non-response, and treatment may be discontinued. A change in HBsAg titres has been suggested as a useful predictor of response, but the test is not widely available in Australia, and its applicability across different genotypes requires further evaluation (13, 14).

PEG-IFN also has a role in the treatment of HBeAg-negative patients. Sustained control of viral replication (<2,000 IU/mL) is seen in 20% of patients after completion of therapy (15). Control of viral loads to these levels should reduce progression to clinically significant liver disease.

The main advantage of PEG-IFN is the fixed duration of therapy (which is particularly attractive to younger patients), and the chance for HBsAg seroconversion. The main disadvantage is the side-effect profile. Flares of viral hepatitis resulting from enhanced immune clearance can be seen in up to 18% of patients, and can be severe in those with advanced underlying liver disease. IFNs are contraindicated in patients with decompensated cirrhosis.

PEG-IFN is generally contraindicated in pregnancy and breastfeeding (see **Chapter 10**).

**Treatment options**

- Direct antiviral agents can be chosen according to their potency, their side effects and the chance of resistance. For treatment-naive patients, entecavir or tenofovir is the best currently available antiviral therapy. For lamivudine-resistant patients, tenofovir added to lamivudine therapy is most effective.
- Pegylated interferon has a different mechanism but comparable efficacy to antiviral agents, with the disadvantage of increased side effects and the advantage of a shorter, fixed-duration therapy without drug resistance. Interferon is not the best choice in patients with cirrhosis.
- Therapy should be individualised.

## Antiviral therapy

Long-lasting, treatment-maintained suppression of HBV DNA without resistance is achievable in most patients by entecavir or tenofovir. A sustained off-treatment response is uncommon, and long-term therapy should be anticipated (16), particularly in patients in the HBeAg-negative phase of infection.

### *Entecavir*

Entecavir, a purine-derived nucleoside analogue, is a highly effective inhibitor of viral replication. Long-term (at least 3 years) entecavir therapy appears to result in the reversal of fibrosis and cirrhosis, and continued improvement in liver histology (17). It has few side effects, the most common being headache (2–4%) and fatigue (1–3%). The rate of

HBeAg clearance with entecavir is similar to that seen with other antiviral agents. Entecavir is recommended at a dose of 0.5 mg for treatment-naive subjects. HBV drug resistance in that clinical scenario is extremely uncommon; it was reported in only 1.2% of cases after 5 years of study. Entecavir is not the best choice of therapy for patients with established lamivudine resistance. Even with a higher dose (1.0 mg daily), 50% of such patients develop entecavir resistance in 5 years. This is due to partial cross-resistance between lamivudine and entecavir.

Entecavir is contraindicated in pregnancy and thus is not a good choice in young women who might be planning to or may accidentally become pregnant.

Entecavir absorption is affected by food, and it should be taken on an empty stomach 2 hours before or after a meal. This food requirement should be discussed with the patient before therapy is started.

***Tenofovir disproxil fumarate***

Tenofovir disoproxil fumarate (TDF, tenofovir), like adefovir, is an acyclic adenine nucleotide with potent activity against HBV. It has been used extensively in the treatment of human immunodeficiency virus (HIV) infection. The recommended dose of tenofovir is 300 mg daily. No patient included in the initial registration trial has developed tenofovir resistance after 5 years of follow up (18). Nephrotoxicity, including Fanconi Syndrome, has been reported in patients receiving tenofovir, although is much less common than in the setting of HIV (19) (17). The risk of renal toxicity is low; however, on treatment, monitoring of renal function (estimated glomerular filtration rate, eGFR) and serum phosphate concentration is important to avoid progressive renal injury. Tenofovir is the agent of choice for patients with lamivudine resistance, because lamivudine and tenofovir have different mutational pathways to resistance. Although adefovir and tenofovir have similar pathways to resistance, the latter is highly effective in patients with prior adefovir resistance, with 60–90% of patients receiving tenofovir having undetectable HBV DNA after 1 year of therapy (20).

## Other agents and combinations

Lamivudine, adefovir and telbivudine are no longer recommended as first-line therapies in Australia; however, they may still be widely prescribed in lower-middle income countries.

Lamivudine was the first antiviral agent made available for the treatment of CHB in Australia. It is an oral nucleoside analogue, well tolerated and without significant side effects. It produced substantial early inhibition of viral replication in most patients which resulted in improved liver histology, and improved liver function in decompensated cirrhosis. Unfortunately prolonged therapy with lamivudine resulted in high rates of viral resistance occurring in 14–32% of patients after 1 year of therapy, and 60–70% of patients after 5 years of therapy (21).

Adefovir is an acyclic nucleotide analogue and an effective antiviral agent. The recommended dose of 10 mg restricted adefovir's antiviral potency, but nephrotoxicity at higher doses was a limiting factor. In the United States, adefovir

was made available for first-line therapy; however, its role in Australia as guided by PBS reimbursements was limited to the treatment of lamivudine resistance. Initially adefovir was used as monotherapy in patients with lamivudine resistance, but the development of resistance to adefovir was common in this situation and it quickly became apparent that combination therapy provided much better control of viral replication (22). Adefovir has largely been replaced by tenofovir due to the latter's superior antiviral activity.

Telbivudine is also a highly effective antiviral agent, but its utility is limited by the rather rapid emergence of resistance variants of HBV (30% in 3 years). A specific side effect of telbivudine is myopathy, and patients on treatment should be monitored for muscle symptoms. Telbivudine has a pregnancy category B listing.

For patients naive to therapy, it might be predicted that dual direct antiviral therapy might be superior to single agent therapy (as is the case for HIV), although to date no benefit has been demonstrated (23). Combining IFN with direct acting antiviral therapy has also not been shown to be superior although studies in this area are ongoing.

In summary, both nucleos(t)ide analogues and PEG-IFN can be prescribed as first-line treatment options for CHB. However, PEG-IFN should only be considered for patients with a high chance of response based on pretreatment and on-treatment factors.

In patients on antiviral agents, a rising ALT or HBV DNA level may indicate viral resistance or non-adherence. In patients on older antiviral agents, a switch to one of the new agents or the addition of a new agent to the original drug must be undertaken.

## Monitoring patients on antiviral therapy

While on therapy, patients should be monitored regularly to document virological response to treatment, detect adverse events early in their evolution, identify the emergence of viral resistance and encourage adherence. Monitoring of patients should be more frequent in patients treated with PEG-IFN compared to oral agents, because of the risk of bone marrow suppression, neuropsychological side effects and other complications of IFN-based therapies. For patients treated with PEG-IFN, frequent monitoring is recommended until treatment dose is stabilised. Patients can then reduce the frequency of their visits to every 4–6 weeks. Particular attention should be paid to the full blood count, white cell count differential and platelet count at each visit, and dosing adjusted as needed.

In patients on direct antiviral therapies, baseline assessment should include renal measures, particularly assessment for proteinuria, eGFR and (if tenofovir therapy is planned) fasting serum phosphate level. On-treatment monitoring is recommended 3-monthly for the first year. Full blood count, liver and renal function (and fasting serum phosphate for patients on tenofovir) and HBV serology (for patients who are HBeAg positive) and HBV DNA is recommended. Dose adjustments may be required, depending on renal

dysfunction. After the first year, or when complete virological control has been achieved, 6-monthly monitoring is reasonable with entecavir and tenofovir, given their low rates of drug resistance in pivotal studies and in the clinical situation (24). One risk of such infrequent monitoring is reduced adherence to therapy. Shared attention to the issue of adherence by patient, specialist and general practitioner is critical for the success of therapy.

**Monitoring on treatment**

- Regular monitoring is required to identify virological response, resistance and hepatitis flares, and to encourage adherence.

| Pegylated interferon | Direct antiviral therapies |
|---|---|
| ▸ Frequent monitoring until treatment dose stabilised, then every 4–6 weeks. Particular attention: FBC, white cell count differential and platelet count at each visit; adjust dosing as necessary. | ▸ Three-monthly for the first year, then 6-monthly. FBC, liver and renal function (and fasting serum phosphate for those on TDF) and HBV serology (for HBeAg positive) and HBV DNA is recommended. |

FBC, full blood count; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; TDF, tenofovir

## Treatment related side effects

The safety profile of oral agents is similar to that of placebo. As mentioned previously, entecavir is well tolerated, with negligible side effects. There have been reports of nephrotoxicity and Fanconi Syndrome developing in patients on tenofovir therapy, although the risk of renal injury is low and can be managed with routine monitoring (as described) plus dose adjustments when required.

In contrast, IFNs have many side effects. Anecdotally, IFN seems better tolerated in patients receiving treatment for HBV compared to those with hepatitis C virus infection. Despite this observation, patients taking IFN may experience many different side effects that require careful management to achieve a safe and effective outcome. Treatment is usually supportive and symptom based (25).

The most common side effects early in treatment are influenza-like symptoms, and simple antiemetics may be of benefit; for example, metoclopramide for nausea; antispasmodics such as buscopan for abdominal cramps; and paracetamol for headaches, fevers, myalgias and arthralgias (avoid nonsteroidal anti-inflammatory agents where possible).

Mood disturbances become more common as therapy continues, and appropriate interventions include benzodiazepines for insomnia, and antidepressants – particularly selective serotonin reuptake inhibitors (SSRIs) for anxiety and depression. Patients already on antidepressants may need a dose increase during IFN therapy. Once patients have commenced an SSRI, it is often continued for about 6 months after completion of the IFN program.

Skin changes are common during therapy, and patients often complain of dry, itchy skin and multiple skin rashes. Therapy is usually based on keeping the skin hydrated through regular use of moisturisers and

emollients. Antihistamines can be added, particularly if pruritus is exacerbating insomnia. Steroid-based creams can be trialled for rashes that do not respond to the above measures. Thyroiditis can also occur, with associated hyperthyroidism and hypothyroidism. Lifestyle issues while on therapy appear to be important. Patients can trial a variety of strategies during therapy to help with IFN-related side effects. Regular exercise before and during therapy seems to help with lethargy and myalgias. Anecdotally, patients who exercise regularly seem to tolerate treatment better than those who are sedentary.

### End point of therapy

The ultimate goal is viral eradication, reflected by sustained off-therapy HBsAg loss and development of protective anti-HBs, but this is rarely achieved. Instead, for most of those affected, the aim is biochemical control (i.e. normalisation of ALT) and virological control (i.e. suppression to <2,000 IU/mL for IFN treatment, and to undetectable for direct antiviral therapy). Ideally, this control should be sustained off-therapy; however, when using direct antiviral therapy, long-term maintenance is required in most patients (4).

For those in the HBeAg-positive phase of infection, HBeAg loss and development of anti-HBe (HBeAg seroconversion) heralds the possibility of sustained off-therapy biochemical and virological control. After a period of consolidation, a trial off therapy is undertaken to determine whether biochemical and virological control will be sustained in that individual. Failure may be due to reversion to HBeAg-positive or anti-HBe-negative state off therapy, or due to the emergence of HBeAg-negative chronic hepatitis (Immune escape phase) (26, 27).

In patients in the immune escape phase of infection, biochemical and virological control is usually only achieved by long-term therapy, although IFN sometimes induces sustained off-therapy responses.

## Stopping oral antiviral treatment

In HBeAg-positive patients, nucleos(t)ide analogue therapy can be used in an attempt to cease antiviral therapy after a sustained period of complete HBeAg seroconversion and undetectable HBV DNA. However, a proportion of patients will relapse after treatment is stopped. The longer the period of consolidation after the HBeAg seroconversion and before cessation of therapy, the less likely the patient is to relapse. Most guidelines recommend a 6–12 month consolidation period before stopping therapy. In HBeAg-negative patients, the risk of virological relapse after stopping therapy is high, and patients usually continue lifelong therapy unless they undergo loss of HBsAg (28).

## References


1. Szpakowski J-L, Tucker L-Y. Causes of death in patients with hepatitis B: A natural history cohort study in the United States. Hepatology. 2013;58(1):21–30.
2. Liaw YF. Reduction of cirrhosis and hepatocellular carcinoma with antiviral therapy in chronic hepatitis B. Hepatology. 2013.
3. Hosaka T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology. 2013;58(1):98–107.

4. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. Journal of Hepatology. 2012;57(1):167–85.

5. Yapali S, Talaat N, Lok AS. Management of hepatitis B: our practice and how it relates to the guidelines. Clinical Gastroenterology & Hepatology. 2014;12(1):16–26.

6. Scott DR, Levy MT. Liver transient elastography (Fibroscan): a place in the management algorithms of chronic viral hepatitis. Antiviral Therapy. 2010;15(1):1–11.

7. Chan HLY, Wong GLH, Choi PCL, Chan AWH, Chim AML, Yiu KKL, et al. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. Journal of Viral Hepatitis. 2009;16(1):36–44.

8. Benson J. Concordance – An alternative term to 'compliance' in the Aboriginal population. Aust Fam Physician. 2005;34(10):831–5.

9. Hajarizadeh B, Wallace J, Ngo N, Richmond J. Hepatitis B patient and clinical practice survey. Melbourne: Australian Research Centre in Sex, Health and Society (ARCSHS), La Trobe University, 2014.

10. Dusheiko G. Treatment of HBeAg positive chronic hepatitis B: interferon or nucleoside analogues. Liver International. 2013;33 Suppl 1:137–50.

11. Tsang PSY, Trinh H, Garcia RT, Phan JT, Ha NB, Nguyen H, et al. Significant prevalence of histologic disease in patients with chronic hepatitis B and mildly elevated serum alanine aminotransferase levels. Clinical Gastroenterology & Hepatology. 2008;6(5):569–74.

12. Papatheodoridis GV. Why do I treat HBeAg-negative chronic hepatitis B patients with nucleos(t)ide analogues? Liver International. 2013;33 Suppl 1:151–6.

13. Sonneveld MJ, Hansen BE, Piratvisuth T, Jia JD, Zeuzem S, Gane E, et al. Response-guided peginterferon therapy in hepatitis B e antigen-positive chronic hepatitis B using serum hepatitis B surface antigen levels. Hepatology. 2013;58(3):872–80.

14. Lampertico P, Vigano M, Colombo M. Why do I treat HBeAg-negative chronic hepatitis B patients with pegylated interferon? Liver International. 2013;33 Suppl 1:157–63.

15. Buster EH, Schalm SW, Janssen HL. Peginterferon for the treatment of chronic hepatitis B in the era of nucleos(t)ide analogues. Best Pract Res Clin Gastroenterol. 2008;22(6):1093–108.

16. Lampertico P, Liaw YF. New perspectives in the therapy of chronic hepatitis B. Gut. 2012;61 Suppl 1:i18–24.

17. Gracey DM, Snelling P, McKenzie P, Strasser SI. Tenofovir-associated Fanconi Syndrome in patients with chronic hepatitis B monoinfection. Antiviral Therapy. 2013.

18. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet. 2013;381(9865):468–75.

19. Dauchy FA, Lawson-Ayayi S, de La Faille R, Bonnet F, Rigothier C, Mehsen N, et al. Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy. Kidney Int. 2011;80(3):302–9.

20. Svarovskaia ES, Curtis M, Zhu Y, Borroto-Esoda K, Miller MD, Berg T, et al. Hepatitis B virus wild-type and rtN236T populations show similar early HBV DNA decline in adefovir refractory patients on a tenofovir-based regimen. Journal of Viral Hepatitis. 2013;20(2):131–40.

21. Zoulim F, Locarnini S. Hepatitis B virus resistance to nucleos(t)ide analogues. Gastroenterology. 2009;137(5):1593–608.

22. Lampertico P, Vigano M, Manenti E, Iavarone M, Lunghi G, Colombo M. Adefovir rapidly suppresses hepatitis B in HBeAg-negative patients developing genotypic resistance to lamivudine. Hepatology. 2005;42(6):1414–9.

23. Lok AS, Trinh H, Carosi G, Akarca US, Gadano A, Habersetzer F, et al. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naive patients with chronic hepatitis B. Gastroenterology. 2012;143(3):619–28.e1.

24. Kitrinos KM, Corsa A, Liu Y, Flaherty J, Snow-Lampart A, Marcellin P, et al. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. Hepatology. 2013.

25. Slim J, Afridi MS. Managing adverse effects of interferon-alfa and ribavirin in combination therapy for HCV. Infect Dis Clin North Am. 2012;26(4):917–29.

26. Song BC, Suh DJ, Lee HC, Chung YH, Lee YS. Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea. Hepatology. 2000;32(4 Pt 1):803–6.

27. Song BC, Cui XJ, Shin JW, Park NH, Cho YK, Song HJ, et al. Response to adefovir depends on mutation patterns in precore region, basal core promoter and reverse transcriptase, and on-treatment responses in Lamivudine-resistant chronic hepatitis B patients. Intervirology. 2010;53(4):203–10.

28. Hadziyannis SJ, Sevastianos V, Rapti I, Vassilopoulos D, Hadziyannis E. Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop long-term treatment with adefovir. Gastroenterology. 2012;143(3):629–36.e1.

# CHAPTER 8: MANAGING PATIENTS WITH ADVANCED LIVER DISEASE


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**LINKS**

**Chapter 2:** Virology: viral replication and drug resistance
**Chapter 3:** Hepatitis B virus testing and interpreting test results
**Chapter 7:** Treatment of chronic hepatitis B virus infection
**Chapter 9:** Hepatitis B virus-related hepatocellular carcinoma

## KEY POINTS

- Determine the phase of the hepatitis B virus (HBV) infection.
- Determine the severity of the liver disease.
- Fully evaluate the patient to identify factors contributing to liver damage.
- Minimise other hepatic injury:
  - manage other causes of liver disease or damage
  - advise on healthy living.
- Offer antiviral therapy where appropriate – treat all patients with antiviral therapy if cirrhotic and detectable HBV DNA.
- Manage the complications of cirrhosis.
- Implement screening for hepatocellular carcinoma as recommended in Chapter 9.

## Introduction

People with chronic hepatitis B (CHB) virus infection are at an increased risk of developing liver cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC), with 15–40% developing complications during their lifetime. Cirrhosis is a histopathological diagnosis, describing liver fibrosis with nodule formation, subsequent to liver cell necrosis and regeneration. Fibrosis in response to hepatocyte death is due to stellate cell activation; it is at first limited in extent, then forms portal-to-portal or portal-to-central vein bridging, finally leading to nodule formation. Cirrhosis leads to altered liver perfusion, with a decrease in portal vein flow and a compensatory increase in hepatic artery input. This adversely affects hepatocyte function over time. Nevertheless, patients with stable cirrhosis may survive for many years without major complications. When liver inflammation continues, fibrosis worsens and progresses to 'decompensated cirrhosis'. This refers to the complications of jaundice, ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy or HCC. If the cause of the liver disease can be removed, early cirrhosis may reverse in some patients.

In hepatitis B virus (HBV) infection, progression of the inflammatory and fibrotic processes is more rapid in those with raised alanine aminotransferase (ALT) levels and in those with detectable HBV DNA.

Patients with advanced liver disease, with or without ongoing hepatic inflammation, present clinicians with significant management challenges. Adding to the complexity of the management process are untreated cofactors such as hepatitis C virus (HCV) infection, alcohol use, non-alcoholic fatty liver disease (NAFLD, with its associated insulin resistance) or smoking. With treatment, these patients may still enjoy months or years of an acceptable quality of life, even if the underlying condition cannot be reversed. Liver transplantation can provide a better quality of life, but availability is limited. This chapter focuses on the management of advanced liver disease in patients with CHB infection, assuming that HBV has been identified as an issue.

## Determine the phase of the hepatitis B virus infection

The phase of the disease must be established, so that appropriate decisions on antiviral therapy can be made (see **Chapters 2** and **3**). Despite barriers to initiating and maintaining therapy, all patients with advanced liver disease should be treated with an oral antiviral agent. Suppression of HBV DNA to undetectable levels is an important goal in cirrhosis caused by CHB. Engaging the patient in a management plan may increase the possibility of ultimately being able to use antiviral therapy.

## Determine the presence or absence of cirrhosis and the severity of the liver disease

Cirrhosis may be present in the absence of symptoms, clinical signs or abnormal liver tests. It is therefore important to determine, where possible, the presence or absence of cirrhosis. Liver biopsy has been the gold standard for determining the degree of hepatic fibrosis, and is

### Assessment of cirrhosis and severity of liver disease

Assessment for the following is required:

- Chronic liver disease
  - spider naevi
  - hepatic palms (palmar erythema)
  - nail changes (leukonychia)
  - gynaecomastia
  - hepatosplenomegaly.
- Portal hypertension
  - collateral vessels on anterior abdominal wall
  - caput medusa (venous structures around the umbilicus)
  - ascites
  - varices (evidenced by ultrasound, computed tomography and endoscopy).
- Fluid and electrolyte and renal problems
  - oedema
  - pleural effusion
  - decreased urine output
  - hyponatraemia
  - hypo/hyperkalaemia
  - rising creatinine.
- Portal systemic encephalopathy (PSE)
  - be aware of minimal PSE, which by definition is not evident on clinical evaluation; number-connection tests or driving-skill tests may be required
  - reversed sleep pattern (daytime somnolence and nocturnal waking) in early PSE
  - slowing of normal response times, reflexes
  - impaired driving skills
  - lack of energy
  - metabolic flap (asterixis)
  - confusion, disorientation
  - increasing drowsiness
  - coma (hepatic failure).
- Hepatic decompensation
  - jaundice
  - bruising, bleeding
  - spontaneous bacterial peritonitis
  - hepatocellular carcinoma
  - impaired glucose homeostasis (hypoglycaemia)
  - impaired renal function (hepatorenal syndrome).
- Extrahepatic manifestations of advanced liver disease
  - cardiomyopathy
  - hepatopulmonary syndrome
  - metabolic bone disease and risk of fractures
  - hormonal complications
    - testicular atrophy and feminisation in men
    - hirsutism and amenorrhoea in women
  - increased risk of serious infections.
- Nutritional assessment
  - body mass index (may not be useful if there is significant fluid retention)
  - waist circumference (may not be useful if ascites)
  - proximal muscle wasting.

See standard texts on liver disease for a more detailed description of these manifestations (1-5).

frequently recommended before therapy. However, non-invasive examinations such as transient elastography (FibroScan®) are becoming more commonly used and accepted.

Many units do not have access to FibroScan®, and patients may prefer to avoid a biopsy. In these instances, ultrasound performed by experienced technicians may identify cirrhosis and portal hypertension. However, the sensitivity of ultrasound in detecting cirrhosis may be as low as 50%; hence, a normal liver ultrasound cannot be used to exclude the presence of cirrhosis.

Having established the presence or absence of cirrhosis, the severity of the liver disease should be assessed. A full physical and laboratory work-up is needed, so that signs of cirrhosis and portal hypertension, and their complications, can be documented at baseline. This allows relevant management strategies to be offered and progress to be evaluated appropriately.

## Fully evaluate the patient to identify all factors contributing to liver damage

All patients should have a detailed history and examination performed to establish:

- underlying medical conditions including co-infection with hepatitis C or D viruses, or human immunodeficiency virus, which will influence the course of the disease
- medication use
  - prescribed
  - alternative or complementary medicine and over-the-counter drugs
- tobacco use
- alcohol use (there is no safe alcohol consumption in cirrhosis)
- recreational drug use (especially cannabis which promotes fibrosis)
- family history of liver disease, diabetes
- weight, body mass index
- evidence of diabetes or other organ system disease
- other forms of liver disease (e.g. haemochromatosis, autoimmune liver disease).

Cofactors for liver disease should be addressed in patients with advanced liver disease, as far as possible. Specifically, obesity should be controlled, and alcohol and cannabis use ceased (or markedly reduced if abstinence is not an option). Paracetamol can be used at a reduced dose, and non-steroidal anti-inflammatory (nephrotoxic) therapy should be avoided. Drugs known to cause liver disease should be used with caution, although underlying liver disease does not increase the risk of hepatotoxicity. Exercise should be maintained, where possible, to help preserve muscle mass, cardiovascular fitness, functional status and quality of life.

Having advised the patient about other factors that can aggravate liver disease, the clinician must then focus on a specific management plan for the advanced liver disease.

## Offer antiviral therapy where appropriate

The treatment of CHB is discussed in detail in **Chapter 7**. All patients should be evaluated for possible antiviral therapy

with an oral nucleos(t)ide analogue (entecavir or tenofovir), because these drugs will significantly modify the progression of the disease. Pegylated interferon is contraindicated in patients with decompensated cirrhosis, but oral antiviral agents are generally well tolerated. All cirrhotic patients with detectable HBV DNA should be placed on antiviral therapy.

## Manage and prevent the complications of advanced liver disease

### Management strategies

Following the diagnosis of cirrhosis, the following steps should be taken.

***a. A gastroscopy or endoscopy.***

This should be considered, to detect oesophageal or gastric varices.

***b. HCC screening (see Chapter 9).***

The risk of HCC must be addressed in patients with CHB infection. Both cirrhotic and, to a lesser extent non-cirrhotic, patients are at risk of this complication. Recommended screening comprises 6-monthly abdominal ultrasound examinations and serum alpha-fetoprotein levels (6).

***c. If the liver disease is advanced, referral to a liver transplant unit for assessment should be considered.***

Not all patients will be suitable for transplant or even for referral to a transplant unit. However, this decision should be considered and documented. Two means of objectively assessing severity of liver disease are the Child Pugh Turcotte score and the Model of End-Stage Liver Disease (MELD) score. The scoring system for the Child Pugh Turcotte model is shown in Table 8.1. The MELD score is calculated using data for serum bilirubin, serum creatinine and the international normalised ratio (INR). Online calculators can easily provide a score if these results are available. Patients who have a high Child's B or Child's C score and MELD score of over 15 should be referred for consideration of transplantation if there are no contraindications. Table 8.2 demonstrates the link between MELD scores and life expectancies.

### Dietary modification in advanced liver disease

Patients with advanced liver disease often eat poorly, and in the past this has been complicated by advice to reduce protein and sodium intake. It is clear that patients do better if they can eat frequent small protein-containing meals daily. Evening food intake enhances hepatic regeneration and recovery from hepatic insults and, in hospital patients, it reduces morbidity and mortality.

### Fluid and electrolyte problems

Fluid and electrolyte problems are managed by:

- salt and water restriction where necessary
- ensuring electrolyte balance
  - cautious diuretic usage to minimise the risk of hepatorenal syndrome
    - spironolactone is the preferred agent, in doses of 25–400 mg/day
    - initial low dose frusemide

**Table 8.1** Child Pugh Turcotte scoring system for cirrhosis

| Measure | 1 point | 2 points | 3 points | Units |
|---|---|---|---|---|
| Bilirubin (total) | <34 (<2) | 34–50 (2–3) | >50 (>3) | µmol/L (mg/dL) |
| Serum albumin | >35 | 28–35 | <28 | g/L |
| International normalised ratio | <1.7 | 1.71–2.20 | >2.20 | No unit |
| Ascites | None | Mild | Mod/severe | No unit |
| Hepatic encephalopathy | None | Grade I–II (or suppressed with medication) | Grade III–IV (or refractory) | No unit |

| Points | Class | One-year survival (%) | Two-year survival (%) |
|---|---|---|---|
| 5–6 | A | 100 | 85 |
| 7–9 | B | 81 | 57 |
| 10–15 | C | 45 | 35 |

  - potassium supplementation if required
  - low dietary saturated fat with adequate dietary protein, fruit and vegetables
  - monitoring of serum creatinine and urine electrolytes (frequency determined by acuteness and severity of fluid overload and need for reversal).

Additional therapy for ascites may be required with regular large volume paracentesis ('ascitic tap'). Medications to avoid in ascites include angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs (NSAIDs) and beta blockers. Some patients are treated with transjugular intrahepatic portosystemic shunt (TIPS) to lower portal pressure and decrease ascites accumulation.

  - All patients presenting with ascites should have a diagnostic tap to exclude or diagnose spontaneous bacterial peritonitis.
  - Patients with recurrent ascites should be referred to a specialist unit, as transplantation may need to be considered at this stage.

## Portal hypertension

Portal hypertension is managed by:

- non-selective beta blockers (propranolol and possibly carvedilol)
- prophylactic variceal band ligation of high-risk oesophageal varices
- treating acute bleeding when it occurs

**Table 8.2** Model of End-Stage Liver Disease score and prognosis in chronic liver disease

| MELD score | Predicted 6-month survival (%) | Predicted 12-month survival (%) | Predicted 24-month survival (%) |
|---|---|---|---|
| 0–9 | 98 | 93 | 90 |
| 10–19 | 92 | 86 | 80 |
| 20–29 | 78 | 71 | 66 |
| 30–39 | 40 | 37 | 33 |

MELD, Model of End-Stage Liver Disease

- considering TIPS if conservative measures fail.

Cirrhotic patients with portal hypertension have a definite risk of portal vein thrombosis (PVT). Currently, there are no formal recommendations about use of low molecular weight heparin in this situation, but there is increasing interest in its use, because it appears to reduce risk of both PVT and mortality from other causes (3).

## Portal systemic encephalopathy

Portal systemic encephalopathy is managed by:

- maintaining electrolyte balance
- using lactulose to clear the colon and alter ammonia metabolism and diffusion (use doses to ensure two to three soft stools per day, and continue use long term)
- considering use of rifaximin, a non-absorbable antibiotic; this is now funded by the Pharmaceutical Benefits Scheme (PBS) for the prevention of hepatic encephalopathy in patients with a prior episode and in whom lactulose is not tolerated or is ineffective
- continuing normal protein intake, which is critical for hepatic regeneration.

## Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is managed by:

- having a low threshold of suspicion in a patient with ascites presenting with fever, abdominal pain, vomiting, onset of or worsening of encephalopathy, deteriorating renal function, renal failure or generally unwell
- early referral to emergency department or for hospital admission if diagnosis is suspected
- confirmation of diagnosis by ascitic tap (white cell count >500/mm$^3$ or neutrophils >250/mm$^3$)
- treatment of acute episode with appropriate IV antibiotics, +/– albumin
- prophylaxis with co-trimoxazole (alternative norfloxacin) for all patients with previous proven episode of SBP, and patients with ascites and low ascitic protein concentration (<10 g/L).

### Advancing hepatic failure

Advancing hepatic failure is managed by:

- avoiding and managing factors that aggravate the liver disease
  - alcohol, cannabis, tobacco
  - some medications (e.g. excess paracetamol, ibuprofen, anti-tuberculosis agents)
  - obesity
  - injecting drug use
  - iron overload
  - diabetes
  - hepatitis C infection
- monitoring Mg, Zn, Ca and fat-soluble vitamins
- regularly checking for infection (e.g. cellulitis, chest infection)
- avoiding certain infection risks (e.g. avoid uncooked oysters because of the risk of *Vibrio vulnificus* infection)
- providing routine vaccination against influenza and pneumonia
- ongoing screening for the risk of HCC.

## References


1. Bajaj JS. Review article: the modern management of hepatic encephalopathy. Aliment Pharmacol Ther. 2010;31(5):537–47.
2. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology. 2005;42(5):1208–36.
3. Jairath V, Burroughs AK. Anticoagulation in patients with liver cirrhosis: complication or therapeutic opportunity? Gut. 2013;62(4):479–82.
4. Schiff ER, Sorrell MF, Maddrey WC. Schiff's Diseases of the Liver (10th edition). Philidephia: Lippincott Williams & Wilkins; 2007.
5. Sherlock S, Summerfield JA. A colour atlas of liver disease. London: Wolfe Medical Publications Ltd; 1979.
6. Wong GL, Chan HL, Tse YK, Chan HY, Tse CH, Lo AO, et al. On-treatment alpha-fetoprotein is a specific tumor marker for hepatocellular carcinoma in patients with chronic hepatitis B receiving entecavir. Hepatology. 2014;59(3):986–95.

# CHAPTER 9: HEPATITIS B RELATED HEPATOCELLULAR CARCINOMA


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| **LINKS** | **Chapter 1:** Prevalence and epidemiology of hepatitis B |

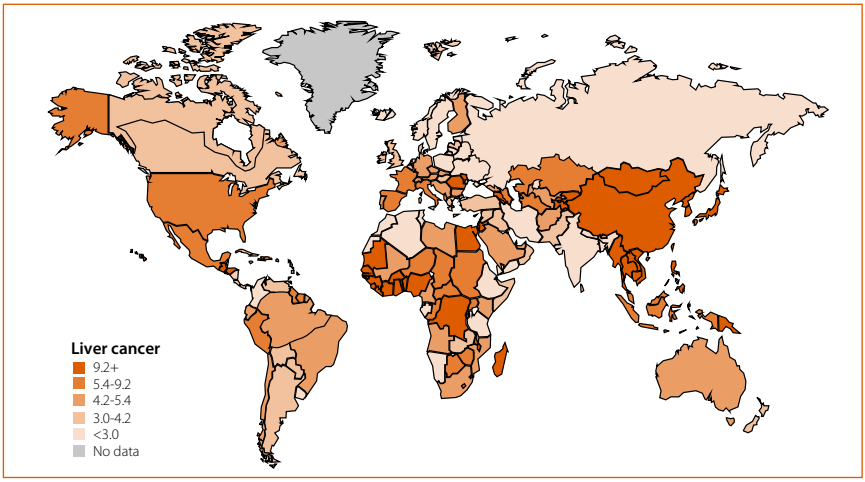
## KEY POINTS

- Hepatitis B Virus (HBV) is an oncogenic virus that is, globally, the most important aetiological factor in the development of hepatocellular carcinoma (HCC).
- Treatment of chronic hepatitis B (CHB) decreases, but does not completely eliminate, risk of HCC, underscoring the need for ongoing HCC surveillance in at-risk individuals.
- HCC surveillance by 6-monthly ultrasound scanning and alpha-fetoprotein level is recommended in patients with cirrhosis, and in patients with CHB who have additional risk factors.
- Early diagnosis of HCC improves access to curative therapy and prognosis.
- Curative therapies include liver transplantation and resection.
- Additional therapies that prolong survival include transarterial chemoembolisation, radiofrequency ablation and sorafenib.

## Hepatocellular carcinoma epidemiology

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related death worldwide. Globally, over 80% of HCC is attributable to the combined effects of chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), which confers a 20 to 100-fold increased risk of developing HCC relative to those without viral hepatitis infections (1, 2). There are large geographic variations in HCC incidence, with the highest prevalence being in eastern Asia and middle or western Africa, where the estimated age-adjusted incidence rates of HCC are about 10 times greater than in Australia and New Zealand (Figure 9.1) (3). In Australia, recent estimates suggest that over 200,000 Australians are living with chronic hepatitis B (CHB) (4), and primary liver cancer incidence rates have been rising faster than any other cancer (5, 6). This has propelled HCC from a rare cancer to among the top 10 causes of cancer death overall, and the seventh cause of cancer death in men (7). In New South Wales (NSW), nearly 90% of hepatitis B related HCC occurs in people born overseas, in particular from countries with high HBV prevalence (8). Standardised incidence rates of HCC are at least six times higher in men born in China, Hong Kong, Indonesia, Korea, Macau and Vietnam, and in women born in China and Vietnam, than in the Australian-born population. This trend mirrors those in the Netherlands and the United States of America (USA), where rising rates of HCC are reported in migrants from Asia and the Pacific Islands that are disproportionate in comparison to the locally born populations (9, 10). Aboriginal

**Figure 9.1** The global distribution of liver cancer (GLOBOCAN data)




Adapted from: Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 01/07/2014.

**Table 9.1** Risk factors for hepatitis B related hepatocellular carcinoma

| Risk factor | Reference |
|---|---|
| Active HBV DNA replication or viral load | Chen et al (2006) (14) |
| HBV genotype C | Yang et al (2002) (15) |
| HBeAg negative core promoter mutation | Yang et al (2002) (15) |
| Cirrhosis | Schiff et al (2006) (16) |
| Male sex | Bosch (1999) (17) |
| Asian, African, Aboriginal and Torres Strait Islander or Australian ethnicity | Fattovich (2003), Parker (2014) (12, 18) |
| Coexisting NAFLD and diabetes | El-Serag (2001) (19) |
| Smoking, alcohol, obesity | Marrero (2005) (20) |
| Positive family history, first-degree relative | Loomba (2013) (21) |

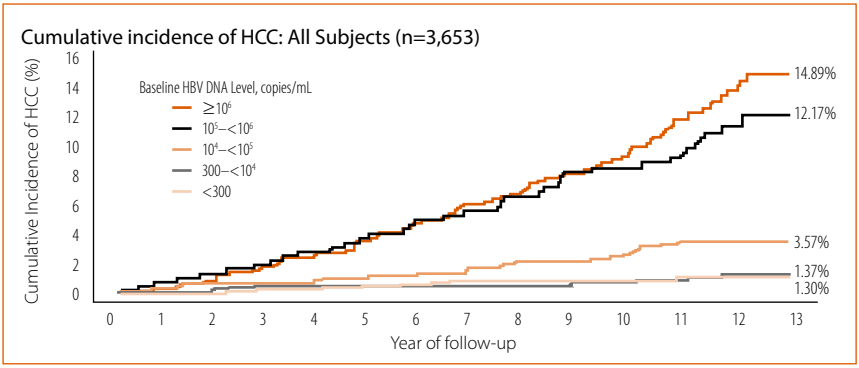
HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; NAFLD, non-alcoholic fatty liver disease

and Torres Strait Islander people are also disproportionately affected by CHB and related liver cancer: the prevalence of HBV in the Aboriginal and Torres Strait Islander population ranges from 3.6% to 26.0%, according to place of residence and age group (11) and, in some Aboriginal and Torres Strait Islander communities, rates of HCC are 5–10 times greater than in non-Indigenous Australians (12, 13). (see **Chapter 1**).

## Risk factors

HBV is an oncogenic virus that increases the risk of HCC occurrence directly (by viral mechanisms) and indirectly (by liver inflammation and cirrhosis). Thus, persistently high HBV DNA and alanine aminotransferase (ALT) are strong independent predictors of HBV-related HCC (22). The significance of HBV replication per se in HCC pathogenesis was demonstrated by the REVEAL study, a community-based natural history study of CHB in Taiwan, which found that HCC risk increased proportionally to serum HBV DNA viral load (Figure 9.2) (14). Chronic replication of HBV increases the risk of progression to cirrhosis and HCC (23). Cirrhosis increases HCC risk overall, and one third of people with cirrhosis develop HCC in their lifetime. Among people with cirrhosis, the annual incidence of HCC is 2–3% in western countries and 6–11% in Asian populations (18, 24). The incidence rates of HCC are two to three times higher in men than in women in all regions of the world (17). At each stage of chronic hepatitis, a positive family history (in first-degree relatives) increases HCC risk (21). Coexisting obesity, diabetes and non-alcoholic fatty liver disease (NAFLD) (19), together with alcohol and cigarette smoking (20), are additive risk factors for HCC development (see Table 9.1).

**Figure 9.2** Viral load as a predictor of hepatocellular carcinoma risk (25)




## Prevention

The most effective and practical means to control HBV infection and its long-term sequelae (cirrhosis and HCC) is to reduce or eliminate viral transmission by primary prevention. Secondary prevention aims to reduce progression to end-stage liver disease and HCC, by optimising medical management. This approach is intuitive, and is based on the close correlation between HBV replication and the risk of disease progression and liver cancer. Data suggest that effective suppression of viral replication may reduce risk of HCC (26-28).

The aim of HCC surveillance is to detect tumours at an early stage, when curative treatment can be offered. However, the benefits of a surveillance strategy have to be balanced against the cumulative risk of developing the disease, and against the costs, sensitivity and specificity of the screening tests. The effect of lead-time bias (i.e. the period by which screening advances diagnosis of the disease) on survival leads to uncertainty about the cost-effectiveness of screening protocols and the effect that antiviral treatment may have on screening for HCC prevention (24, 29). Nevertheless, current clinical practice guidelines recommend HCC screening by ultrasound scanning as being of benefit in all patients with cirrhosis (30). Liver ultrasound is considered the HCC screening test of choice because it can detect tumours as small as 1–2 cm in diameter (sensitivity 94%); however, it is operator dependent and does not reliably discriminate between HCC and other liver pathology (e.g. haemangiomas or cirrhotic nodules). In HBV patients with complete viral suppression on antiviral therapy, in particular, the addition of serum alpha-fetoprotein (AFP) measurement increases detection of HCC, and elevation of AFP may precede the detection of HCC by ultrasound by 6 months (31). However, serum AFP may be significantly elevated in patients undergoing an HBV flare, and may not be a useful marker of HCC in that situation. Serum AFP alone is inadequate for HCC surveillance because AFP is secreted by only about 50% of small HCC

lesions, and levels may remain normal even in the setting of advanced disease. HCC screening using both ultrasound and AFP is recommended by the Asian Pacific Association for the Study of the Liver (32) and the Gastroenterological Society of Australia (33).

Surveillance has been shown to decrease HCC-related mortality in Chinese patients with CHB, regardless of the presence of cirrhosis (34). This randomised controlled trial (RCT) enrolled over 18,000 people with CHB, and reported a 37% reduction of mortality in people screened for HCC compared to those receiving usual medical care (34).

**Target groups for HCC surveillance**

- those with cirrhosis
- those without cirrhosis but with any of the following additional risk factors:
  - Asian men over 40 years
  - Asian women over 50 years
  - Africans over 20 years
  - Aboriginal and Torres Strait Islander people over 50 years
  - those with a family history of HCC.

The benefit of HCC surveillance in pre-cirrhotic CHB patients is controversial, and population-based HCC screening of high-risk groups is currently not systematically practised in Australia. However, guidelines from the American Association for the Study of Liver Disease (AASLD) highlight some important sub-populations that may benefit from surveillance in the absence of cirrhosis. These include HBV-infected Asian-born males over the age of 40, Asian-born females over the age of 50, African-born people over the age of 20 and those with a family history of primary liver cancer (35). Given that the individual annual risk of HCC in HBV-infected Aboriginal and Torres Strait Islander people over 50 years of age is estimated to be 0.34–0.86%, this population should be also be included in HCC surveillance (12).

A negative screening result cannot reliably exclude the presence of a HCC; hence, enrolment in a regular surveillance programme is required (36). Generally a 6-month interval is recommended between screenings, which takes into consideration the estimated doubling time of HCCs smaller than 5 cm in diameter (37).

## Diagnosis

Unequivocal diagnosis of HCC is required if there is an abnormal screening test. Diagnosis of HCC can be made non-invasively through imaging, on the basis of its radiological hallmark, enhancement with contrast in the arterial phase and washout in the portal or delayed phase. Diagnostic imaging modalities include four-phase computed tomography (CT) scanning and magnetic resonance imaging (MRI) (30). Diagnosis can be confirmed by one radiological technique in nodules over 2 cm; however, two techniques (CT, and MRI or contrast-enhanced ultrasound) are recommended in lesions 1–2 cm. Typical imaging findings in one modality with serum AFP greater than or equal to 100 ng/mL is also diagnostic.

Histological diagnosis by guided liver biopsy is not often required, but is recommended for nodules occurring in non-cirrhotic livers and nodules with inconclusive or atypical imaging appearances in cirrhotic livers.

## Staging and treatment

Historically, HCC has been diagnosed in advanced disease stages, when prognosis is uniformly poor; with earlier detection, outcomes have been improving. Predictors of HCC prognosis include tumour-related factors (size, number, vascular invasion and metastases), AFP level, age, severity of liver disease (Child-Pugh classification) and the degree of existing functional reserve. The Barcelona Clinic Liver Cancer (BCLC) staging system incorporates these factors, and is now widely adopted to determine prognosis and allocate therapies (Figure 9.3) (30, 38).

Very early HCC is defined as a single HCC of less than 2 cm with good performance status; however, less than 10% of all patients are diagnosed at this very early stage. They are amenable to curative treatments; these include orthotopic liver transplantation (OLT) and liver resection, which are associated with 5-year survival rates of over 80% and over 70%, respectively.

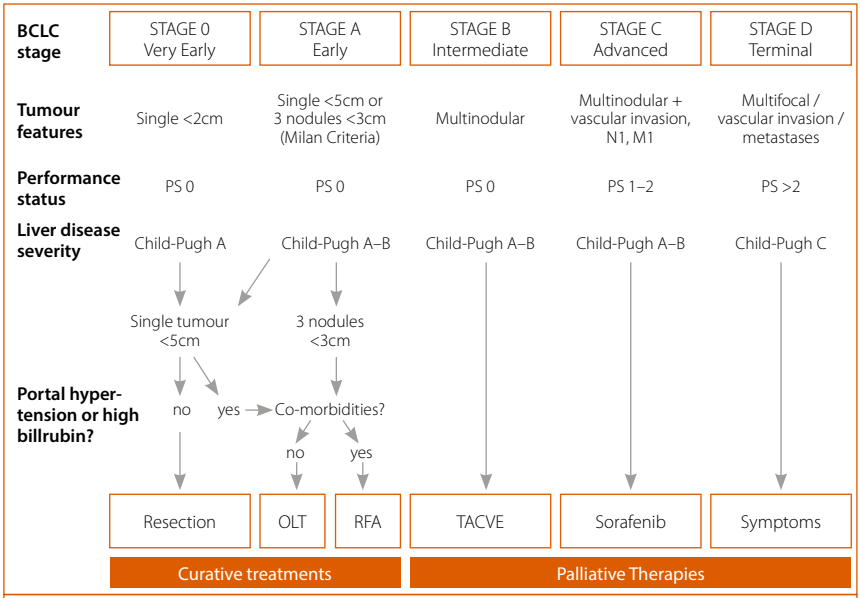
Early HCC is defined as a single tumour over 2 cm, or three nodules of less than 3 cm, performance status 0, and Child-Pugh class A or B. OLT is considered in cases where there is a single tumour less than or equal to 5 cm, or up to three nodules less than or equal to 3 cm (Milan Criteria). OLT remains the only curative option for those with resectable tumours and decompensated cirrhosis, because it removes not only the tumour, but also the underlying liver disease. However, the lack of available livers for transplantation means that many of those on the waiting list may ultimately be denied transplantation, because of tumour advancement during the waiting period.

The local ablation of HCC is an acceptable alternative to resection for small liver cancers (<3 cm) in Child-Pugh class A patients. Tumour ablation is also first-line treatment for unresectable, small HCCs with up to three nodules in Child-Pugh class A or B cirrhosis. Image-guided percutaneous ablation of tumours is generally performed with radiofrequency ablation (RFA) or microwave ablation, using extreme temperature to destroy tumour cells. Other ablation techniques that may be used include instillation of chemicals such as ethanol or acetic acid (39, 40), or the use of laser or cryotherapy. Choice of ablative therapies is determined by tumour position in relation to vascular structures, size and number, as well as the resources and expertise available.

Transcatheter arterial embolisation (TAE) and transcatheter arterial chemoembolisation (TACE) may be indicated in non-surgical patients who are free of vascular invasion or extrahepatic tumour extension. These techniques aim to obstruct the blood supply to intermediate-sized tumours; they use an embolising agent (e.g. gelfoam, starch microspheres or metallic coils) that, in the case of TACE, is combined with a chemotherapeutic agent (e.g. doxorubicin or cisplatinum).

Systemic therapies for HCC are recommended for the treatment of advanced stage patients who are not suitable for loco-regional therapies and who have good liver function. Cytotoxic therapies are not routinely recommended, but the multi-tyrosine kinase inhibitor

**Figure 9.3** Barcelona Clinic Liver Cancer staging system




BCLC, Barcelona Clinic Liver Cancer; OLT, orthotopic liver transplantation; PS, performance status; RFA, radiofrequency ablation; TAE, transcatheter arterial embolisation; TACE, transcatheter arterial chemoembolisation

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sorafenib is increasingly being used, based on a demonstrated survival benefit in advanced HCC in phase III clinical trials. In the SHARP trial, sorafenib increased median survival to 10.7 months, compared to 7.9 months with placebo (41). This treatment is indicated for advanced HCC with well-preserved liver function, or for tumours that are progressing despite loco-regional therapies.

Patients with advanced HCC and very poor performance status have a poor prognosis, with a median survival of only 3–4 months. They should be offered the best supportive palliative care to alleviate symptoms.

## Conclusion

Hepatitis B related HCC is an important global disease. Primary prevention of HBV infection remains the most effective long-term intervention; however, for those diagnosed with CHB, early detection and treatment of HCC has led to improved outcomes. HCC surveillance may increase the proportion being diagnosed at a curable stage. Although screening for HCC remains a topic for debate, earlier detection of these tumours has been associated with good results in the short and intermediate term. Disease recurrence and the treatment of advanced cancer remain a challenge. It is likely that the treatment of CHB infection will continue to make a

significant impact on end-stage disease, and reduce the probability of developing liver cancer, but these benefits will take a long time to become apparent.

## References


1. Amin J, Dore GJ, O'Connell D L, Bartlett M, Tracey E, Kaldor JM, et al. Cancer incidence in people with hepatitis B or C infection: A large community-based linkage study. J Hepatol. 2006;45(2):197–203.
2. Chu CM. Natural history of chronic hepatitis B virus infection in adults with emphasis on the occurrence of cirrhosis and hepatocellular carcinoma. J Gastroenterol Hepatol. 2000;15 Suppl:E25–30.
3. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74–108.
4. MacLachlan J, Allard N, Towell V, Cowie B. The burden of chronic hepatitis B virus infection in Australia, 2011. Aust NZ J Public Health. 2013;37(5):416–22.
5. Coates M, Tracey E. Cancer in New South Wales: Incidence and mortality 1997. NSW Public Health Bull. 2001;12(2):40–2.
6. Tracey E, Chen S, Baker D, Bishop J, Jelfs P. Cancer in New South Wales: Incidence and Mortality 2004. Sydney: Cancer Institute NSW, 2006.
7. Australian Institute of Health and Welfare & Australasian Association of Cancer Registries. Cancer in Australia: an overview, 2012. Canberra: Australian Institute of Health and Welfare, 2012; Cat. no. CAN 70.
8. Amin J, O'Connell D, Bartlett M, Tracey E, Kaldor J, Law M, et al. Liver cancer and hepatitis B and C in New South Wales, 1990–2002: a linkage study. Aust N Z J Public Health. 2007;31(5):475–82.
9. Seeff LB, Hoofnagle JH. Epidemiology of hepatocellular carcinoma in areas of low hepatitis B and hepatitis C endemicity. Oncogene. 2006;25(27):3771–7.
10. Visser O, van Leeuwen FE. Cancer risk in first generation migrants in North-Holland/Flevoland, The Netherlands, 1995–2004. Eur J Cancer. 2007;43(5):901–8.
11. Nguyen V, Dore G. Prevalence and epidemiology of hepatitis B; B positive – all you wanted to know about hepatitis B: Australasian Society for HIV Medicine (ASHM), 2008.
12. Parker C, Tong S, Dempsey K, Condon J, Sharma S, Chen J, et al. Hepatocellular carcinoma in Australia's Northern Territory – high incidence and poor outcomes. MJA. 2014;Accepted January 2014.
13. Wan X, Mathews JD. Primary hepatocellular carcinoma in aboriginal Australians. Aust J Public Health. 1994;18(3):286–90.
14. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. Journal of the American Medical Association. 2006;295(1):65–73.
15. Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med. 2002;347(3):168–74.
16. Schiff ER. Prevention of mortality from hepatitis B and hepatitis C. Lancet. 2006;368(9539):896–7.
17. Bosch FX, Ribes J, Borras J. Epidemiology of primary liver cancer. Semin Liver Dis. 1999;19(3):271–85.
18. Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis. 2003;23(1):47–58.
19. El-Serag HB, Richardson PA, Everhart JE. The role of diabetes in hepatocellular carcinoma: a case-control study among United States Veterans. Am J Gastroenterol. 2001;96(8):2462–7.
20. Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. J Hepatol. 2005;42(2):218–24.
21. Loomba R, Liu J, Yang HI, Lee MH, Lu SN, Wang LY, et al. Synergistic effects of family history of hepatocellular carcinoma and hepatitis B virus infection on risk for incident hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2013.
22. Chen CF, Lee WC, Yang HI, Chang HC, Jen CL, Iloeje UH, et al. Changes in serum levels of HBV DNA and alanine aminotransferase determine risk for hepatocellular carcinoma. Gastroenterology. 2011;141(4):1240–8, 8 e1–2.
23. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006;130(3):678–86.

24. De Masi S, Tosti ME, Mele A. Screening for hepatocellular carcinoma. Dig Liver Dis. 2005;37(4):260–8.

25. Chen CJ, Yang HI, Su J, Jen CL, You SL. Lu SN for the REVEAL-HBV Study Group. Risk of hepatocullular carcinoma across a biological gradient of serum hepatitis B virus DNA level. Journal of the American Medical Association. 2006;295(1):65–73.

26. Fung SK, Lok AS. Treatment of chronic hepatitis B: who to treat, what to use, and for how long? Clin Gastroenterol Hepatol. 2004;2(10):839–48.

27. Lai CJ, Terrault NA. Antiviral therapy in patients with chronic hepatitis B and cirrhosis. Gastroenterol Clin North Am. 2004;33(3):629–54, x–xi.

28. Lok AS, McMahon BJ. Chronic hepatitis B: update of recommendations. Hepatology. 2004;39(3):857–61.

29. Plesch FN, Kubicka S, Manns MP. Prevention of hepatocellular carcinoma in chronic liver disease: molecular markers and clinical implications. Dig Dis. 2001;19(4):338–44.

30. Bruix J, Sherman M, American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020–2.

31. Wong GL, Chan HL, Tse YK, Chan HY, Tse CH, Lo AO, et al. On-treatment alpha-fetoprotein is a specific tumor marker for hepatocellular carcinoma in patients with chronic hepatitis B receiving entecavir. Hepatology. 2014;59(3):986–95.

32. Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int. 2010;4(2):439–74.

33. Australian and New Zealand chronic hepatitis B (CHB) recommendations Mulgrave, Victoria: Gastreoenterological Society of Australia 2009.

34. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130(7):417–22.

35. Sherman M. Pathogenesis and screening for hepatocellular carcinoma. Clin Liver Dis. 2004;8(2):419–43, viii.

36. Sherman M. Hepatocellular carcinoma: epidemiology, risk factors, and screening. Semin Liver Dis. 2005;25(2):143–54.

37. Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. J Hepatol. 2003;39(6):1076–84.

38. European Association for the Study of the Liver (EASL), European Organisation for Research and Treatment of Cancer (EORTC). EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908–43.

39. Kawamoto C, Ido K, Isoda N, Nagamine N, Hozumi M, Ono K, et al. Prognosis of small hepatocellular carcinoma after laparoscopic ethanol injection. Gastrointest Endosc. 1999;50(2):214–20.

40. Ohnishi K, Nomura F, Ito S, Fujiwara K. Prognosis of small hepatocellular carcinoma (less than 3 cm) after percutaneous acetic acid injection: study of 91 cases. Hepatology. 1996;23(5):994–1002.

41. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90.

# CHAPTER 10: MANAGEMENT OF HEPATITIS B VIRUS IN PREGNANCY AND CHILDREN


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**LINKS**

Chapter 6: Clinical assessment of patients with hepatitis B virus infection
Chapter 7: Treatment of chronic hepatitis B infection

## KEY POINTS

- All pregnant women should be tested for hepatitis B surface antigen (HBsAg). A woman identified as HBsAg positive should be tested for hepatitis B e antigen (HBeAg) and hepatitis B virus (HBV) DNA, to determine risk of transmission to the infant and the degree of infectivity.
- If a pregnant woman has HBV, health professionals should take the opportunity to provide education about disease management, plan ongoing care, and test family and close contacts.
- The risk of mother-to-child transmission of HBV can be significantly reduced. The baby should be given a combination of hepatitis B immunoglobulin (HBIG) and the first dose of hepatitis B vaccine within 12 hours of birth, followed by a full course of hepatitis B vaccine.
- For HBsAg-positive women with high viral loads (>10 million IU/mL or 7 log IU), referral should be made to a specialist for consideration of antiviral therapy, to further reduce the risk of perinatal transmission.
- There is no evidence of HBV transmission as a result of breastfeeding.
- Children born to HBsAg-positive mothers should be followed up and tested for infection once vaccination has been completed.
- Most children with chronic hepatitis B (CHB) are asymptomatic and have little liver damage, but have high viral loads.
- Children with CHB should be monitored annually, with liver function tests and HBV serology/viral load.
- Ensure adolescents are appropriately transferred from paediatric to adult care.

## General considerations

In some areas of the world, up to 20% of women of child-bearing age are infected with chronic hepatitis B (CHB). In Australia, individuals who have migrated from countries with high hepatitis B virus (HBV) prevalence are often unaware of their infection, because testing is not part of routine migration health assessment. Pregnancy is the only time universal testing for infection with HBV occurs; and as a result, this is often the first time women become aware of their HBV infection. HBV can have significant health implications for the mother and her baby, and the issues for each should be considered independently.

Assessment of the mother should include consideration of the likely duration of infection; any prior or current therapy; liver function tests; and pre-pregnancy liver ultrasound, liver biopsy or non-invasive assessment of liver fibrosis (e.g. FibroScan®). This consultation is an important educational opportunity. The mother should receive information about infection control, routes of transmission, vaccination, the phases of HBV infection and recommendations for follow up at each phase (see **Appendix 2** for education resources). This is also an opportunity to offer testing to family members, and household and sexual contacts of the patient. Any treatment decisions (e.g. initiating or stopping therapy in the case of an unexpected pregnancy) should take into consideration the toxicity of therapies on the developing foetus, as discussed below.

## Perinatal transmission

HBV testing is universal in pregnancy, to allow for interventions to reduce transmission to the infant. This is important because more than 90% of infected infants will develop chronic infection, with the potential for significant adverse health outcomes. In contrast, 80% of older children and 95% of adults are able to clear HBV after infection. One hypothesis to explain the infant's failure to resolve HBV infection is that maternal hepatitis B e antigen (HBeAg) crosses the placenta and has a negative effect on the developing foetal immune system (1).

**Preventing perinatal transmission**

All babies of HBsAg-positive mothers should:

1. be given HBIG and the first dose of HBV vaccine within 12 hours of birth
2. have three subsequent doses of HBV vaccine, at 2, 4 and 6 months of age
3. be tested for HBsAg and anti-HBs after 9–12 months of age (at least 3 months after final dose of HBV vaccine).

During pregnancy, the mother's viral load should be tested; if it is high (>7 $\log_{10}$ IU/mL or 10,000,000 IU/mL), third-trimester antiviral therapy should be considered.

anti-HBs, antibodies to surface antigen; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IU, international unit

The cornerstone of prevention of HBV perinatal transmission is the combination of hepatitis B immunoglobulin (HBIG) and the first dose of hepatitis B vaccine, which is delivered within 12 hours of birth, followed by a full course of hepatitis B

vaccine. Babies should be checked after 9 –12 months of age for HBsAg to diagnose infection and antibodies to surface antigen (anti-HBs) to confirm vaccine response. Overall efficacy of this strategy is reported to be greater than 95% (2). There is no evidence that prematurity, premature rupture of membranes, low birth weight, meconium staining or breastfeeding lead to the failure of passive active immune prophylaxis (3). Such failure was thought to be largely the result of protocol error; however, it has become clear that failure of immune prophylaxis is related to HBeAg positivity and maternal HBV DNA level (3-5). In one Australian study, transmission despite appropriate prophylaxis was documented only in mothers with high viral load (>7 $\log_{10}$ IU/mL), at rates approaching 10% (4).

Based on available evidence, HBV transmission usually occurs during the birth process (as opposed to earlier in pregnancy). In support of this hypothesis, there has been some evidence that elective (but not urgent) caesarean section may be protective; however, the evidence for this is conflicting. The studies that support caesarean section are not high quality, and no international obstetric guidelines recommend this approach, and nor does the World Health Organization. Other strategies are more effective and are discussed below (5-7).

## Antiviral therapy to prevent perinatal transmission

Antiviral therapy to prevent perinatal transmission of human immunodeficiency virus (HIV) infection is well established; antiviral therapy is also emerging as an effective strategy to reduce transmission in HBV infection. A number of reviews have been written on this topic, and guidelines suggest this approach; however, as yet, there are no standardised recommendations for the optimum choice or duration of agent, or even the HBV DNA threshold for initiating therapy (8-11).

Despite the paucity of randomised trials in this setting, the available data confirm the efficacy of antepartum lamivudine in reducing perinatal transmission, although the effect is modest and variable (12-14). Also, despite the short duration of antiviral exposure in this setting, lamivudine's lack of antiviral potency and selection of HBV mutants resistant to antiviral therapy make this drug a suboptimal choice (15, 16).

Tenofovir has superior potency to lamivudine and telbivudine, and no emergence of resistance mutations has been described to date (17). There is limited evidence of the efficacy of tenofovir in pregnancy to reduce perinatal transmission, although no transmission was reported in two small series (18, 19).

Tenofovir is probably the optimal choice, and should be started at 32 weeks gestation in mothers with viral load above 7 $\log_{10}$ IU/mL. Optimal thresholds have not been clearly established (many studies report in copies/mL rather than IU, and therefore cannot be extrapolated). Therapy should continue for at least 2 weeks postpartum, and possibly up to 12 weeks (the latter may be preferable for reasons related to maternal health, as discussed below).

### Antiviral safety

The Therapeutic Goods Administration (TGA) pregnancy categories for HBV therapies reflect the limited human safety data but absence of human toxicity; thus, all therapies are classified in category B. The differences lie in evidence of animal toxicity. Interferons (IFNs) are generally contraindicated in pregnancy and cessation should be recommended when a woman becomes pregnant. There is limited data on the safety of entecavir in pregnancy, and its use is therefore not recommended. Seeking specialist advice is recommended. Lamivudine and tenofovir are categorised by the TGA as B3 and telbivudine as B1, based on animal toxicity data. The lack of animal toxicity for telbivudine is of interest, although data on human pregnancy experience with this agent are lacking. The toxicity concern with tenofovir is based largely on animal models where, in the setting of high doses, effect on foetal growth and development was observed. Human data (albeit mainly in the setting of HIV) are available. Tenofovir has not been shown to be teratogenic; concerns about growth and bone density have not been completely resolved, but findings are reassuring overall (20).

Reassuring data regarding the safety of both tenofovir and lamivudine in human pregnancy are provided by a prospective registry, largely in the setting of HIV infection. The registry shows no increase in birth defects after exposure to either of these agents (21). However, the registry is limited by the voluntary reporting structure, review but not verification of submitted information, lack of long-term follow up or information on developmental delay, and low sensitivity (able to detect only a twofold increase in birth defect rates). Nevertheless, results of studies in the setting of HIV that more closely examine the effect of in utero exposure to tenofovir, with a follow up of up to 4 years, are reassuring, with only one report of isolated reduced growth parameters at age 1 year (but not 2) in one study (22).

#### Advice about breastfeeding

There is no evidence of HBV transmission as a result of breastfeeding. Tenofovir, and not the bioavailable pro-drug, tenofovir disoproxil fumarate, is present in the breast milk (11, 23). In addition, when used in children, tenofovir has been shown to be safe. Therefore, women should be provided the available information and not discouraged from breastfeeding. Although no definitive recommendation is possible, it is reasonable for a woman to consider breastfeeding after being given the available information (24).

## Postpartum period – care of the mother

A major consideration in care for a pregnant woman is for the optimal health of the developing foetus; however, the mother's health is of prime importance. During the relatively immune-tolerant state of pregnancy, hepatitis B is commonly relatively silent, but a flare of hepatitis commonly occurs in the postpartum period (in 30–50% of HBeAg-positive mothers with high viral load), with onset at approximately 10 weeks postpartum (25). Postpartum flares have also been observed in HBeAg-negative mothers. Flares are usually asymptomatic and

settle spontaneously (25). If a flare is noted, it can be observed for up to 6 months to assess whether it will resolve spontaneously, or require treatment. It does not appear that antiviral therapy in pregnancy will increase the rate or severity of postpartum flares (13, 26, 27), nor that extending antiviral therapy beyond birth prevents the postpartum flare, although data are limited (25). During the postpartum period, the mother's liver function should be monitored every 1–2 months. All HBsAg-positive women should be enrolled in ongoing care, and have a plan formed for the management of their HBV. See **Chapters 6** and **7** for more information on this topic.

In summary, although guidelines provide scant specific instruction, the goal is complete prevention of every case of perinatal HBV transmission. In Australia, the optimal regimen is tenofovir 300 mg daily, commencing at 32 weeks gestation, continuing for up to 12 weeks postpartum, with subsequent ongoing monitoring and care of the mother. Detailed discussion by experts with expectant parents is required to explain the risks and benefits of this strategy. Ongoing contribution to the international pregnancy registry of antiviral therapy or participation in observational research or data collection will help to improve the Safety Data Set.

## Hepatitis B in children

### Natural history

Most children who have perinatally acquired HBeAg-positive HBV infection remain in the immune tolerance phase, with high viral loads and little liver damage. Cirrhosis is uncommon (although not unheard of) with 1.7–4.5% of children infected at birth having cirrhosis at liver biopsy; only 0.01–0.03% will develop hepatocellular carcinoma (HCC) during childhood (28). In specific populations a slow rate of seroconversion (from HBeAg to antibodies to e antigen [anti-HBe]) during childhood has been shown, with up to 25% in the first decade and up to 65% by the second decade becoming HBeAg-negative (29). After seroconversion, most patients will remain in the immune control phase, with normal liver function tests and low viral loads. In childhood, about 10% will develop HBeAg-negative chronic hepatitis with moderate or high viral loads and abnormal alanine aminotransferase (ALT), with a more severe disease progression and higher risk of HCC.

### Clinical manifestations

Acute HBV infection in children is usually asymptomatic; however, when clinical manifestations do occur, they are generally similar to those in adults. Fulminant disease is uncommon, but in infants it appears to be associated with maternal HBeAg-negative CHB. Most CHB in children is asymptomatic, and is accompanied by normal physical examination and normal growth (30).

### Management

Children diagnosed with HBV infection should be considered for referral to a paediatric hepatitis specialist. Management of children with CHB involves counselling the patient and family regarding the natural history of the disease, modes of transmission and treatment options. All susceptible

household members should be tested for HBV infection, and vaccinated if not immune. The affected child should also be vaccinated against hepatitis A, if susceptible. Frequency of monitoring is based on low-quality evidence and (largely) on expert opinion. In general, children should be reviewed every 6 months from diagnosis – with clinical examination, liver function tests and hepatitis B eAg serology – and monitored every 6 –12 months for HCC if there is evidence of cirrhosis (30). Degree of fibrosis may be assessed using FibroScan® in children, and is available in specialist centres. In those with persistently abnormal liver function test whom are being considered for treatment, a liver biopsy may be required.

**Monitoring of children with chronic hepatitis B**

Children with chronic hepatitis B should have all of the following:

- 6-monthly clinical review
- liver function tests
- hepatitis B virus serology (HBeAg and anti-HBe).

HBeAg, hepatitis B e antigen; anti-HBe, hepatitis B e antibody

**Which children should be prioritised for referral?**

Children should be prioritised for referral if they have:

- abnormal liver function tests
- signs of chronic liver disease (e.g. splenomegaly, spider naevi)
- acquired hepatitis B virus overseas (such children should be assessed by a specialist soon after arrival, to determine the monitoring plan depending on viral genotype, degree of fibrosis, etc.).

### Antiviral therapy

The selection of patients for antiviral therapy is based on an elevated ALT that is repeatedly more than 1.5 times the upper level of normal, DNA of over 2,000 IU/mL and moderate to severe inflammation or fibrosis on liver biopsy (31). The treatments studied in children to date are conventional interferon-alfa (IFN-alfa), lamivudine, a combination of IFN and lamivudine, and adefovir (6, 7). The advantages of IFN-alfa are the finite duration of therapy and lack of induction of antiviral resistance. IFN is tolerated better in children than in adults and may also be more effective – one study demonstrated an HBeAg seroconversion rate of 23%, with HBsAg loss in 10% of patients (32). The use of pegylated-IFN (PEG-IFN) to treat HBV in children is currently been investigated, with dosing based on trials in children with hepatitis C virus (HCV) infection. Entecavir has been used in children with abnormal liver functions tests in case reports and small case series, but is currently under study in a larger multicentre trial. Based on suggestive evidence from a small case series, clinical trials of combination therapy with PEG-IFN and lamivudine or entecavir for children in the immune tolerance phase of HBV are currently underway.

In general, treatment of HBV in children should only be undertaken after specialist review; currently available therapies generally reserved for children requiring treatment based on disease severity.

## Management of adolescents

At the age of 18, or the end of secondary education, children should be transitioned to adult viral hepatitis care, either in

primary care or an adult viral hepatitis clinic that is convenient to their place of study or work. Often the primary care practitioner is best placed to suggest a local specialist for ongoing care. If the patient has advanced disease, then the paediatric gastroenterologist may suggest an adult hepatologist service with expertise in management of HBV-related advanced liver disease.

## References


1. Chu CM, Liaw YF. Natural history of chronic hepatitis B virus infection: an immunopathological study. Journal of Gastroenterology & Hepatology. 1997;12(9-10):S218–22.
2. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009;50(3):661–2.
3. Wen W-H, Chang M-H, Zhao L-L, Ni Y-H, Hsu H-Y, Wu J-F, et al. Mother-to-infant transmission of hepatitis B virus infection: Significance of maternal viral load and strategies for intervention. Journal of Hepatology. 2013;59(1):24–30.
4. Wiseman E, Fraser MA, Holden S, Glass A, Kidson BL, Heron LG, et al. Perinatal transmission of hepatitis B virus: an Australian experience. Medical Journal of Australia. 2009;190(9):489–92.
5. Guo Z, Shi XH, Feng YL, Wang B, Feng LP, Wang SP, et al. Risk factors of HBV intrauterine transmission among HBsAg-positive pregnant women. Journal of Viral Hepatitis. 2013;20(5):317–21.
6. Pan CQ, Zou HB, Chen Y, Zhang X, Zhang H, Li J, et al. Cesarean section reduces perinatal transmission of hepatitis B virus infection from hepatitis B surface antigen-positive women to their infants. Clinical Gastroenterology & Hepatology. 2013;11(10):1349–55.
7. Yang J, Zeng X-m, Men Y-l, Zhao L-s. Elective caesarean section versus vaginal delivery for preventing mother to child transmission of hepatitis B virus – a systematic review. Virology Journal. 2008;5:100.
8. Liaw YF, Omata M. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatol Int. 2012;Hepatol Int(6):531–61.
9. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. Journal of Hepatology. 2012;57(1):167–85.
10. Levy M. Preventing Perinatal Transmission of HBV: An Australian Perspective. Current Hepatitis Reports. 2012;11(4):206–12.
11. Giles M, Visvanathan K, Sasadeusz J. Antiviral therapy for hepatitis B infection during pregnancy and breastfeeding. Antiviral Therapy. 2011;16(5):621–8.
12. van Zonneveld M, van Nunen AB, Niesters HGM, de Man RA, Schalm SW, Janssen HLA. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. Journal of Viral Hepatitis. 2003;10(4):294–7.
13. Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. Journal of Viral Hepatitis. 2009;16(2):94–103.
14. Shi Z, Yang Y, Ma L, Li X, Schreiber A. Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. Obstetrics & Gynecology. 2010;116(1):147–59.
15. Ayres A, Yuen L, Manoharan S, Glass A, Maley M, Levy M, et al. Ultradeep pyrosequencing identifies multidrug resistant HBV in pregnancy women undergoing lamivudine therapy. Hepatology. 2011;October 1074A.
16. Galluzzo C, Liotta G, Andreotti M, Luhanga R, Jere H, Mancinelli S, et al. Emergence of lamivudine resistance hepatitis B virus mutations in pregnant women infected with HBV and HIV receiving antiretroviral prophylaxis for the prevention of mother-to-infant transmission in Malawi. Journal of Medical Virology. 2012;84(10):1553–7.
17. Kitrinos KM, Corsa A, Liu Y, Flaherty J, Snow-Lampart A, Marcellin P, et al. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. Hepatology. 2013.
18. Greenup A-J, Tan PK, Nguyen V, Glass A, Davison S, Chatterjee U, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of Hepatitis B Virus. Heptology AASLD ABSTRACT. 2013.

19. Pan CQ, Mi LJ, Bunchorntavakul C, Karsdon J, Huang WM, Singhvi G, et al. Tenofovir disoproxil fumarate for prevention of vertical transmission of hepatitis B virus infection by highly viremic pregnant women: a case series. Digestive Diseases & Sciences. 2012;57(9):2423–9.

20. Van Rompay KKA, Brignolo LL, Meyer DJ, Jerome C, Tarara R, Spinner A, et al. Biological effects of short-term or prolonged administration of 9-[2-(phosphonomethoxy)propyl]adenine (tenofovir) to newborn and infant rhesus macaques.[Erratum appears in Antimicrob Agents Chemother. 2994 Jan;48(6):2346]. Antimicrobial Agents & Chemotherapy. 2004;48(5):1469–87.

21. Brown RS, Jr., Verna EC, Pereira MR, Tilson HH, Aguilar C, Leu C-S, et al. Hepatitis B virus and human immunodeficiency virus drugs in pregnancy: findings from the Antiretroviral Pregnancy Registry. Journal of Hepatology. 2012;57(5):953–9.

22. Wang L, Kourtis AP, Ellington S, Legardy-Williams J, Bulterys M. Safety of Tenofovir During Pregnancy for the Mother and Fetus: A Systematic Review. Clinical Infectious Diseases. 2013.

23. Van Rompay KKA, Hamilton M, Kearney B, Bischofberger N. Pharmacokinetics of tenofovir in breast milk of lactating rhesus macaques. Antimicrobial Agents & Chemotherapy. 2005;49(5):2093–4.

24. Vigano A, Bedogni G, Manfredini V, Giacomet V, Cerini C, di Nello F, et al. Long-term renal safety of tenofovir disoproxil fumarate in vertically HIV-infected children, adolescents and young adults: a 60-month follow-up study. Clin Drug Investig. 2011;31(6):407–15.

25. Nguyen V, Tan PK, Greenup AJ, Glass A, Davison S, Samarasinghe D, et al. Anti-viral therapy for prevention of perinatal HBV transmission: extending therapy beyond birth does not protect against post-partum flare. Aliment Pharmacol Ther. 2014;39(10):1225–34.

26. ter Borg MJ, Leemans WF, de Man RA, Janssen HLA. Exacerbation of chronic hepatitis B infection after delivery. Journal of Viral Hepatitis. 2008;15(1):37–41.

27. Pan C, guo-rong H, Jiang h-x, Zhao W, Cao M-k, Want C-m, et al. Telbivudine Prevents Vertical Transmission from HBeAg psotive women with Chroinic Hepatitis B. Clinical Gastroenterology & Hepatology. 2012;10:520–6.

28. Bortolotti F, Guido M, Bartolacci S, Cadrobbi P, Crivellaro C, Noventa F, et al. Chronic hepatitis B in children after e antigen seroclearance: final report of a 29-year longitudinal study. Hepatology. 2006;43(3):556–62.

29. Roushan MR, Bijani A, Ramzaninejad S, Roushan MH, Amiri MJ, Baiani M. HBeAg seroconversion in children infected during early childhood with hepatitis B virus. J Clin Virol. 2012;55(1):30–3.

30. Sokal EM, Paganelli M, Wirth S, Socha P, Vajro P, Lacaille F, et al. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines: consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Hepatol. 2013;59(4):814–29.

31. Jonas MM, Block JM, Haber BA, Karpen SJ, London WT, Murray KF, et al. Treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. Hepatology. 2010;52(6):2192–205.

32. Sokal EM, Conjeevaram HS, Roberts EA, Alvarez F, Bern EM, Goyens P, et al. Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial. Gastroenterology. 1998;114(5):988-95.

# CHAPTER 11: COMPLEX SITUATIONS: CO-INFECTION & IMMUNOSUPPRESSION


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**LINKS**

**Chapter 1:** Prevalence and epidemiology of hepatitis B
**Chapter 3:** Hepatitis B virus testing and interpreting test results
**Chapter 4:** Natural history of hepatitis B virus infection
**Chapter 5:** Primary prevention of hepatitis B virus infection
**Chapter 6:** Clinical assessment of patients with hepatitis B virus infection
**Chapter 7:** Treatment of chronic hepatitis B virus infection
**Chapter 10:** Managing hepatitis B virus and pregnancy and children

## KEY POINTS

- Co-infection with hepatitis B virus (HBV) and human immunodeficiency virus or hepatitis C or D virus results in worse outcomes for patients in terms of all-cause mortality, liver disease and hepatocellular carcinoma.
- All individuals with chronic hepatitis B should be tested for co-infection following appropriate pre-test discussion.
- People with ongoing risk factors for co-infection should be offered repeat testing, particularly in the setting of clinical deterioration.
- The approach to treatment for patients with co-infection is more complex than in the setting of mono-infection, and can be associated with increased risk of adverse outcomes.
- All patients undergoing significant immune suppression should be tested for HBV infection because viral reactivation and associated flares of hepatitis can occur, and can be fatal.

## Introduction

There are a number of special situations in which the complexity of managing the care of a patient with hepatitis B virus (HBV) infection is increased. Primary care practitioners are optimally placed to recognise and respond to these situations, and to coordinate management and referral to specialist services, to maximise the health and wellbeing of people living with chronic hepatitis B (CHB).

## Co-infection

HBV, hepatitis C and D viruses (HCV, HDV) and human immunodeficiency virus (HIV) have shared modes of transmission. The prevalence of co-infections varies widely globally depending of the endemicity of HBV and HDV (see **Chapter 1**), and the predominant modes of transmission for HIV and HCV. All patients with CHB should be offered testing for the presence of all these co-infections, following appropriate pre-test discussion (1). Each virus affects the natural history of CHB infection, and complicates treatment approaches. The management of co-infection is complex, and usually requires shared care with a specialist physician.

### HBV/HIV co-infection

#### *Epidemiology*

Globally, where CHB prevalence is high (>8%) or intermediate (2–8%), and is most often acquired in early childhood, co-infection in HIV-infected individuals is common, and reflects the background population prevalence. In Australia, which has a low prevalence of both viruses, new HBV infections are most commonly transmitted though parenteral exposure or unprotected sexual contact, and may be transmitted simultaneously with, before or after exposure to HIV (2). An estimated 6% of Australia's 25,000 HIV-infected individuals (3) are HBV/HIV co-infected (4, 5). Incident HBV infections are more common in HIV-infected individuals and men who have sex with men (MSM) – a population also at increased risk for HIV infection. Recent Australian studies estimate rates around 10 times those of the total population, at about 2 per 1,000 person years (5-8), and highlight the importance of testing, vaccination and (for HIV-infected individuals) boosting vaccination when the titre of antibodies to the hepatitis B surface antigen (anti-HBs) falls below 10 mIU/mL (9) (see **Chapter 5**).

#### *Natural history*

Co-infection with HIV has a significant impact on the natural history of CHB. Progression to chronic infection following acute HBV is more common in people with HIV infection than in immune competent adults (5), with the likelihood of failing to clear HBV related to the degree of immunodeficiency (10). High HBV DNA levels and detectable hepatitis B e antigen (HBeAg) are more common in patients with HIV co-infection, and the rate of viral reactivation is also higher, particularly in more immunocompromised patients (11). Occult infection (isolated antibodies to the hepatitis B core antigen [anti-HBc] with detectable HBV DNA) is more common in patients co-infected with HBV and HIV. Anti-HBs-positive patients with a history of resolved HBV infection can undergo reactivation, with reappearance of hepatitis B surface antigen (HBsAg)

(reverse seroconversion) and HBV DNA. This is a rare event, but may be more common in the setting of advanced immunodeficiency (12, 13).

Progression to advanced liver disease, such as cirrhosis and hepatocellular carcinoma (HCC), is more rapid, and liver-related mortality is higher, in the setting of HBV and HIV co-infection, despite typically lower alanine aminotransferase (ALT) values and reduced inflammatory activity on biopsy (13). This disparity of less necroinflammatory activity but faster disease progression is not fully understood. In contrast to the significant impact of co-infection on the natural history of HBV, there is little evidence to suggest that the HBV affects progression of HIV infection (13).

With the reduction in mortality related to acquired immune deficiency syndrome (AIDS) and incidence of opportunistic infections since the advent of combined antiretroviral therapy (cART), the burden of liver-related morbidity and mortality has increased (2). HBV infection contributes to liver-related illness either alone or in combination with other factors. Antiretroviral agents can cause liver toxicity, particularly in patients with pre-existing liver disease, such as chronic viral hepatitis (2).

***Management***

The indication for treatment of HBV in the setting of HIV co-infection is similar to that for HBV mono-infection, and the aims are essentially the same (14). If there is indication to start treatment for CHB alone, then treatment with HBV-active cART should be considered, regardless of CD4 level (13). Monotherapy for HBV with any agent (including tenofovir and entecavir) must be avoided, because this can induce HIV-resistance mutations that will make subsequent choice of cART regimens more difficult (2). ALT levels can be low in the presence of significant liver damage; therefore, assessment with FibroScan® or liver biopsy (or both) is important to determine the degree of liver fibrosis. Current treatment of HBV and HIV co-infection usually includes tenofovir in the cART regimen, to allow treatment of both infections. Sole HBV-active agents with a lower barrier to resistance (particularly lamivudine) in a cART regimen are likely to select for HBV resistance (15); therefore, patients should be switched to a regimen that includes tenofovir. Although there is an increased risk of HCC, particularly at lower CD4 counts, routine 6-monthly screening for HBV/HIV co-infected individuals is not currently recommended, and screening for HCC should occur as per guidelines (see **Chapter 6**) (16).

Immune reconstitution inflammatory syndrome (IRIS) occurs when there is a resurgent immune response to chronic infections in people living with HIV following commencement of cART. HBV flares in the setting of immune reconstitution are more common in patients with a high baseline HBV viral load (13) and low starting CD4 counts (e.g. <200), and can result in significant liver disease and in mortality, particularly in patients with advanced liver disease. However, flares can also lead to HBeAg clearance and sustained suppression of viral replication in some patients. Caution when changing cART regimens in

co-infected patients is also necessary, because ceasing HBV-active agents can cause reactivation. Continuation of these antiviral agents should be considered, even if they add little to the patient's HIV therapy.

## HBV/HCV co-infection

### *Epidemiology*

HBV/HCV is the most common co-infection in people living with CHB in Australia. HCV infection in Australia is most commonly associated with parenteral exposure, and HBV/HCV co-infected individuals can either be exposed due to this shared mode of transmission or have an independent risk factor for CHB; for example, country of birth, Aboriginal and Torres Strait Islander status or sexual risk (see **Chapter 1**). About 5% of Australians living with CHB are estimated to be co-infected with HCV.

### *Natural history*

In contrast to co-infection with HIV, reduced replication of HBV is common in HCV co-infection, with lower viral loads than in patients with HBV mono-infection, although these may fluctuate over time and should be assessed at regular intervals (14). The suppression of HBV is through the direct interference with replication by HCV (10). As with HIV, occult (HBsAg-negative) CHB is also more common in patients with HCV co-infection, and consideration should be given to testing for the presence of HBV DNA in people living with chronic hepatitis C with isolated anti-HBc on serologic testing (note: this test is not Medicare rebatable in the absence of HBsAg). HBV/HCV co-infection is associated with more severe liver disease, an increased risk of progression to cirrhosis and a higher incidence of HCC (14, 17). A large Australian linkage study showed that those co-infected with HBV and HCV experienced higher mortality rates (liver related and all cause) than those infected with either HBV or HCV alone; patients with co-infection had mortality rates about three times higher than patients with HBV mono-infection (18).

Acute co-infection (usually acquired through injecting drug use) has been associated with an increased incidence of fulminant hepatitis.

### *Management*

Patients need to be assessed fully for both viruses and evidence of liver fibrosis. The aim of management of HCV in HBV/HCV co-infection is cure with sustained viral suppression. The aim of treatment of HBV in HBV/HCV co-infection is adequate suppression of the virus and prevention of further liver damage. HCV treatment should be offered to co-infected patients (14) even if HBV infection predominates.

In people co-infected with HBV/HCV and treated for HCV, HBV clearance during treatment with pegylated-interferon (PEG-IFN) and ribavirin is as high as 30%, and can occur during up to 5 years of follow-up, with comparable response rates of treatment for HCV infection (19). Reactivation of previously suppressed HBV replication can occur following successful treatment for HCV, but also during treatment; hence, both viruses need to be monitored at regular intervals. Addition of anti-HBV agents (tenofovir and entecavir) in patients who have an increase in HBV DNA during treatment is recommended. There are no

large studies that support the routine addition of an HBV oral antiviral as a standard approach to an HBV/HCV co-infected individual undergoing treatment where HBV replication is suppressed.

## HBV/HDV co-infection

**Testing in HBV/HDV co-infection**

A positive HDV antibody test should be followed up by HDV RNA PCR testing (such tests are available at a limited number of laboratories; check for availability and charges).

HBV/HDV co-infection requires specialist management because outcomes are worse than mono-infection, and there are special considerations around the treatment approach.

HBV, hepatitis B virus; HDV, hepatitis D virus; PCR, polymerase chain reaction

### *Epidemiology*

HDV (sometimes called hepatitis delta) relies on HBV infection to replicate. Worldwide, HDV is more common in parts of sub-Saharan Africa, Eastern and Mediterranean Europe, the Amazon Basin and parts of Asia, but can vary within countries and regions (20). HDV prevalence varies widely between populations, but is estimated to affect around 5% of people with HBV infection in Australia (21). As with other co-infections, it can be acquired simultaneously with HBV infection or as a superinfection. In non-endemic countries such as Australia, HBV/HDV infection has been more commonly associated with injecting drug use, although the epidemiology is changing as migration from higher HDV prevalence areas increases and country of birth becomes an increasingly important determinant (21).

HDV/HBV co-infection appears to be rare in Aboriginal and Torres Strait Islander people who do not have other risk factors for infection, based on a recent study from the Northern Territory (22); however, evidence on prevalence among Aboriginal and Torres Strait Islander people in other areas of Australia is lacking.

### *Natural history*

HDV is a satellite virus that requires HBV co-infection to synthesise new virions; it therefore cannot infect hepatocytes in the absence of HBV. Similar to the situation of HBV/HCV co-infection, HDV infection usually results in suppression of HBV replication with low or undetectable HBV DNA levels, although this is not uniformly the case (23).

Acute co-infection with HBV/HDV is typically indistinguishable from HBV mono-infection, but has been associated with a higher incidence of fulminant hepatitis. The rate of progression to chronicity is no different from that for HBV infection alone. HDV superinfection in a person with CHB can present as an acute hepatitis flare, and progression to chronic HDV infection is usual. Chronic HBV/HDV co-infection has been associated with more severe liver disease; evidence regarding the influence on HCC incidence is mixed (24).

### *Management*

HBV/HDV co-infected patients need to be assessed as usual (see **Chapter 6**) and the decision for treatment should be made on similar criteria. Initial testing of HDV antibody for all people with CHB should be followed with HDV RNA polymerase chain reaction (PCR) for any

patient with a positive result (21); serum HDV RNA results fluctuate, and referral for specialist management is advisable. Antiviral agents for HBV infection are not effective against HDV, but, as is the case in HBV/HCV co-infection, they may be required for the treatment of HBV infection, depending on viral predominance and degree of underlying liver disease (23). Treatment of HBV/HDV co-infection is with a prolonged (1–2 year) course of IFN-alfa, conventional or PEG-IFN (1) although treatment is successful in a minority of patients and relapse following therapy is common (25).

### Multiple co-infections

Multiple co-infections with a combination of HBV, HCV, HDV or HIV occur uncommonly and, in the Australian context, are most likely to be associated with a history of injecting drug use.

## Immunosuppression and reactivation

All patients should be offered testing for the presence of resolved or current HBV infection before immunosupression (14, 26, 27). This is particularly the case when considering that nearly half of all people living with CHB in Australia are estimated to remain undiagnosed (28). Universal testing for people undergoing cancer chemotherapy or other significant immunosuppression is recommended in Australia's National Hepatitis B Testing Policy[1] (14). Use of 'biologics' (drugs that modify the body's immunological responses, such as rituximab, infliximab and adalimubab) is increasing in the setting of cancer therapy, rheumatology, dermatology and other specialist fields; thus, the primary care provider needs to be aware of the potential impact of CHB infection in diseases where immunosupression is a treatment modality. Reactivation of CHB is also observed with other immuno-suppressant medications (e.g. steroids and methotrexate) and in the setting of organ transplantation. The short-term use of low-dose steroids in individuals without advanced liver disease is unlikely to cause significant reactivation of the virus.

Primary care providers should be aware of the need for this testing, especially for priority population groups (see **Chapter 1**) because not all specialist services routinely perform HBV testing for people undergoing immunosuppression (29).

There are two clinical scenarios to consider in the setting of planned immuno-supression after a full panel of HBV testing has been performed (see **Chapter 3**):

- an HBsAg-positive individual (CHB)
- an individual with resolved infection (anti-HBc positive +/– anti-HBs positive >10 mIU/mL) at risk of seroreversion and reactivation in the setting of profound immunosuppression.

The natural history of HBV infection is fundamentally related to the dynamic balance between viral replication and host immune response (see **Chapter 4**). It is therefore not surprising that immunosuppressive therapy (ongoing, or cyclical, as in the case of cancer chemotherapy) can have a marked impact on chronic HBV infection.

1 Available at http://testingportal.ashm.org.au/hbv

Significant immunosuppression is associated with a reactivation in viral replication and rising HBV DNA. Immunosuppression-associated HBV reactivation and flares have been observed in patients undergoing chemotherapy, organ transplantation, treatment for autoimmune diseases and glucocorticoid therapy. Glucocorticoid therapy both suppresses the host immunity and acts directly on the virus to enhance transcription.

Profound immunosuppression can also cause reactivation of HBV infection in patients with serologically resolved infection or seroreversion (HBsAg negative → positive in an anti-HBc-positive patient), because patients with this serological pattern have HBV DNA present in hepatocytes. This has particularly been noted in the setting of the treatment of haematological malignancies; for example, CHOP chemotherapy[2] plus rituximab in the setting of lymphoma (14, 29).

Reactivation of HBV replication, in either scenario, can be followed by a flare of hepatitis with rising ALT levels. This is particularly noted following the withdrawal of immunosuppressive treatment, commonly over a period of weeks or months, although it can occur after a prolonged delay. The mechanism is similar to flares post pregnancy (see **Chapter 10**) or in IRIS seen with cART for HIV infection (see above), where the restoration of immune function leads to an increase in the destruction of HBV-infected hepatocytes.

Although many hepatitis flares in the context of immunosuppression are asymptomatic, a full spectrum of presentations is possible, through to liver failure and death. Risk factors for reactivation are shown in Table 11.1 (30). The rate of withdrawal of immunosuppression is an important determinant of the severity of flares. The increased incidence of flares observed in the setting of cancer chemotherapy compared with other immunosuppressive regimens may relate to the cyclical nature of such therapy, with repeated episodes of immune suppression and restoration.

**Table 11.1** Risk factors for reactivation

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|---|
| Intensity of immunosuppression or chemotherapy regimen |
| Specific agents including glucocorticoids and biologics (e.g. rituximab, infliximab and adalimubab) |
| Longer duration chemotherapy |
| High baseline HBV DNA |
| HBeAg positive |
| Young age |
| Male gender |
| Cyclical therapy |
| Absence of anti-HBs in HBsAg negative anti-HBc positive |

anti-HBc, antibodies to hepatitis B c antigen; anti-HBs, antibodies to hepatitis B surface antigen; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen

### *Management*

Presumptive treatment with antiviral therapy has been shown to substantially reduce the incidence of hepatic flares and associated mortality. This prophylaxis

2 Chemotherapy that includes cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone

should be given to all HBsAg-positive patients before chemotherapy or other immunosuppressive therapy (1, 14). Pre-emptive treatment has been shown to have better outcomes than starting treatment once reactivation has been detected (30).

The choice of antiviral agent depends on the baseline HBV DNA viral load, the intensity and duration of immunosuppression, and the degree of baseline liver disease. Lamivudine may be considered for limited duration of less intense immunosuppression with little or no baseline HBV replication in a person without advanced fibrosis; otherwise, the treatments of choice are entecavir or tenofovir (see **Chapter 7**). PEG-IFN is not used in this context.

The approach to patients who are HBsAg negative and anti-HBc positive is less clear, with the risk of reactivation in the setting of profound immunosuppression (e.g. CHOP + rituximab) greater in those who are anti-HBs negative. Current guidelines suggest monitoring with HBV DNA to detect reactivation early (26), although a recent small randomised controlled trial suggested a role for prophylaxis with a significant reduction in reactivation at 0, 5 and 18 months (31).

## Conclusion

Special situations of HBV infection, including co-infection and immunosuppression, are potentially associated with worse outcomes, and need coordinated primary and specialist care to prevent unnecessary morbidity and mortality. As patients living with CHB age and are treated with immunosuppressive therapy for cancers and other conditions, primary care needs to be involved in screening and detection of those at risk of reactivation.

## References


1. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2007;45(2):507–39.
2. Cowie BC, Dore G, Sasadeusz J, editors. Co-infection: HIV and viral hepatitis - a guide for clinical management. 4 ed. Darlinghurst: Australasian Society for HIV Medicine; 2010.
3. The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: Annual Surveillance Report 2013. Sydney: The Kirby Institute, The University of New South Wales; , 2013.
4. Lincoln D, Petoumenos K, Dore GJ. HIV/HBV and HIV/HCV coinfection, and outcomes following highly active antiretroviral therapy. HIV Med. 2003;4(3):241–9.
5. Body A, Hoy J, Cheng A, Giles M. Incident Hepatitis B virus (HBV) infection subsequent to the diagnosis of HIV infection in a Melbourne cohort; missed opportunities for prevention. Sex Health. 2013.
6. Gamagedara N, Weerakoon AP, Zou H, Fehler G, Chen MY, Read TR, et al. Cross-sectional study of hepatitis B immunity in MSM between 2002 and 2012. Sex Transm Infect. 2013.
7. Australian Government Department of Health and Ageing. National Notifiable Diseases Surveillance System. 2013; Available from: http://www9.health.gov.au/cda/Source/CDA-index.cfm.
8. Wheeler E, Cowie B. Be aware--hepatitis B as an STI. Australian nursing journal. 2011;19(6):41–2.
9. The Australian Immunisation Handbook. 10th ed: ATAGI, NHMRC, Department of Health and Ageing, Australian Government; 2013.
10. Shukla NB, Poles MA. Hepatitis B virus infection: co-infection with hepatitis C virus, hepatitis D virus, and human immunodeficiency virus. Clin Liver Dis. 2004;8(2):445–60, viii.

11. Thio CL, Locarnini S. Treatment of HIV/HBV coinfection: clinical and virologic issues. AIDS Rev. 2007;9(1):40–53.
12. Rouphael NG, Talati NJ, Rimland D. Hepatitis B reverse seroconversion in HIV-positive patients: case series and review of the literature. Aids. 2007;21(6):771-4.
13. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. Hepatology. 2009;49(5 Suppl):S138–45.
14. Cancer incidence projections: Australia, 2011 to 2020. Canberra: Australian Institute of Health and Welfare, 2012; Cat. no. CAN 62.
15. Matthews GV, Avihingsanon A, Lewin SR, Amin J, Rerknimitr R, Petcharapirat P, et al. A randomized trial of combination hepatitis B therapy in HIV/HBV coinfected antiretroviral naive individuals in Thailand. Hepatology. 2008;48(4):1062–9.
16. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology. 2005;42(5):1208–36.
17. Amin J, Dore GJ, O'Connell DL, Bartlett M, Tracey E, Kaldor JM, et al. Cancer incidence in people with hepatitis B or C infection: a large community-based linkage study. J Hepatol. 2006;45(2):197–203.
18. Amin J, Law MG, Bartlett M, Kaldor JM, Dore GJ. Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study. Lancet. 2006;368(9539):938–45.
19. Yu ML, Lee CM, Chen CL, Chuang WL, Lu SN, Liu CH, et al. Sustained hepatitis C virus clearance and increased hepatitis B surface antigen seroclearance in patients with dual chronic hepatitis C and B during posttreatment follow-up. Hepatology. 2013;57(6):2135–42.
20. Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. Lancet. 2011.
21. Shadur B, Maclachlan J, Cowie B. Hepatitis D Virus in Victoria 2000-2009. Intern Med J. 2013.
22. Davies J, Tong SY, Davis JS. Hepatitis D is rare or non-existent in hepatitis B virus-infected Indigenous Australians in the Northern Territory. Aust N Z J Public Health. 2013;37(2):188-9.
23. Wedemeyer H. Re-emerging interest in hepatitis delta: new insights into the dynamic interplay between HBV and HDV. J Hepatol. 2010;52(5):627–9.
24. Wu JC, Chen TZ, Huang YS, Yen FS, Ting LT, Sheng WY, Tsay SH, Lee SD. Natural history of hepatitis D viral superinfection: significance of viremia detected by polymerase chain reaction. Gastroenterology. 1995;108(3):796-802.
25. Alavian SM, Tabatabaei SV, Behnava B, Rizzetto M. Standard and pegylated interferon therapy of HDV infection: A systematic review and meta-analysis. J Res Med Sci. 2012;17(10):967–74.
26. Lubel JS, Angus PW. Hepatitis B reactivation in patients receiving cytotoxic chemotherapy: diagnosis and management. J Gastroenterol Hepatol. 2010;25(5):864–71.
27. Feld J. HBV treatment in a patient who will be receiving immunosuppressive therapy. Clinical Liver Disease. 2013;2(1):34–7.
28. MacLachlan JH, Allard N, Towell V, Cowie BC. The burden of chronic hepatitis B virus infection in Australia, 2011. Aust NZ J Public Health. 2013;37(5):416–22.
29. Tsutsumi Y, Ogasawara R, Miyashita N, Tanaka J, Asaka M, Imamura M. HBV reactivation in malignant lymphoma patients treated with rituximab and bendamustine. Int J Hematol. 2012;95(5):588–91.
30. Lalazar G, Rund D, Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. Br J Haematol. 2007;136(5):699–712.
31. Huang YH, Hsiao LT, Hong YC, Chiou TJ, Yu YB, Gau JP, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. J Clin Oncol. 2013;31(22):2765–72.

# CHAPTER 12: INFECTION CONTROL AND OCCUPATIONAL HEALTH


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| **LINKS** | **Chapter 3:** Hepatitis B virus testing and interpreting test results<br>**Chapter 5:** Primary prevention of hepatitis B virus infection<br>**Chapter 13:** Privacy, confidentiality and other legal responsibilities |

## KEY POINTS

- The potentially infectious nature of all blood and body substances necessitates the implementation of infection control practices and policies in the health-care setting.
- The current best-practice guidelines for infection control procedures in Australian health-care settings are outlined in the *Australian guidelines for the prevention and control of infection in healthcare* (2010) (1).
- The universal application of standard precautions is the minimum level of infection control required in the treatment and care of all patients to prevent transmission of hepatitis B virus (HBV).
- Vaccination is an important infection control strategy for the prevention of HBV. All health-care workers should be vaccinated (if appropriate) and be aware of their vaccination status.
- Clinicians and other health-care workers who regularly perform exposure-prone procedures have a responsibility to be regularly tested for human immunodeficiency virus (HIV), hepatitis C virus (HCV) and HBV if they are not immune.
- Health-care workers who are infected with HIV, HBV or HCV should not perform exposure-prone procedures.

## Introduction

The aim of this chapter is to provide:

- detail about standard precautions and infection control guidelines for health-care settings
- advice about hepatitis B prevention in health-care settings, and guidance on the management of blood and body-substance exposures and incidents.

### Myths and facts about infection control

**MYTH** – Wearing gloves means you do not need to wash your hands.
**FACT** – Gloves are not a substitute for effective hand washing.

**MYTH** – Health-care workers should use transmission-based precautions (formerly referred to as additional precautions) when caring for a patient with HBV, to prevent transmission.
**FACT** – Implementation of standard precautions ensures a high level of protection against transmission of HBV in the health-care setting.

**MYTH** – Health-care workers need to have booster dose of hepatitis B vaccine every 5 years.
**FACT** – Booster doses are no longer recommended in immunocompetent individuals after a primary course of HBV vaccine, because the evidence suggests that a completed course of HBV vaccination provides long-lasting protection.

**MYTH** – Health-care workers with HBV must not have contact with patients because of the risk of transmission.
**FACT** – Health-care workers with HBV are generally advised to avoid performing exposure-prone procedures; however, they can still have non-invasive contact with patients.

HBV, hepatitis B virus

It is essential to maintain the safety of the health-care environment for patients and health professionals; this necessitates the implementation of infection control guidelines. The current best-practice guidelines for infection control procedures in Australia are outlined in the *Australian guidelines for the prevention and control of infection in healthcare (2010)* (1). State and territory health departments in Australia have adopted the principle of standard precautions. Such precautions ensure a high level of protection against transmission of infection in the health-care setting, and are required in the treatment and care of all patients to prevent transmission of blood-borne infections.

Infection control guidelines are relevant in social and domestic contexts, as well as in occupational settings. The implementation of infection control guidelines in social and domestic settings can help patients with hepatitis B virus (HBV) to reduce the risk of transmitting the disease to unvaccinated significant others. Clinicians should be able provide advice for patients in relation to infection control in their daily environment. This chapter provides an overview of the current Australian infection control guidelines and their relevance in treating patients with HBV.

## Transmission

Modes of HBV transmission and risk of transmission are outlined in **Chapter 3**.

The risk of blood-borne virus transmission depends on a number of factors. Incidents involving blood-to-blood contact with infectious blood are associated with a high risk of infection when:

- there is a large quantity of blood, indicated by visible contamination
- there is insertion of a needle directly into a vein or artery or deep cavity
- the patient has high levels of HBV DNA and detectable hepatitis B e antigen (HBeAg); hepatitis C virus (HCV) RNA detected by polymerase chain reaction (PCR); advanced human immunodeficiency virus (HIV) disease or high HIV viral load
- the immunisation status of the exposed individual (in the case of HBV) is unknown.

Patient-to-patient transmission of HBV, although rare, has been associated with oral surgery, inadequate use or disinfection of medical devices (e.g. blood glucose finger-stick devices), and multidose vials (2-6). Transmission of HBV in the health-care setting can be prevented through hepatitis B vaccination programs for health-care workers, patients and community, and strict adherence to standard precautions.

## Standard precautions

The universal application of standard precautions is the minimum level of infection control required in the treatment and care of all patients to prevent transmission of blood-borne viruses. These precautions include personal hygiene practices (particularly hand washing) before and after every episode of patient contact, use of personal protective equipment (e.g. gloves, gowns and protective eye wear), aseptic non-touch technique, safe disposal systems for sharps and contaminated matter, routine environmental cleaning, reprocessing of reusable medical equipment and instruments, ensuring that single use items are only used once and disposed of after single use (including single use of multidose vials), respiratory hygiene and waste management.

Standard precautions should be implemented for all patients all of the time, regardless of information or assumptions about a patient's blood-borne virus status. This practice will help to reduce potential stigma and discrimination in the health-care setting.

### Hand hygiene

Hand hygiene practices are generally considered the most important hygiene measure in preventing the spread of infection. However, hand hygiene alone is insufficient to prevent and control infection, it needs to be used as part of a multifactorial approach to infection control. Clinicians should wash their hands or use an alcohol-based hand rub before and after contact with any patient, and after activities that may cause contamination.

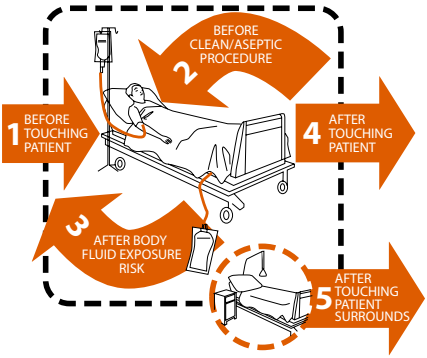
Hand hygiene must be performed before and after every episode of patient contact. This includes:

- before touching a patient
- before a procedure
- after a procedure or body-substance exposure risk
- after touching a patient
- after touching a patient's surroundings.

Hand hygiene must also be performed after the removal of gloves.

The 'five moments for hand hygiene' shown in Figure 12.1 were developed by the World Health Organization (WHO) (7) and adopted by Hand Hygiene Australia (8).

**Figure 12.1** Five moments for hand hygiene (7)




Adapted with permission from: Sax H, Allegranzi B, Uçkay I, Larson E, Boyce J, Pittet D. 'My five moments for hand hygiene': a user-centred design approach to understand, train, monitor and report hand hygiene. J Hosp Infect. 2007;67(1): 9–21.

Skin care is important because healthy, unbroken skin provides a valuable, natural barrier to infection. Skin breaks should be covered with a water-resistant occlusive dressing. Alcohol-based hand rubs are more effective against most common infectious agents on hands than hand hygiene with plain or antiseptic soap and water.

## Gloves

Gloves are a form of personal protective equipment. Clinicians and other health-care workers should wear gloves whenever there is a risk of exposure to blood or body substances. They should change their gloves and wash their hands after contact with each patient, and during procedures with the same patient if there is a chance of cross contamination. Gloves must be used when:

- handling blood or body substances (or both)
- performing venepuncture
- touching mucous membranes
- touching non-intact skin
- handling contaminated sharps
- performing invasive procedures
- cleaning body-substance spills or any equipment (instruments), materials (linen) or surface that may have been contaminated by body substances.

Gloves do not need to be used for every episode of patient contact unless the above points apply.

Further information about the appropriate use of gloves is given in the Australian guidelines (1).

## Other personal protective equipment

Personal protective equipment should be readily available and accessible in all health-care settings. The type of protective equipment required depends on the nature of the procedure, the equipment used and the skill of the operator. For example, the use of protective equipment is recommended in the following circumstances:

- protective eyewear and face shields should be worn during procedures where there is potential for splashing, splattering or spraying of blood or other body substances

- impermeable gowns and plastic aprons should be worn to protect clothing and skin from contamination with blood and body substances
- footwear should be enclosed to protect against injury or contact with sharp objects.

## Occupational exposure

### Prevention of occupational exposure (needlestick or sharps injuries)

Inappropriate handling of sharps is a major cause of accidental exposure to blood-borne viruses in health-care settings. To minimise the risk of a needlestick or sharps injury, needles, sharps and clinical waste should be handled carefully at all times. Specifically, clinicians and other health-care workers should:

- minimise their handling of needles, sharps and clinical waste
- not bend or recap needles, or remove needles from disposable syringes
- use safe needle-handling systems, including rigid containers for disposal (these should be kept out of the reach of children)
- ensure that 'sharps' containers are available at the point of use or in close proximity to work sites, to aid immediate disposal.

Importantly, the person who has used a sharp instrument or needle must be responsible for its immediate safe disposal following its use.

### Management of occupational exposures

All clinicians and health-care workers should have access to infection control guidelines that advise about the management of an occupational injury, including clear written instructions on the appropriate action to take in the event of a needlestick and other blood or body-substance exposures involving either patients or health-care workers. Clinicians and health-care workers should be encouraged to report occupational exposures immediately, and all testing procedures and follow-up treatment should be fully documented. Confidentiality should be maintained.

In general, if an injury or incident occurs where blood or body substances come into contact with non-intact skin or membranes, the following action should be taken:

- Wash exposed membrane or injury with soap and water (an antiseptic could also be used on the skin).
- If eyes have been exposed, thoroughly rinse the eyes with tap water or saline while open.
- If mouth has been exposed, thoroughly rinse the mouth with water and spit out.
- Seek medical advice immediately for assessment of nature of the exposure, the risk of transmission of blood-borne viruses and the need HIV or HBV post-exposure prophylaxis.
- If the exposure is significant and the source patient is known, their consent for HIV, HCV and HBsAg testing should be sought.

### Hepatitis B immunoglobulin as post-exposure prophylaxis in the health-care setting

Initiation of hepatitis B immunoglobulin (HBIG) depends on the type of exposure, the source patient's HBsAg status and the exposed person's HBV immunisation history.

#### *Unvaccinated individual*

In the case of an unvaccinated individual who is exposed to HBV infected blood or body substances, HBIG should be administered within 72 hours of the exposure, to prevent HBV infection. The first dose of the HBV vaccine should also be administered as soon as possible.

#### *Vaccinated individual*

For individuals who have been vaccinated and who have a documented protective response after vaccination (anti-HBs level ≥10 mIU/mL), HBIG is not recommended. If an individual's response to the vaccine has not been determined, this should be done immediately. If there is no protection, the individual should be offered a dose of HBIG and HBV vaccine.

## Issues for health-care workers

### Vaccination

Vaccination is an important infection control strategy to prevent the transmission of HBV. For further information on the HBV vaccination regime and groups to be vaccinated, see **Chapter 5**.

### Testing

The mandatory testing of clinicians and other health-care workers for HBV, HCV and HIV is not warranted, due to the low risk of transmission if standard precautions are followed. Testing for blood-borne viruses should only be undertaken on the basis of clinical assessment or where testing is in the interests of patients and health-care workers (e.g. a needlestick injury) (1). Clinicians and other health-care workers who regularly perform exposure-prone procedures have a responsibility to be regularly tested for HIV, HCV and HBV if they are not immune. The provision of confidentiality, privacy and consent for testing should be applied.

### Infected health-care workers

Clinicians and other health-care workers have a legal obligation to care for the safety of others in the workplace, and this includes colleagues and patients. Clinicians and other health-care workers infected with HBV should consult state or territory regulations to determine what restrictions are placed on their clinical practice. In general, it is recommended that they do not perform procedures that carry a high risk of transmission of the virus from health-care worker to patient (i.e. exposure-prone procedures).

Health-care workers must not perform exposure-prone procedures if they are HBeAg positive or hepatitis B DNA positive at high titres. Those who are currently HBsAg positive and HBV DNA negative must obtain ongoing medical advice about their potential infectiousness and the appropriateness of their continued performance of such procedures (1).

### Infection control in the primary-care setting

The general principles of infection control that apply to large health-care settings also apply to office practices; specific issues related to office practices are outlined in the *The Australian guidelines for the prevention and control of infection in healthcare (2010)* (1) and the Royal Australian College of General Practice (RACGP) infection control standards (9).[3]

### Management of blood and body-substance spills in the health-care setting

Management of blood and body-substance spills depends on the nature of the spill, type of surface and the area involved. The basic principles of spills management are:

- standard precautions, including use of personal protective equipment, apply where there is a risk of contact with blood or body substances
- spills should be cleaned up before the area is disinfected
- the spill should be confined and contained, and visible matter should be cleaned with disposable absorbent material, and the used cleaning materials discarded in the appropriate waste container
- generation of aerosols from spilled material should be avoided.

Use of chemical disinfectants such as sodium hypochlorite should be based on assessment of risk of transmission of infectious agents from the spill.

Prompt removal of spots and spills of blood and body substances, followed by cleaning and disinfection of the area contaminated, is sound infection control practice and meets occupational health and safety requirements (1). Further information about management of blood or body fluid spills is given in the Australian guidelines (1).

## Legal and ethical issues

Legal liability may occur if inadequate care has been taken to prevent the transmission of infection. Regulatory authorities (e.g. environmental protection) and the Australian Government, states or territories, and local governments enforce laws and regulations relating to infection control and waste disposal. These regulations can vary considerably throughout Australia, and should take precedence over the general information presented in this chapter. Further information can be obtained from state and territory health departments, and from medical and other professional boards. Legal issues are considered in greater detail in **Chapter 13**.

## Conclusion

Standard precautions and infection control procedures protect against transmission of blood-borne viruses, including HBV, HCV and HIV, in the health-care setting. Regardless of the perceived risk, infection control procedures must be followed in all clinical settings, to

3 The *RACGP Infection prevention and control standards for general practices and other office-based and community-based practices* (5th Edition) can be accessed electronically at http://www.racgp.org.au/publications/ordering/standards/.

minimise the risk of accidental transmission of blood-borne viruses. Clinicians and other health-care workers should be vaccinated against HBV, and should know their vaccination response. Exposures to blood and body substances should be reported immediately and monitored.

## References


1. National Health and Medical Research Council (NHMRC). Australian guidelines for the prevention and control of infection in healthcare. Canberra: Commonwealth of Australia, 2010.
2. Redd JT, Baumbach J, Kohn W, Nainan O, Khristova M, Williams I. Patient-to-patient transmission of hepatitis B virus associated with oral surgery. The Journal of Infectious Diseases. 2007;195(9):1311–4.
3. Polish LB, Shapiro CN, Bauer F, Klotz P, Ginier P, Roberto RR, et al. Nosocomial transmission of hepatitis B virus associated with the use of a spring-loaded finger-stick device. The New England Journal of Medicine. 1992;326(11):721–5.
4. Hutin YJ, Goldstein ST, Varma JK, O'Dair JB, Mast EE, Shapiro CN, et al. An outbreak of hospital-acquired hepatitis B virus infection among patients receiving chronic hemodialysis. Infection Control and Hospital Epidemiology. 1999;20(11):731–5.
5. Dumpis U, Kovalova Ž, Jansons J, Čupane L, Sominskaya I, Michailova M, et al. An outbreak of HBV and HCV infection in a paediatric oncology ward: epidemiological investigations and prevention of further spread. Journal of Medical Virology. 2003;69(3):331–8.
6. Samandari T, Malakmadze N, Balter S, Perz JF, Khristova M, Swetnam L, et al. A large outbreak of hepatitis B virus infections associated with frequent injections at a physician's office. Infection Control and Hospital Epidemiology. 2005;26(9):745–50.
7. World Health Organization (WHO). Guidelines on hand hygiene in healthcare. Geneva: WHO; 2009; Available from: http://www.who.int/patientsafety/information_centre/documents/en/index.html.
8. Grayson L, Russo P, Ryan K. Hand Hygiene Australia Manual: Australian Commission for Safety and Quality in Healthcare and World Health Organization; 2009.
9. Royal Australian College of General Practitioners (RACGP). Infection control standards for office based practices. Melbourne: RACGP; 2006.

# CHAPTER 13: PRIVACY, CONFIDENTIALITY AND OTHER LEGAL RESPONSIBILITIES


| | |
|---|---|
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Disclaimer: This chapter does not constitute legal advice. Instead, it references (and in some cases summarises) key Federal and state laws and policies related to privacy, confidentiality and duty of care, and summarises relevant jurisprudence. Practitioners faced with uncertainty in this area are strongly advised to seek legal advice, or to contact their local health department or applicable privacy office.

This chapter has been adapted from the *Australasian contact tracing manual* (1).


**LINKS** **Chapter 12:** Infection control and occupational health


## KEY POINTS

- In Australia, it is illegal to discriminate against a person because they have or are presumed to have any disease, including hepatitis B virus (HBV) infection.
- HBV is a notifiable disease in every Australian state and territory, which means that it is mandatory for health-care practitioners to report any confirmed case. Mandatory notification does not legally breech a patient's right to privacy, although patients should be informed that notification will occur.
- Information relating to an individual's health and health-related treatment is sensitive, and an individual's right to privacy around this information is protected by state, territory and Federal legislation.
- The *Privacy Act 1988 (Commonwealth)* ('the Act') is the primary piece of legislation governing privacy of health-care information in Australia. The *Privacy Amendment (Enhancing Privacy Protection) Act 2012* (the 'Privacy Amendment Act') was passed in November 2012, and came into force on 14 March 2014. The Privacy Amendment Act increases restrictions on the handling of personal information obtained from a third party, and provides the Privacy Commissioner with greater powers and increased penalties for privacy breaches.


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- State and territory governments have also enacted jurisdictional laws and regulations that affect privacy practices. These state and territory instruments may intersect or overlap with the Commonwealth Privacy Act and, as a result, health-care practitioners must make themselves aware of the privacy and confidentiality obligations that relate to their practice within their respective jurisdiction.
- Health-care practitioners should only collect health information about a patient with that patient's informed consent, and should advise the patient of the potential use of that information as part of obtaining informed consent. There should be systems in place for secure storage of physical and electronic records, and all staff should be trained in these systems, and aware of their privacy and confidentiality obligations.
- Health-care workers are required to disclose their status if they are carrying out exposure-prone procedures, applying for the defence forces, or applying for relevant particular types of insurance. They may also be required to disclose to their sexual partners if they are not taking reasonable precautions not to transmit the infection.

## Why is privacy and confidentiality important?

The Australian Medical Association *Code of ethics* ('the Code')[4] requires medical practitioners to maintain a patient's confidentiality. The Code notes that exceptions to patient confidentiality 'must be taken very seriously. They may include where there is a serious risk to the patient or another person, where required by law, or where there are overwhelming societal interests.'

The protection of health-related information attracts special treatment because of the extremely sensitive nature of personal health information, the impact of breaches of these policies on the affected individuals, and the high rate of health-related complaints to state or territory and Commonwealth privacy offices.

### Importance of privacy and confidentiality

It is important to maintain privacy and confidentiality because:

- patients are concerned about the stigma and discrimination associated with their HBV status and related conditions
- patients want to know that they can choose who can access their health information
- patients are far more likely to seek medical care, and give full and honest accounts of their symptoms, if they feel comfortable, respected and secure
- a health-care system with strong privacy mechanisms will promote public confidence and trust in health-care services generally.

HBV, hepatitis B virus

4 Available from https://ama.com.au/codeofethics

The terms 'privacy' and 'confidentiality' are commonly used interchangeably, but they are not identical concepts in the legal sense. 'Privacy' laws regulate the handling of personal information (including health information) through enforceable privacy principles, whereas 'confidentiality' refers to the legal duty that the health-care practitioner owes to their patient in relation to the protection of their personal health information.

## Legal requirements for health-care practitioners

Issues relating to the management of privacy in the health sector are covered by the *Privacy Act 1988 (Commonwealth)* ('the Act'). The Act applies to all private sector organisations that provide health services or hold health information. A 'health service' can be broadly defined as any activity that involves:

- assessing, recording, maintaining or improving a person's health; or
- diagnosing or treating a person's illness or disability; or
- dispensing a prescription drug or medicinal preparation by a pharmacist.

Consequently, health services include traditional health-service providers (e.g. private hospitals and day surgeries, medical practitioners, pharmacists and allied health professionals), as well as complementary therapists, gyms, weight loss clinics and many others.

There is no Federal legislation that relates specifically to the diagnosis, treatment or contact tracing of patients with HBV (or other notifiable diseases).

In the absence of Federal legislation, each state and territory has developed its own approach to privacy and confidentiality. Some jurisdictions have developed specific, targeted laws and policies, whereas others rely on more generic laws and processes.

The Act generally covers all health-sector employees (e.g. medical practitioners, nurses, administrators, trainers and cleaners) not directly employed by a state or territory government, because they are usually covered by state laws. Further information on who is covered by the Act is available from the Office of the Australian Information Commissioner.[5]

The Act contains 13 Australian privacy principles[6] (APPs), which outline minimum privacy standards for handling health information. These APPs are legally binding; hence, all practitioners should familiarise themselves with these principles.

Some APPs outline specific obligations for health-service professionals, whereas others simply mandate that a practitioner 'take reasonable steps' to meet the stated obligations. Practitioners should seek legal advice if they are unsure of the application of the APPs to particular situations.

In some instances, the layers of Commonwealth, state and territory laws and regulations may overlap across particular privacy obligations. However, under the Australian Constitution, when a state

5 See http://www.oaic.gov.au/privacy/who-is-covered-by-privacy

6 See http://www.oaic.gov.au/privacy/privacy-resources/privacy-fact-sheets/other/privacy-fact-sheet-17-australian-privacy-principles

or territory law is inconsistent with a Commonwealth law, the Commonwealth law prevails. Consequently, all private sector health-service providers are required to comply first and foremost with the provisions of the Commonwealth Privacy Act, and secondly with any additional and non-conflicting state or territory laws.

It is important to understand both state and Commonwealth-based laws. In New South Wales (NSW), for example, state privacy legislation (the *Health Records and Information Privacy Act 2002*) applies to public sector and private sector health-care providers, and to holders of health records located in NSW. Consequently, private sector health-service providers must comply with two sets of privacy legislation (Federal and NSW) that are largely, but not wholly, compatible. The two sets of legislation impose similar obligations on private health-care providers. However, it could be argued that the NSW legislation has a higher compliance threshold, so that if a health-care practitioner complies with the NSW *Health Records and Information Privacy Act,* they will generally also comply with the *Commonwealth Privacy Act*.

Most states now have laws severely restricting the transfer of information in the health sector, and in some states, breaches of confidentiality may amount to a criminal offence. In addition to these intersecting laws, many states also have multiple layers of regulation. Those seeking advice on state or territory privacy laws should contact the agencies shown in Table 13.1.

**Table 13.1** State and territory agencies relevant to privacy laws

| State or territory | Relevant agency |
|---|---|
| Australian Capital Territory | Office of the Australian Information Commissioner<br>1300 363 992<br>enquiries@oaic.gov.au |
| New South Wales | NSW Information and Privacy Commission<br>1800 472 679<br>ipcinfo@ipc.nsw.gov.au |
| Northern Territory | Office of the Information Commissioner<br>1800 005 610<br>infocomm@nt.gov.au |
| Queensland | Office of the Information Commissioner<br>(07) 3234 7373<br>enquiries@oic.qld.gov.au |
| South Australia | Privacy Committee of South Australia<br>(08) 8204 8786<br>Privacy@sa.gov.au |
| Tasmania | Ombudsman Tasmania<br>1800 001 170<br>ombudsman@ombudsman.tas.gov.au |
| Victoria | Office of the Victorian Privacy Commissioner<br>1300 666 444<br>enquiries@privacy.vic.gov.au |
| Western Australia | Although Western Australia's public sector does not currently have a legislative privacy regime, numerous confidentiality provisions cover government agencies, and some of the privacy principles are covered under the *Freedom of Information Act 1992*. Depending on the nature of the questions, the Office of the Information Commissioner may be able to provide assistance: 1800 621 244<br>info@foi.wa.gov.au |

## Legal requirements for patients

Health-care practitioners should refer patients to seek independent legal advice if the patients have particular concerns about their disclosure obligations and the possible risks associated with failure to disclose in certain situations. However, practitioners should be aware of general rules around disclosure that can be communicated to patients.

Laws around disclosure are based on the idea that individuals should not intentionally or negligently harm others, and that individuals have a right to be warned of a possible risk of transmission where there is a real danger of that risk. Therefore, disclosure is only mandatory where there is no other way to avoid the risk of transmission; generally, disclosure is only required in a few discrete circumstances. In particular, patients will need to know their responsibilities around employment, insurance and sexual partners.

Patients are not legally obligated to disclose their status to sexual partners where they are taking 'reasonable precautions' against transmission; such precautions may include the use of condoms and lubricants. Patients are legally obligated to disclose their status to their partner or partners before engaging in unprotected sexual activity, including vaginal, oral or anal intercourse. There have been no cases of criminal prosecution for the transmission of HBV. However, the intentional transmission of HBV might attract criminal penalties where the Court finds that the impact of transmission is sufficiently detrimental to the individual who now has the disease, and that the individual who transmitted the virus had the necessary intention.

### Circumstances requiring mandatory disclosure of status

It is mandatory for patients to disclose their status in a few exceptional circumstances:

- Health-care workers engaging in exposure-prone procedures are required to disclose to employers or potential employers. This particularly applies to surgeons, dentists or nurses working in these areas.
- Applicants or serving individuals in the Australian Defence Force (ADF) are required to disclose their status. The ADF is exempt from Federal anti-discrimination legislation, and can test applicants and serving individuals, and remove them from service if they are found to have a blood-borne virus.
- Insurance companies require disclosure where the type of insurance being applied for is 'relevant' to the health condition (e.g. life, disability or income protection). If a patient fails to disclose their status where relevant, the insurance company may not have to pay out on any claim that is made.

## Privacy issues

There are a number of broad privacy-related issues that face general practitioners and other primary health-care providers. These issues, discussed below, include collecting information, ensuring that consent is 'informed', advising use, notification, accessing personal records, security and storage of health information, and information for teams.

## Collecting information

General practitioners should only collect health information about patients with the patients' informed consent. It can be reasonable to imply informed consent where the information in question is noted from details provided by the patient during a consultation, and where it can be demonstrated that the patient understands what information is being recorded and how the information will be used. Record keeping must be thorough and accurate. This will ensure the best possible ongoing treatment for a patient and, in the worst-case scenario, can be used to support the practitioner should a patient attempt to make a case against a treating doctor for breach of privacy or confidentiality.

## Ensuring consent is 'informed'

All medical procedures require informed consent. Practitioners need to appreciate the potential consequences and impact of an HBV diagnosis on a patient; although running tests and delivering diagnosis may be standard for the health-care practitioner, receiving the results may be anything but routine for the patient. The provision of information both before the test and with the delivery of test results should allow the health-care practitioner to discuss the risks and benefits to the patient in that person's particular situation, thereby facilitating the patient's decision-making process.

When offering a test to patients with low proficiency in English, an accredited interpreter should be used to ensure that the patient understands what they are being offered and has the opportunity to ask any questions. The Translating and Interpreting Service is available 24 hours, 7 days a week.[7] Telephone interpreting is usually well accepted because it allows patients to maintain anonymity.

## Advising use

Patients can only provide informed consent about the use of their health information if they are clear about where the information will go and why. Therefore, patients should be advised of the intended use of their information when it is collected. This point also relates to instances when personal information cannot be shared or disclosed. For example, in a 2003 NSW case (PD), a doctor failed to inform two patients attending a joint consultation that the results of each person's tests could not be disclosed to the other person. The doctor consequently failed to ensure that both patients understood this situation, and also did not seek their informed consent to share the individual test results with the other patient. One patient tested positive for HIV and later infected the other patient, who had believed the clinic would make her aware if either of them tested positive for HIV. The Court found that the doctors had breached their duty of care and awarded substantial financial damages to the aggrieved patient.[8]

## Notification

There is no absolute right to privacy under Australian or international law. The Commonwealth Privacy Act provides exceptions to privacy where use or disclosure is required by law, generally in order to protect the public from the spread

7 Contact the Doctor's Priority Line on 1300 131 450
8 An outline of this and other cases is available at http://www.ashm.org.au/HIVLegal/

of infectious diseases. In developing Australian privacy laws, the right to individual privacy has been weighed against the rights of the public and against matters that benefit society as a whole.

HBV is a notifiable disease in all Australian states and territories. Legal obligations informing notification are mandated by state laws, which define a doctor's duty to notify the respective health department of a notifiable disease.

## Accessing personal records

Patients are entitled to access their health records, except for a limited number of exceptions outlined under APP 12 (previously NPP 6). These exceptions include where the request for access is frivolous or vexatious, or where providing access would be likely to prejudice an investigation of possible unlawful activity.[9]

Individuals contacted through the process of notification, also known as 'contact tracing', either as an index case (original person identified with an infection) or a subsequent contact, are not entitled to any information relating to their contact's identity, behaviour or diagnosis without that person's consent, even if that information is in the patient's records. Should a patient wish to access their own record, details of the identity of any contacts contained in their record should be redacted.

9 The full list of current exemptions listed under APP12 is available at http://www.oaic.gov.au/images/documents/privacy/privacy-resources/privacy-fact-sheets/privacy-fact-sheet-17-australian-privacy-principles_2.pdf.

## Security and storage of health information

A range of laws apply to the storage of health information. In summary, health agencies must have:

- procedures that ensure that only authorised individuals have access to patient health information
- security measures to prevent unauthorised access to the records
- where practicable, procedures for storing the information so that patient identity is not readily apparent from the face of the record (e.g. by the use of identification codes)
- procedures for destroying the records that protect the privacy of the information, in cases where the record is not to be retained.

Electronic records pose different challenges. Although they offer greater convenience of data retrieval and transfer, they also create greater risks of data leakage, access or 'browsing' by unauthorised staff and hacking. Agencies and businesses, including medical practices, need to consider the security of their data storage and transfer systems, and the problem of staff intentionally or inadvertently accessing prohibited electronic records. This issue is currently being tackled by the Commonwealth and a number of states through the development of electronic health records systems.

## Information for teams

Multidisciplinary treating teams are common practice in Australian health care. Health-care practitioners work together and share necessary information

to deliver optimum health care. All transfers of information without the informed consent of the patient require careful ethical consideration.

Although the question has not yet been legally tested, private sector health-service providers may not always require a patient's consent to disclose specific health information to another member of a multidisciplinary team for a health-care purpose where the patient would *reasonably* expect that disclosure. Because this has not been legally tested, it is still advisable to directly obtain patient consent about how their information will be handled, to avoid relying on implied consent.

Doctors in group practices should formulate clear internal communication protocols in order to exercise reasonable care (e.g. when communicating test results or considering contact tracing issues). The cross-referencing of files per se will generally not breach statutory confidentiality because results need to be checked; however, information should not be disclosed without explicit patient permission. All staff must be aware of their obligations, and systems must be in place for protecting patient privacy.

## Exemptions to privacy and confidentiality obligations

Use and disclosure of health information is defined in the Privacy Act under APP6 (previously NPP 2), which states that an organisation must not use or disclose personal information about an individual for a purpose other than the primary purpose of collection except for a number of limited circumstances. Such circumstances include the following:

- where the person would reasonably expect the information to be disclosed for a secondary purpose (even if the information is not sensitive, it must be related to the primary purpose; and if it is sensitive, it must be directly related to the primary purpose)
- to lessen or prevent a serious threat to the life, health or safety of an individual, or to public health or safety, where it is unreasonable or impractical to gain consent
- to take appropriate action in relation to suspected unlawful activity or serious misconduct
- where to do so is reasonably necessary for establishing, exercising or defending existing or anticipated legal proceedings in a court or tribunal, or for alternative dispute resolution
- to locate a person reported as missing
- where to do so is necessary to prevent a serious threat to the life, health or safety of a genetic relative (special conditions apply).

Disclosure of health information to a person's carer is also allowed:

- when the person is physically or legally incapable of consent; and
- the disclosure is necessary to provide appropriate care or treatment of the individual or for compassionate reasons; and
- the disclosure is not contrary to any wish expressed by the individual before he or she became unable to give consent of which the carer is aware, or could reasonably be expected to be aware; and

- the disclosure is limited to the extent reasonable and necessary to provide appropriate care or treatment of the individual, or to fulfil the purpose of making a disclosure for compassionate reasons.

There are a number of specific exemptions to APP 6 allowing disclosure of private health information.[10]

In summary, health-care workers must not disclose a person's health information except in a limited number of circumstances. These may generally be summarised as:

- communicating necessary information to others directly involved in the treatment of a patient during a particular episode of care
- cases of needle-stick injury where a professional is aware of a patient's HBV-positive status and a health-care worker has been exposed in circumstances where there is a real risk of transmission and it is not possible to conceal the identity of the source patient who has refused to consent to disclosure
- provision of medical services in a particular instance of care where there is a need to know the infection status for treatment purposes of benefit to the patient (e.g. in an emergency or if the patient is unconscious); this should not, however, detract from the observance of standard infection control precautions.

It is strongly recommended that practitioners familiarise themselves with the APPs and contact the Office of the Australian Information Commissioner or obtain legal advice if they wish to clarify the manner in which the APPs might relate to specific situations.

## Duty of care to third parties

The practice of contact tracing raises potential conflicts between breaching a patient's privacy and confidentiality, and alerting a third party to the fact that they may be at risk of HBV infection or have contracted the disease. Health practitioners' obligations have not yet been legally tested on this point, but it is possible that a practitioner could be found negligent for failing to inform a third party that they may be at risk of, or may have contracted, HBV. Fortunately, public health services afford practitioners expert guidance to resolve the potential conflict between the duties to maintain confidentiality and privacy, with the possible duty of care owed to third parties. In instances where practitioners suspect a person may be putting others at risk, the practitioner should notify the health department, using the methods prescribed in the relevant state or territory. Public health authorities then become responsible for making decisions around contact tracing, including management of privacy issues.

10 The full list can be accessed under APP 6 at: http://www.oaic.gov.au/privacy/privacy-resources/privacy-fact-sheets/other/privacy-fact-sheet-17-australian-privacy-principles with 'permitted health situations' explained at: http://www.oaic.gov.au/privacy/applying-privacy-law/app-guidelines/chapter-d-permitted-health-situations and 'permitted general situations' explained at: http://www.oaic.gov.au/privacy/applying-privacy-law/app-guidelines/chapter-c-permitted-general-situations

## Criminal law

There are two types of criminal offences associated with HBV and other blood-borne viruses. The first relates to disclosure of information regarding a person who has or is suspected of having HBV or other blood-borne virus infection, as discussed above. There are also general criminal laws in every state and territory that arguably could be used if a Court considered the harms associated with HBV transmission sufficiently serious, and determined that the individual who transmitted the infection had the sufficient knowledge of and intent to transmit. There have been no criminal prosecutions for HBV transmission within Australia, but there have been numerous prosecutions around the transmission of HIV.

## Antidiscrimination

Antidiscrimination laws operate in all Australian states and territories, and prohibit the discrimination of individuals on the basis of their actual or perceived HBV status. Discrimination based on disease status is legislatively prohibited under 'disability or impairment'. It is important that health-care practitioners avoid behaviours that are or could be perceived as discriminatory by a patient when testing and managing people with HBV. Such behaviours could include refusing to see a patient, offering different or inappropriate treatment, or placing a patient last on a consultation or operating list. As outlined in **Chapter 12,** standard precautions ensure a high level of protection against transmission of infection in the health-care setting, and are the level of infection control required in the treatment and care of all patients to prevent transmission of blood-borne infections.

## Health-care workers with hepatitis B virus infection

**Chapter 12** outlines the obligations of health-care practitioners infected with HBV who perform exposure-prone procedures.

## References

1. Australasian Society for HIV Medicine (ASHM). Australasian Contact Tracing Manual. Edition 3. Canberra: Commonwealth of Australia, 2006.

# CHAPTER 14: THE ROLE OF COMPLEMENTARY MEDICINE IN HEPATITIS B


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| | |
|---|---|
| **LINKS** | **Chapter 7:** Treatment of chronic hepatitis B virus infection |


## KEY POINTS

- Complementary medicines (CMs) are used by many patients with chronic liver disease.
- In most clinical settings, there are no convincing data that CMs or treatments alter the course of the illness significantly.
- Recent studies have shown certain activities for a range of herbal products, including anti-inflammatory, anti-fibrotic, antioxidant anti-cancer, immunomodulatory and antiviral activities. However, more work is needed in clinical situations before the use of these individual agents can be recommended.
- Much of the fear of toxicity relating to herbal products is based on studies that have been poorly carried out or reported.

## Introduction

Complementary medicine (CM) is used by a large percentage of the Australian community, with more than half the population reporting use in 2004 (1) and 2005 (2). The estimated annual expenditure on CM products by the Australian population was $1.86 billion, whereas the total national expenditure on CM (including visits to CM practitioners and the use of CM products) was about $4.3 billion (2).This means that more than half of out-of-pocket health-care costs in Australia were spent on CM (2).

The increasing use of CM is not driven by a large body of scientific evidence for its efficacy, and the phenomenon remains poorly explained; nevertheless, CM is steeped in tradition and ancient prescribing patterns. Many patients using CM will experience an improvement in symptoms and wellbeing while taking these products.

Across the world, efforts are being made to undertake meaningful studies of these products in a range of clinical and laboratory settings, and the data from these trials will have the potential to change clinical practice in the years ahead.

## The role of complementary medicine in the treatment of chronic hepatitis B patients

Results of studies of CMs in a range of settings suggest that these products (or their isolated constituents) may be targeting different aspects of the hepatitis B virus (HBV) disease process, such as viral replication (3-6), inflammatory mediators (7), fibrotic change and chemoprevention of malignant change (8, 9). Some agents appear to improve overall wellbeing, at least initially (9).

## The pharmacological approach to the use of complementary medicines

According to Wang (2012) (10), CM treatment in hepatitis B aims '(a) to relieve the symptoms and improve quality of life of patients; (b) to ameliorate liver inflammation; (c) to ameliorate hepatic fibrosis; (d) to improve immune function; and (e) to regulate lipid metabolism.'

Traditional Chinese medicine (TCM) and western herbal medicine use a number of plant-based chemicals with synergistic and overlapping pharmacological actions to address the above aims. Herbal medicines are chosen for their intrinsic characteristics to treat diseases, and to modulate viral and human physiological processes (11).

### Studies demonstrating specific activities relevant to HBV management

A number of recent studies have attempted to randomise patients to active treatment with CM or control treatments, and have examined the effects of CM on both HBV kinetics and liver disease activity and severity. These studies have been analysed in a recent review (12), which makes it quite clear that – although many questions remain about the quality of some of the studies undertaken (an issue many reviewers have with studies from institutions in the western world) – the studies demonstrate some activity of the agents used against HBV.

The review shows that results can be achieved with TCM, although clinicians remain reluctant to take up the challenge of using them. The introduction of highly active and safe antiviral agents, such as entecavir and tenofovir, has radically changed the approach to the use of any other agents. The capacity of antiviral agents to control HBV DNA in over 90% of patients, with little drug resistance over 5 years of treatment, makes the use of interferon and lamivudine unnecessary in those countries where the new agents can be afforded and used widely. The role of TCM in this era needs further clarification.

## Studies of the mechanism of action of complementary medicine products or their constituents

Other studies are seeking to define active components in CM medications, and the role of these components in various conditions. A recent paper examined the chemical nature of flavones isolated from one herbal product, and showed which components of the flavone molecules conferred anti-HBV activity. These data have been analysed in the review by Zhang et al (12). The mechanisms of action of CM products or constituents are summarised in Table 14.1.

**Table 14.1** Mechanisms of action of complementary products or constituents

| Agent or herb | Action | Reference | Comment |
|---|---|---|---|
| Pu-erh tea extracts | Inhibition of HBV replication | Pei et al (2011) (13) | Possessed anti- HBV activity and had low cytotoxicity |
| *Vitis vinifera* Suosuo grape | Dose-dependent inhibition of HBsAg, HBeAg and HBV DNA from HepG2.2.15 cells | Liu et al (2010) (14) | The total triterpenes (20 µg/ml), total flavonoids (50 µg/ml) and total polysaccha-rides (50 µg/ml) had the highest inhibitory effects on HBeAg |
| Anluohuaxian | Improves efficacy of adefovir, reduces fibrosis | Jiang et al (2012) (8) | |
| SPNS therapy 160 CHB patients 80 (LAM + SPNS) 80 (LAM alone) | LAM + SPNS Decreased YMDD variation at weeks 36 and 52 ($p<0.05$) | Feng and Zhang (2010) (15) | Possible mechanism: regulation of $CD_4$ levels, $CD4/CD_8$ ratio and Th1/Th2 balance |
| *Stellaria media* (chickweed) | Reduced HBsAg, HBeAg and HBV DNA in HepG2.2.15 cell lines; antiviral activities attributed to flavonoid C-glycosides, polysaccha-rides and protein | Ma et al (2012) (16) | First report of anti-HBV effects of chickweed in vitro |

| Agent or herb | Action | Reference | Comment |
|---|---|---|---|
| Artemisinin/ artesunate | Inhibitors of HBV production | Romero et al (2005) (17) | Strong inhibition of HBV DNA and HBsAg |
| A flavonoid, wogonin, from *Scutellaria baicalensis* (baical skullcap) | Suppressed HBsAg production in an HBV-transfected liver cell line (MS-G2), and inhibited duck-HBV DNA polymerase in duck-HBV infected ducks | Guo et al (2007) (6) | Wogonin showed anti-HBV activity both in vitro and in vivo |
| A flavonoid apigenin/*Ocium basilicum* (sweet basil) | Reduced production and release of HB s and e antigens in HepG 2.2.15 cell lines | Chiang et al (2005) (18) | |
| *Sophora flavescens* kurorinone | Reported to lower ALT and clear HBV DNA in a percentage of patients | Chen et al (2000) (19) | |
| *Radix Sophorae flavescentis* Oxymatrine | Down regulates the expression of heat stress cognate 70 (HSC70), which is required for HBV DNA replication | Wang et al (2010) (20) | Host HSC70 could be a novel drug target against HBV |
| 13 flavones in *Euphorbia humifusa* were tested for anti-HBV activity in vitro in HepG2.2.15 cells | Apigenin-7-O-β-D-glucopyranoside inhibited HBsAg by 77.2 % and HBeAg by 55.5% (40 μg/ml$^{1}$) and apigenin-7-O-(6″- O-galloyl)-β-D-glucopyranoside inhibited HBsAg by 88.2% and HBeAg by 65.6% (80 μg/ml$^{-1}$) | Tian et al (2010) (4) | Galloyl group on the flavones (C-6 of glucoside) may be responsible for the anti-HBV activity |
| TCM formulation Compound 861<br>*Salvia miltiorrhiza* (scarlet root; Dan Shen), *Astragalus membranaceus* (milk-vetch root; Huang Qi) and *Spatholobus suberectus* (millettia root; Ji Xue Teng) | Inhibition of human hepatic stellate cell (LX-2) proliferation | Wang et al (2004) (21) | |

| Agent or herb | Action | Reference | Comment |
|---|---|---|---|
| Silibinin a flavonolignan in *Silybum marianum* (Saint Mary's thistle) | Significantly reduced viability of human hepatocellular carcinoma Hep3B cells after 12 hours of treatment ($p \leq 0.001$); also induced apoptosis | Varghese et al (2005) (22) | |
| *Astragalus membranaceus* (Huang Qi) | Inhibition of HBV reverse transcriptase and DNA polymerase; inhibits secretion of HBsAg and HBeAg in HepG 2.215 cell line; lowers ALT, HBeAg and HBV DNA in treated patients | Yang et al (1997) (23) | May act in part by inducing endogenous IFN in vivo |
| *Astragalus membranaceus* (Huang Qi) | Astragaloside (100 µg) suppressed HBsAg by 23.6% and HBeAg by 22.9% after 9 days of treatment | Wang et al (2009) (24) | Inhibitory effect of astragaloside is more potent than 3TC |
| *Astragali compound* 208 HBV patients, (116 AC, 92 controls) for 2 months | Negative seroconversion of HBeAg by 27.7% (13/47) ($p<0.01$) and 28% (14/50) of HBV DNA, ($p<0.05$) compared to controls | Tang et al (2009) (5) | May inhibit HBV replication to some degree (5) |
| *Polygonum cuspidatum* (Hu Zhang) (its most active and studied component, resveratrol) | Suppresses lipid peroxidation, may inhibit HBV replication in HepG2.2.15 cells | Huang et al (1998) (25) | Resveratrol found in skin of red grapes |
| Radix et rhizome rhei (Da Huang); emodin an active component | Inhibits duck-HBV reverse transcriptase and DNA polymerase; inhibits secretion of HBsAg and HBeAg from HepG2.2.15 cell line | Li et al (2007) (26) | |
| *Phyllanthus urinaris* (Ye Xian Zhu); ellagic acid, a flavonoid, an active component | May block HBV messenger RNA transcription in Huh-7 cell lines; may block HBeAg-induced immune tolerance | Ott et al (1997) (27)<br>Liu et al (2001) (28)<br>Xia et al (2011) (29) | Expensive, not used as often as other cheaper herbal products<br>Phyllanthus species plus antiviral drugs may be better than the same antiviral drug alone |

| Agent or herb | Action | Reference | Comment |
|---|---|---|---|
| *Radix bupleuri* Saikosaponin C | Inhibits viral DNA replication and HBeAg production | Chiang et al (2003) (30) | Reduction in HBV DNA level was more potent than LAM |
| RDBPCT of 300 HBV carriers were given Chinese herbal formulae (CHF) for 52 weeks | Reduction in HBV DNA >2 $\log_{10}$ IU ml in 19% (38/200) in CHF group compared to 5% (5/100) in the control group at week 52 (p=0.0011)<br><br>Reduction in HBsAg by >0.5 $\log_{10}$ in 27% (54/200) in CHF group compared to 7% (7/100) in the control group (p=0.0000); no difference between HBeAg loss and seroconversion between the groups; increased IFN-γ and IL-2 and decreased IL-4 IL-6 and IL-10 in CHF group compared to control group (p=0.0000) | He et al (2013) (3) | Increases in the Th1 cytokines (IFN-γ and IL-2), which have been associated with viral clearance |

ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IFN, interferon; IL, interleukin; LAM, lamivudine; RDBPCT, randomised, double-blind, placebo-controlled clinical trial

Products:

AC = *Radix Astragali* 45 g, *Bupleurum chinense* 12 g, *Curcumae* 12 g, *Paeoniae radix* 12 g, *Peony radix* 15 g, *Radix Salvia miltiorrhiza* 20 g in three divided doses in hot water infusion for 10 minutes. The control group = silibinin 77 mg, oleanolia acid 40 mg and Yi-Gan Ling 2 g.

CHF = *Achyranthes bidentata* 15 g, *Astragalus membranaceus* 15 g, *Atractylodes macrocephala* 15 g, *Cuscuta chinensis* 10 g, *Epimedium brevicornum* 30 g, *Eucomnia ulmoides* 15 g, *Fructus aurantii* 15 g, *Lycium barbarum* 15 g, *Panax notoginseng* 5 g, *Phyllanthus urinaria* 15 g, *Polyphorus umbellatus* 10 g, *Poria cocos* 15 g, *Radix curcumae* 15 g, *Salvia miltiorrhiza* 20 g.

SPNS, *Radix Astragali, Placenta hominis, Zhiling hypha, Fructus Ligustri lucidi, Radix Panax notoginseng*. Each tablet containing 1.5 g crude drug, 4 tablets tds.

Previous claims that specific agents have had a beneficial role in the management of HBV have been questioned in more recent systematic reviews. These reviews have rigorously examined published work, and they conclude that the quality of the studies reported makes it impossible to recommend the use of agents reported in clinical treatment regimens. The call is for more and better research into the mechanisms of action and efficacy of herbal products, and their active components, in the treatment of HBV. Even for *Phyllanthus* species, which have been used in several countries for centuries, with clinical results that suggest an efficacy, it seems there is no documented evidence for the apparent efficacy (29).

Given the early stages of most of these clinical and laboratory studies, it is appropriate to suggest that none of these treatments should be given in place of the current highly effective antiviral agents available in Australia: entecavir and tenofovir (see **Chapter 7**).

## Safety of herbal medicines

A major area of concern in western medicine relates to the safety of herbal products in patients with liver disease.

### *Hepatotoxicity*

Herbal medicines with well-documented evidence of hepatotoxicity are:

- *Teucrium chamaedrys* (wall germander) and *Teucrium polium,* both of which cause zonal necrosis, hepatitis and fibrosis (31-33)
- *Mentha pulgeium* (pennyroyal), which causes necrosis and microvesicular steatosis (32)
- *Atractylis gummifera* (pine thistle), which leads to panlobular hepatic necrosis and renal failure (31-36)
- certain pyrrolizidine alkaloids that can cause veno-occlusive disease (31, 32, 34-36)
- *Larrea tridenta* (chapparal), the ingestion of which has led to zonal necrosis (31-36).

There are, however, conflicting reports of hepatotoxicity in the literature, and case reports alone (without laboratory testing and verification of the presence of each of the listed ingredients) mean that it is difficult to make firm conclusions about hepatotoxicity.

In Australia, a recent death was attributed to the ingestion of Kava 1800 Plus. On laboratory analysis, *Piper methysticum* (kava) and *Passiflora incarnata* (passionflower) were found to be present in the formulation. However, *Scutellaria lateriflora* (skullcap), which was also listed as an ingredient in this product, was not found. The identity of the third ingredient has yet to be established (37). *Teucrium* is similar in appearance to skullcap, and there have been other reports of substitution of *Teucrium* for *Scutellaria*. *Teucrium* can lead to hepatotoxicity and renal failure, and has been banned as a slimming agent in Europe.

When hepatotoxicity occurs, it is important to verify each listed ingredient in a formulation, to accurately identify the causative agent so that both general practitioners and CM practitioners are aware of herbal medicines with demonstrated hepatotoxicity. Regardless, kava should be avoided in patients with chronic liver injury.

The variability in potency among different crops, the use of incorrect plant species, lack of product standardisation and the possibility of contamination (by fungi, bacteria or pesticides) are specific challenges associated with the therapeutic use of botanical products (38, 39). These problems are compounded by the fact that the Therapeutic Goods Administration (TGA) considers CM as 'listed products' (rather than 'registered products'), which have to meet less stringent standards of safety and quality of manufacture (40).

The Australian and New Zealand expert group reviewing the safety of black cohosh (*Actea racemosa*, formerly named *Cimicifuga racemosa*) concluded that 'there appears to be an association between the use of black cohosh and liver damage, but that it is very rare'. It is a TGA requirement that this advice appear on the label of products containing black cohosh (41).

From January to December 2004, all patients with chronic hepatitis B admitted to a Hong Kong hospital for liver biochemistry irregularities were prospectively screened for an intake of TCM within 6 months before admission. The inclusion criteria included a bilirubin of over two times the upper limit of normal (ULN), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) over five times the ULN; alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) over two times the ULN. Exclusion criteria were HBV exacerbation (associated with HBV DNA level >1,000,000 viral copies/mL); co-infection with hepatitis A, C, D or E virus; intake of western medicine with known hepatotoxicity; alcohol intake of over 20 g/day for women and over 30 g/day for men; and any other liver disease apart from chronic hepatitis B (CHB) (42).

Of the 45 hospital admissions due to liver dysfunction in CHB patients, 15.6% were attributed to TCM-induced hepatoxicity. There were two deaths related to TCM intake, one of which appeared to be related to pre-existing cirrhosis. In another two patients, hepatotoxicity was based on a temporal relationship, although specific hepatotoxic elements were not found in the herbal formulae (42).

One study examined the risk of liver injury associated with Chinese herbal medicine products containing *Radix bupleuri* in 639,779 patients with HBV infection in Taiwan. It found that prescribing Xiao-Chai-Hu-Tang and Long-Dan-Xie-Gan-Tang, or Chinese herbal medicine products containing more than 19 g of *Radix bupleuri*, might increase the risk of liver injury (43). However, the authors did stress that this association may not be causal. Xiao-Chai-Hu-Tang contains 3–9 g of *Radix bupleuri* daily (43).

## Conclusion

There are currently no herbal products that can be recommended for use by HBV patients, based on well-designed, large, randomised clinical trials. Some agents shown to have anti–inflammatory effects or anti-fibrotic effects will continue to be recommended by CM practitioners, and they may well have some beneficial effects in those with active inflammation. In an age where effective antiviral agents are available on the Pharmaceutical Benefits Scheme, it is imperative that,

where appropriate, patients receive these drugs, which are safe, highly effective and funded by the government. Although the emphasis must be on effective antiviral therapy for the hepatitis B patient, CM may have a role in reducing the side effects of the antiviral therapy without interfering with its efficacy; and in some instances, CM may enhance the efficacy of the antiviral therapy (12). Due to drug resistance and adverse side effects of antiviral therapy, plant-based medicines warrant further examination (44).

There is clearly a need for well-designed, multicentre studies of the role of CM agents in HBV replication and control. It is to be hoped that such studies are undertaken soon. The consensus is clear that more rigorous studies are required to provide more definite results to guide the management of our hepatitis B patients (45). However, a Cochrane Collaboration for TCM in 2009 concluded that true evidence-based TCM is becoming a reality (46).

Patients should consult an accredited practitioner of TCM or western herbal medicine if they are interested in pursuing CMs. Details of TCM practitioners can be obtained from the Australian Health Practitioner Regulation Agency,[11] and details of western herbal medicine or naturopathic practitioners from the National Herbalists Association of Australia.[12]

11 www.ahpra.gov.au or 1300 419 495
12 www.nhaa.org.au or 02 8765 0071

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## References

1. MacLennan AH, Myers SP, Taylor AW. The continuing use of complementary and alternative medicine in South Australia: costs and beliefs in 2004. Med J Aust. 2006;184(1):27–31.
2. Xue CC, Zhang AL, Lin V, Da Costa C, Story DF. Complementary and alternative medicine use in Australia: a national population-based survey. J Altern Complement Med. 2007;13(6):643–50.
3. He J, Zhou D, Tong G, Xing Y, Chen Y, Zhang X, et al. Efficacy and safety of a chinese herbal formula (invigorating kidney and strengthening spleen) in chronic hepatitis B virus carrier: results from a multicenter, randomized, double-blind, and placebo-controlled trial. Evid Based Complement Alternat Med. 2013;2013:961926.
4. Tian Y, Sun LM, Liu XQ, Li B, Wang Q, Dong JX. Anti-HBV active flavone glucosides from Euphorbia humifusa Willd. Fitoterapia. 2010;81(7):799–802.
5. Tang LL, Sheng JF, Xu CH, Liu KZ. Clinical and experimental effectiveness of Astragali compound in the treatment of chronic viral hepatitis B. J Int Med Res. 2009;37(3):662–7.
6. Guo Q, Zhao L, You Q, Yang Y, Gu H, Song G, et al. Anti-hepatitis B virus activity of wogonin in vitro and in vivo. Antiviral Res. 2007;74(1):16–24.
7. Yin SS, Wang BE, Wang TL, Jia JD, Qian LX. [The effect of Cpd 861 on chronic hepatitis B related fibrosis and early cirrhosis: a randomized, double blind, placebo controlled clinical trial]. Zhonghua Gan Zang Bing Za Zhi. 2004;12(8):467–70.
8. Jiang YF, Ma J, He B, Li NP, Tang W, Gong GZ. [The therapeutic effect of Anluohuaxian capsule combined with adefovir dipivoxil on patients with chronic hepatitis B and influence on hepatic histology]. Zhonghua Gan Zang Bing Za Zhi. 2012;20(5):344–7.

9. Wang BE. Treatment of chronic liver diseases with traditional Chinese medicine. J Gastroenterol Hepatol. 2000;15 Suppl:E67–70.
10. Wang G, Zhang L, Bonkovsky HL. Chinese medicine for treatment of chronic hepatitis B. Chin J Integr Med. 2012;18(4):253–5.
11. Zhang W, Wang LQ, Liu YB. Evaluation on quality of life and analysis on its correlation with TCM syndromes in patients of chronic hepatitis B. Chin J Integr Med. 2009;15(1):30–3.
12. Zhang L, Wang G, Hou W, Li P, Dulin A, Bonkovsky HL. Contemporary clinical research of traditional Chinese medicines for chronic hepatitis B in China: an analytical review. Hepatology. 2010;51(2):690–8.
13. Pei S, Zhang Y, Xu H, Chen X, Chen S. Inhibition of the replication of hepatitis B virus in vitro by pu-erh tea extracts. J Agric Food Chem. 2011;59(18):9927–34.
14. Liu T, Zhao J, Li H, Ma L. Evaluation on anti-hepatitis viral activity of Vitis vinifer L. Molecules. 2010;15(10):7415–22.
15. Feng H, Zhang YH. Effect of Chinese medicine therapy for strengthening-Pi and nourishing-Shen in preventing lamivudine induced YMDD mutation and its immunologic mechanism. Chin J Integr Med. 2010;16(1):19–22.
16. Ma L, Song J, Shi Y, Wang C, Chen B, Xie D, et al. Anti-hepatitis B virus activity of chickweed [Stellaria media (L.) Vill.] extracts in HepG2.2.15 cells. Molecules. 2012;17(7):8633–46.
17. Romero MR, Efferth T, Serrano MA, Castano B, Macias RI, Briz O, et al. Effect of artemisinin/artesunate as inhibitors of hepatitis B virus production in an "in vitro" replicative system. Antiviral Res. 2005;68(2):75–83.
18. Chiang LC, Ng LT, Cheng PW, Chiang W, Lin CC. Antiviral activities of extracts and selected pure constituents of Ocimum basilicum. Clin Exp Pharmacol Physiol. 2005;32(10):811–6.
19. Chen C, Guo SM, Liu B. A randomized controlled trial of kurorinone versus interferon-alpha2a treatment in patients with chronic hepatitis B. J Viral Hepat. 2000;7(3):225–9.
20. Wang YP, Liu F, He HW, Han YX, Peng ZG, Li BW, et al. Heat stress cognate 70 host protein as a potential drug target against drug resistance in hepatitis B virus. Antimicrob Agents Chemother. 2010;54(5):2070–7.
21. Wang L, Wang J, Wang BE, Xiao PG, Qiao YJ, Tan XH. Effects of herbal compound 861 on human hepatic stellate cell proliferation and activation. World J Gastroenterol. 2004;10(19):2831–5.
22. Varghese L, Agarwal C, Tyagi A, Singh RP, Agarwal R. Silibinin efficacy against human hepatocellular carcinoma. Clin Cancer Res. 2005;11(23):8441–8.
23. Yang ZM, Yang XB, Gao WB, Shao XW, Chen HS. Inhibition of extracts of five traditional medicines on DHBV-RT-DNAP in vitro [In Chinese]. Special J Pharmacy of people's Mil Surg. 1997;13:71–3.
24. Wang S, Li J, Huang H, Gao W, Zhuang C, Li B, et al. Anti-hepatitis B virus activities of astragaloside IV isolated from radix Astragali. Biol Pharm Bull. 2009;32(1):132–5.
25. Huang ZS, Wang ZW, Liu MP. The protective effect of resveratrol on rat hepatocytes injured by CCl4 in vitro [In Chinese]. J Pharmacol China. 1998;14:543.
26. Li Z, Li LJ, Sun Y, Li J. Identification of natural compounds with anti-hepatitis B virus activity from Rheum palmatum L. ethanol extract. Chemotherapy. 2007;53(5):320–6.
27. Ott M, Thyagarajan SP, Gupta S. Phyllanthus amarus suppresses hepatitis B virus by interrupting interactions between HBV enhancer I and cellular transcription factors. Eur J Clin Invest. 1997;27(11):908–15.
28. Liu J, Lin H, McIntosh H. Genus Phyllanthus for chronic hepatitis B virus infection: a systematic review. J Viral Hepat. 2001;8(5):358–66.
29. Xia Y, Luo H, Liu JP, Gluud C. Phyllanthus species for chronic hepatitis B virus infection. Cochrane Database Syst Rev. 2011(4):CD008960.
30. Chiang LC, Ng LT, Liu LT, Shieh DE, Lin CC. Cytotoxicity and anti-hepatitis B virus activities of saikosaponins from Bupleurum species. Planta Med. 2003;69(8):705–9.
31. Gunawan B, Kaplowitz N. Clinical perspectives on xenobiotic-induced hepatotoxicity. Drug Metab Rev. 2004;36(2):301–12.
32. Schiano TD. Hepatotoxicity and complementary and alternative medicines. Clin Liver Dis. 2003;7(2):453–73.

33. Stedman C. Herbal hepatotoxicity. Semin Liver Dis. 2002;22(2):195–206.

34. Seeff LB, Lindsay KL, Bacon BR, Kresina TF, Hoofnagle JH. Complementary and alternative medicine in chronic liver disease. Hepatology. 2001;34(3):595–603.

35. Stewart MJ, Steenkamp V. Pyrrolizidine poisoning: a neglected area in human toxicology. Ther Drug Monit. 2001;23(6):698–708.

36. Pittler MH, Ernst E. Systematic review: hepatotoxic events associated with herbal medicinal products. Aliment Pharmacol Ther. 2003;18(5):451–71.

37. Australian Government Department of Health and Ageing. Information for sponsors: safety of kava-containing medicines. Canberra: Therapeutic Goods Administration; 2002; Available from: http://www.tga.gov.au/safety/alerts-medicine-kava-020826.htm#.U4iYbpWKBow.

38. Ko RJ. Adulterants in Asian patent medicines. N Engl J Med. 1998;339(12):847.

39. Murch S, KrishnaRaj S, Saxena P. Phytopharmaceuticals: problems, limitations and solutions. Scientific Rev Alternative Med. 2000;4:33–7.

40. Expert Committee on Complementary Medicines in the Health System. Complementary medicines in the Australian health system: Report to the Parliamentary Secretary to the Minister for Health and Ageing. Canberra: Commonwealth of Australia, 2003.

41. Australian Government Department of Health and Ageing. New labelling requirements and consumer information for medicines containing Cimicifuga racemosa. Canberra: Therapeutic Goods Administration 2007; Available from: http://www.tga.gov.au/safety/alerts-medicine-black-cohosh-070529.htm#.U4iX5JWKBow.

42. Yuen MF, Tam S, Fung J, Wong DK, Wong BC, Lai CL. Traditional Chinese medicine causing hepatotoxicity in patients with chronic hepatitis B infection: a 1-year prospective study. Aliment Pharmacol Ther. 2006;24(8):1179–86.

43. Lee CH, Wang JD, Chen PC. Risk of liver injury associated with Chinese herbal products containing radix bupleuri in 639,779 patients with hepatitis B virus infection. PLoS One. 2011;6(1):e16064.

44. Wohlfarth C, Efferth T. Natural products as promising drug candidates for the treatment of hepatitis B and C. Acta Pharmacol Sin. 2009;30(1):25–30.

45. Zhan T, Wei X, Chen ZQ, Wang DS, Dai XP. A systematic review of RCTs and quasi-RCTs on traditional Chinese patent medicines for treatment of chronic hepatitis B. J Tradit Chin Med. 2012;31(4):288–96.

46. Manheimer E, Wieland S, Kimbrough E, Cheng K, Berman BM. Evidence from the Cochrane Collaboration for Traditional Chinese Medicine therapies. J Altern Complement Med. 2009;15(9):1001–14.

# APPENDIX 1
# FACT SHEET – FOR PEOPLE LIVING WITH CHRONIC HEPATITIS B

**Marina Suarez** Multicultural HIV and Hepatitis Service, Sydney, NSW

## What is hepatitis B?

Hepatitis B is a liver infection caused by the hepatitis B virus. Your liver is very important for your wellbeing. When your liver is inflamed or damaged, it may not work properly and this can affect your health.

### Hepatitis B can be 'acute' or 'chronic'

Most adults who get infected with hepatitis B will get rid of the virus (clear it) within 6 months and develop protection against it. This short-term illness is called 'acute hepatitis B'. Once they clear the virus, they cannot be infected with the hepatitis B virus again, and cannot pass it on to others.

When the infection lasts for more than six months, the person has developed 'chronic hepatitis B'. This happens to 90% of people who are infected at birth or before one year of age.

Chronic hepatitis B can cause liver damage, liver scarring (cirrhosis) and liver cancer; however, there are effective medicines that can greatly reduce liver damage and prevent cancer. There is also a lot you can do to help your liver. The most important thing is to have regular checks with your doctor every six to twelve months.

## How do you get hepatitis B?

Hepatitis B is found in body fluids such as the blood, semen and vaginal fluids of an infected person. The virus is passed on (transmitted) when body fluids from an infected person enter another person's bloodstream. Even amounts of fluid too small to be seen can transmit the virus.

In babies and young children transmission occurs:

- From a mother with hepatitis B to her baby around the time of birth if the baby is not vaccinated. This is the most common way the virus is spread in many developing countries.
- From a child with hepatitis B to another child who is not vaccinated against hepatitis B, through cuts and sores that are not covered.

In adults transmission occurs through:

- Vaginal, anal or oral sex without a condom.
- Sharing needles, syringes or any other equipment to inject drugs.
- Tattooing or body piercing done with equipment that has not been sterilised properly.
- Sharing toothbrushes, razors, nail files or other personal items that may carry blood, including dry blood.
- Blood transfusions in some parts of the world, particularly in developing countries. In most developed countries, including Australia, donated blood is checked for hepatitis B and other viruses, so the risk of infection is extremely low.
- Medical and dental procedures in some developing countries may put people at risk, but they are safe in Australia.
- Accidental injury with a needle or splashing of infected blood or body fluids, especially for health-care workers.
- Contact sports.

**Hepatitis B CANNOT be transmitted through:**

- hugging
- kissing
- sharing food and utensils for eating
- insect bites
- coughing
- sharing bathroom and toilet facilities
- swimming pools.

## Regular checks with your doctor

Having chronic hepatitis B means you will need to think of your health a little differently. With many illnesses, you can tell if you are getting worse and need to see your doctor, because the illness makes you feel unwell. However, hepatitis B is different, and you cannot rely on how you feel to know how the illness is affecting your liver. In fact, it is often the case that by the time you feel unwell, there is already liver damage.

Not every person with chronic hepatitis B will need treatment, but you will need to see your doctor every six to twelve months for regular checks, even if you feel well and have no symptoms. This is called 'monitoring'.

Chronic hepatitis B is a complex disease that changes over time, and it is only through regular monitoring that you can know what the disease is doing to your liver, and when to get treatment if you need it.

As well as blood tests, your doctor may order tests such as a Fibroscan®, a liver ultrasound or a liver scan. The tests allow your doctor to see whether there have been any changes in the disease; whether there is liver damage, scarring of the liver (cirrhosis) or cancer; and decide if and when you may need treatment. If you need treatment, your doctor will refer you to a liver clinic or a liver specialist.

Seeing your doctor for regular monitoring is **the most important thing** you can do to look after yourself and your liver when you have chronic hepatitis B, because treatment at the right time can prevent scarring of the liver and cancer.

## Treatment for hepatitis B

There are effective medications available that can control the virus. They can reduce the damage to your liver and the risk of liver cancer, and also help the liver repair itself.

The most common treatment consists of taking one pill a day, and it is usually a lifelong treatment.

There is another type of treatment that is offered to some patients. It consists of a weekly injection, for up to twelve months. This treatment can be very effective for certain patients, but can have serious side effects.

Each treatment has different benefits and your specialist will discuss with you which one is best for you.

## Reducing the risk of liver damage

There are a number of things you can do to reduce the risk of liver damage:

- drink less alcohol or none at all
- eat a balanced healthy diet, avoiding too much fat
- maintain a healthy body weight

- stop or reduce smoking
- exercise regularly
- manage your stress and get support
- tell your doctor if you are taking any medicines or herbal remedies, including Chinese medicines; some medications and herbs can be harmful to the liver, especially if taken in high doses or for a long time
- protect yourself from other infections such as HIV and other hepatitis viruses, because they can severely affect your health and cause further liver damage:
  - get vaccinated for hepatitis A if you are not already protected against it
  - do not share equipment for injecting drugs, to avoid getting hepatitis C
  - practice safe sex (using condoms and lubricant), to avoid getting HIV.

Your doctor can refer you to services that can help you with these.

## Protecting others from hepatitis B

You need to prevent passing hepatitis B on to others by taking the following precautions:

- Make sure that people you have close contact with are vaccinated against hepatitis B.
- Practice safe sex: use condoms and lubricant during vaginal, anal and oral sex.
- Avoid blood-to-blood contact: do not share toothbrushes, razors or other personal items that may contain blood, including dry blood.
- Cover any open wounds and clean blood spills with bleach. Do not allow other people to touch your wounds or blood unless they are wearing gloves.
- Throw away personal items such as tissues, sanitary pads, tampons and bandages in a sealed plastic bag.
- Do not share needles, syringes or other equipment used to inject drugs.
- Do not donate blood, sperm, organs or body tissue.
- If you are pregnant or planning to have a baby, talk to you doctor about the vaccinations your baby will need to be protected. You will be able to breastfeed.
- If you are a health-care worker who performs invasive procedures (such as a surgeon or dentist), you should seek expert medical advice, and expert occupational health and safety advice.

## Vaccination

The hepatitis B vaccine is very safe and provides immunity (protection against the virus) more than 95% of the time. The vaccine is usually given in two or three injections over six months, depending on the age of the person. In Australia, all mothers are offered free vaccination for their babies when they are born. To be fully protected, the baby will need additional doses in the first twelve months. All children younger than one year old are provided with hepatitis B vaccination for free. Vaccination is recommended for adolescents aged ten to thirteen years who have not already been vaccinated.

A baby born to a mother with hepatitis B will receive an extra shot of hepatitis B immunoglobulin (HBIG) within twelve hours of birth. This can offer the baby the best available protection against hepatitis B. Once they are nine months old, babies need to be tested to check whether they have become immune to hepatitis B.

Other people at high risk of contracting hepatitis B, such as health-care workers, should also be tested one month after the final dose of vaccine, to show whether they have developed immunity or not.

## Do I need to tell others that I have hepatitis B?

While you don't have to tell everyone that you have hepatitis B, you need to tell the people who live in your house and your sexual partner or partners, so that they can be tested and vaccinated. If you need help telling them, talk to your doctor to get some advice.

There are also some situations in which you have to tell other people you have chronic hepatitis B. These include if:

- you are applying to join the Australian Defence Force
- your insurance company requires information about infections and illnesses
- you are a health-care worker who performs invasive procedures (such as a surgeon or dentist)

You may want to tell your family so they can also be tested, especially if you come from a country where hepatitis B is common, or you are Aboriginal or Torres Strait Islander.

Telling health-care workers, such as your dentist or other doctors, can help them give you the best medical care, but this is your choice. If you decide to tell them, they have a responsibility to protect your privacy and keep your information confidential, and they cannot discriminate against you.

You may find it helpful to talk to other people who can understand and support you, but should take your time to decide who you feel you can trust.

## Interpreters

Hepatitis B can be complex and difficult to understand. If you do not speak or understand English well and you need help to communicate with your doctor, you can ask for an interpreter. An interpreter may help you to:

- understand everything you are being told
- ensure everything you say is understood
- ask questions and get answers
- give permission for tests or treatment.

Interpreters must protect your confidentiality.

Telephone interpreters can help you connect with services in your own language. Call TIS on 131 450 for the cost of a local call and ask to speak to someone in your language.

## Where can I find more information?

If you need more information, talk to your GP or liver specialist. You can also check:

***Hepatitis Australia***

www.hepatitisaustralia.com

***For information in English and in other languages visit***

www.mhahs.org.au

www.ashm.org.au/resources

www.hepatitisaustralia.com/community-resources/

***For personal stories of people who have chronic hepatitis B***

www.ashm.org.au/BeSeenBeHeard

***The Hepatitis Council in your state or territory can provide information about hepatitis B, and what health and support services are available in your area.***

New South Wales – www.hep.org.au

Victoria – www.hepcvic.org.au

South Australia – www.hepatitissa.asn.au

Western Australia – www.hepatitiswa.com.au

Northern Territory – www.ntahc.org.au

Australian Capital Territory – www.hepatitisresourcecentre.com.au

Queensland – www.hepqld.asn.au

Tasmania – www.tascahrd.org.au

# APPENDIX 2:
# LIST OF USEFUL ORGANISATIONS AND RESOURCES ON HEPATITIS B

## ORGANISATIONS

The following list provides websites for a range of organisations and groups that can be contacted for further resources and support information. It is anticipated that these contacts may be useful for primary health care providers and patients.

Please consult the online **ASHM Directory: HIV, hepatitis and related services** at: www.ashm.org.au/ashm-directory/ for additional services and support organisations.

## NATIONAL

**Australian Acupuncture and Chinese Medicine Association Ltd (AACMA)** – able to provide contact details of qualified practitioners

Web: www.acupuncture.org.au

**Australasian Chapter Sexual Health Medicine of RACP (AChSHM)** – Register of Public Sexual Health Clinics in Australia and New Zealand

http://www.racp.edu.au/page/australasian-chapter-of-sexual-health-medicine/

**Australian Chinese Medical Association Inc (ACMA)** – offers a wide range of services, including ACMA Medical Practitioner Directory

Web: www.acma.org.au

**Australian Drug Foundation (ADF)** – provides information and resources about alcohol and other drug problems

Web: www.adf.org.au

**Australian Federation of AIDS Organizations (AFAO)**

Web: www.afao.org.au

**Australian Government Department of Health and Ageing** – provides information and support on infectious diseases and health related issues

Web: www.health.gov.au

**Australian Immunisation Handbook** – the online resource provides information on vaccination procedures

Web: www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home

**Australian Childhood Immunisation Register** – enquiries (ACIR) 1800 653 809
Email: acir@humanservices.gov.au

Web: www.humanservices.gov.au/customer/services/medicare/australian-childhood-immunisation-register

**Infection Control Guidelines** – outlines the principles involved in, and the procedures necessary for, the prevention of the transmission of infectious diseases

Web: www.health.gov.au/internet/main/publishing.nsf/Content/icg-guidelines-index.htm

**Medical Services Advisory Committee (MSAC)** – hepatitis B DNA testing for chronic hepatitis B

Web: www.health.gov.au/internet/msac/publishing.nsf/Content/app1096-1

**National Notifiable Diseases Surveillance System (NNDSS)** – surveillance program

Web: www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-nndssintro.htm

**National Hepatitis B Strategy –** sets aspirational targets and outlines priority actions to reduce transmission of, and morbidity and mortality caused by, hepatitis B

Web: http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-bbvs-hepb

**National Aboriginal and Torres Strait Islander Sexual Health and Blood Borne Virus Strategy** – sets aspirational targets and outlines priority actions to reduce the transmission of and morbidity and mortality caused by BBVs and STIs in Aboriginal and Torres Strait Islander communities

http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-bbvs-atsi

**Australian Injecting and Illicit Drug Users League (AIVL)** – provides information and education on illicit drug use

Web: www.aivl.org.au

**Australian Research Centre in Sex, Health and Society**

Web: www.latrobe.edu.au/arcshs

**Hepatitis B Patient and Clinical Practice Survey** – study of the knowledge and attitudes of people with hepatitis B in relation to the virus and its clinical management

Web: http://www.latrobe.edu.au/__data/assets/pdf_file/0009/575172/ARCSHS-Hepatitis-B-Patient-Survey-Report.pdf

**Stigma, Discrimination and Hepatitis B** – review of current knowledge of hepatitis B related stigma and discrimination

Web: http://www.latrobe.edu.au/__data/assets/pdf_file/0008/558638/Stigma-Discrimination-and-Hepatitis-B-A-review-of-current-research.pdf

**National Hepatitis B Needs Assessment Report** – aims to raise public awareness of hepatitis B and advocate for a national strategy

Web: www.latrobe.edu.au/arcshs/downloads/arcshs-research-publications/national_hep_b_needs_assesmt.pdf

**Australasian Society for HIV Medicine (ASHM)** – supports the HIV, viral hepatitis and sexual health workforce through the provision of training and resources. Administers the hepatitis B GP prescriber program

Web: www.ashm.org.au
ASHM training: www.ashm.org.au/courses
ASHM resources: www.ashm.org.au/resources

**Australasian Contact Tracing Manual** – reflects best practice for contact tracing in Australasia

Web: ctm.ashm.org.au

**Aboriginal and Torres Strait Islander Health Workers and Blood-Borne Viruses**

Web: www.ashm.org.au/images/publications/booklets/PBB_ATSI_WEB_CORRECTION_v0.1.pdf

**Antenatal Testing and Blood-Borne Viruses (BBVs)**

Web: www.ashm.org.au/images/pdfs/publications/1976963383_antenatal_web.pdf

**B Seen, B Heard: Hepatitis B from our perspective**

Web: www.wdp.org.au/health-promotion/hepatitis-b

**Co-infection HIV & Viral Hepatitis: a guide for clinical management (2010)**

Web: www.ashm.org.au//images/Publications/Monographs/Coinfection_HIV_ViralHep_2010/Coinfection_2010_Full.pdf

**Decision Making in HBV**

Web: www.ashm.org.au/images/Publications/DecisionMakingTools/HBV_DecisionMaking_PRINT_May13.pdf

**Hepatitis B and Primary Care Providers**

Web: www.ashm.org.au/images/Publications/Booklets/PBB_HepB_PrimaryCare_V11.0_WEB.pdf

**Hepatitis B mapping project** – uses a range of indicators to estimate the burden of disease and also the uptake of treatment and care

Web: www.ashm.org.au/hepatitis-B/mapping

**Patient factsheets in multiple languages and further resources:**

Web: www.ashm.org.au/resources

**Federal Privacy Commissioner** – legislation, regulations, codes, determinations and guidelines which affect health service providers

Web: www.privacy.gov.au

**Gastroenterological Society of Australia (GESA)** – guidelines and promotion of research and clinical standards

Web: www.gesa.org.au

**Chronic Hepatitis B Recommendations** – Australia and New Zealand (2010)

Web: www.gesa.org.au/professional.asp?cid=9&id=109

**Hepatitis B Virus Fact Sheet –** information and facts about hepatitis B

Web: www.gesa.org.au/consumer.asp?id=83

**Hepatitis Australia** – provides useful information on hepatitis B

Web: www.hepatitisaustralia.com

**Hepatitis B Fact Sheets under 'Hepatitis B – What you need to know'**

Web: www.hepatitisaustralia.com/community-resources/

**National Aboriginal Community Controlled Health Organisation (NACCHO)** – the national peak Aboriginal health body representing Aboriginal Community Controlled Health Services throughout Australia

Web: www.naccho.org.au

**National Centre for Education and Training on Addictions (NCETA)** – provides resources for health-care workers on issues of drug and alcohol

Web: www.nceta.flinders.edu.au

**The Kirby Institute for infection and immunity in society** – coordinates national surveillance programs, population health and epidemiological research, clinical research and clinical trials.

Web: http://kirby.unsw.edu.au/

**Annual Surveillance Reports** – comprehensive analysis of HIV, viral hepatitis and sexually transmissible infections in Australia

Web: http://kirby.unsw.edu.au/surveillance/Annual-Surveillance-Reports

**Centre for Social Research in Health** – provides social research information in relation to HIV/AIDS and hepatitis C.

Web: https://csrh.arts.unsw.edu.au/

**National Herbalists Association of Australia (NHAA**) – qualified herbalist

Web: www.nhaa.org.au/

**Sexual Health and Family Planning Australia** – peak body for Sexual Health (SH) and Family Planning Organisations (FPOs)

Web: www.shfpa.org.au

**Telephone Interpreter Services (TIS**) – provides free telephone service

Web: www.immi.gov.au/tis

## STATE AND TERRITORY

### NSW

**Aboriginal Health and Medical Research Council of NSW (AH&MRC)** – is the peak representative body and voice of Aboriginal communities on health in NSW

Web: www.ahmrc.org.au

**Cancer Council NSW** – provides support and practical information to patients and other affected populations

Web: www.cancercouncil.com.au/metro

**Hepatitis B Screening and Liver Cancer Surveillance Program** – prevention strategy for liver cancer

Web: www.cancercouncil.com.au/editorial.asp?pageid=2384

**Hepatitis NSW** – provides information and resources to people living with viral hepatitis and healthcare workers

Web: www.hep.org.au

**Multicultural Health Communication Service NSW** – provides information and services to assist health professionals to communicate with culturally and linguistically diverse communities throughout NSW

Web: www.mhcs.health.nsw.gov.au

**Multicultural HIV and Hepatitis Service (MHAHS)** – works to respond to HIV and hepatitis among culturally and linguistically diverse communities; provides support services and resources in many languages

Web: www.mhahs.org.au

**Hepatitis B. It's Family business** (available in Arabic, Chinese, Indonesian, Khmer, Korean, Thai, Vietnamese and plain English)
Web: www.mhahs.org.au/images/pdf/hbv_orderform.pdf

**NSW Health** – provides resources, information and statistical data on health issues

Web: www.health.nsw.gov.au/index.html

**Questions and Answers about Hepatitis B Vaccination**
Web: www.health.nsw.gov.au/PublicHealth/Immunisation/school_prog/hepb_qa.asp

**The Children's Hospital at Westmead**

**Hepatitis B Fact Sheet for Parents**

Web: www.chw.edu.au/parents/factsheets/hepb.htm

## ACT

**ACT Health** – provides resources and information on health issues

Web: www.health.act.gov.au/c/health

**ACT Hepatitis Resource Centre** – provides information and health promotion activities to raise awareness about viral hepatitis to people in the Canberra community

Web: http://www.hepatitisresourcecentre.com.au/

**Winnunga Nimmityjah Aboriginal Health Service** – provide a culturally safe, holistic health care service for the Aboriginal and Torres Strait Islander people of the ACT and surrounding regions

Web: www.winnunga.org.au

## QLD

**Department of Health QLD** – provides resources and information on health issues

Web: www.health.qld.gov.au/about_qhealth/default.asp

**Ethnic Communities Council of Queensland Ltd (ECCQ) –** represents in the interests of people from CALD backgrounds

**Hepatitis B Fact Sheet**
Web: http://www.eccq.com.au/eccq/index.php?module=menu&action=view&id=683

**Queensland Aboriginal and Islander Health Council (QAIHC)** – is the peak body representing the Community Controlled Health Sector in Queensland at both a state and national level

Web: www.qaihc.com.au

**Hepatitis Queensland** – provides support services, information and training to people affected by, or at risk of viral hepatitis

Web: www.hepqld.asn.au

**University of Queensland – Schools of Medicine** – provides education for Queensland health care professionals, specialising in the domains of HIV, sexual health, and viral hepatitis

Web: http://www.som.uq.edu.au/hivandhcvprojects

## VIC

**Department of Health Victoria** – provides information and resources on public health issues

Web: www.health.vic.gov.au

**Hepatitis B- immunisation for children**

Web: http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Hepatitis_B_immunisation_for_children

**HIV, Hepatitis & STI Education and Resource Centre** – provides resources and information on HIV/AIDS, hepatitis and sexually transmissible infections

Web: www.hivhepsti.info

**Hepatitis Victoria –** provide access and referral to information, care, treatment and support for people affected by or at risk of viral hepatitis

Web: www.hepcvic.org.au

**Victorian Aboriginal Community Controlled Health Organisation (VACCHO)** – is Victoria's peak representative Aboriginal health body and champions community control and health equality for Aboriginal communities

Web: www.vaccho.org.au

## SA

**Aboriginal Health Council of South Australia (AHCSA)**

Web: www.ahcsa.org.au

**Department of Health SA** – provides resources and information on health issues

Web: www.health.sa.gov.au/PEHS/Default.aspx

**Hepatitis South Australia** – provides information and services to South Australians affected by hepatitis C and hepatitis B

Web: http://hepatitissa.asn.au/

## WA

**Aboriginal Health Council of Western Australia (AHCWA) –** is the peak body representing 20 Aboriginal Community Controlled Health Services across Western Australia at a State and National level

Web: www.ahcwa.org

**Department of Health WA** – provides resources and information on health issues

Web: www.health.wa.gov.au/home/

**Hepatitis Western Australia** – provides support for people affected by hepatitis and works to raise community awareness in relation to hepatitis

Web: www.hepatitiswa.com.au/

## NT

**Aboriginal Medical Services Alliance Northern Territory (AMSANT)**

Web: www.amsant.com.au

**Department of Health NT – Centre for Disease Control** – provides resources and information on health issues

Web: www.health.nt.gov.au

**Hepatitis B Vaccination Policy and Public Health Management** – treatment protocol

Web: http://www.nt.gov.au/health/cdc/protocols.shtml

**The Hepatitis/AIDS Council Northern Territory –** works to prevent transmission of HIV, Hepatitis C & STIs

Web: www.ntahc.org.au

### TAS

**Department of Health and Human Services Tasmania** – provides resources and information on health issues

Web: www.dhhs.tas.gov.au

**Hepatitis B: Why does my newborn baby need protection**

Web: www.dhhs.tas.gov.au/__data/assets/pdf_file/0003/92325/Hepatitis_B_Brochure_DHHS_2011_WEB.pdf

**Tasmanian Aboriginal Health Service**

Email: ahs@tacinc.com.au

**The Hepatitis/AIDS Council of Tasmania –** provides information and resources and works to minimize the impact of HIV/AIDS and hepatitis C in the community

Web: www.tascahrd.org.au

## NEW ZEALAND

**The Hepatitis Foundation of New Zealand** – promotes education and research of viral hepatitis, early detection and long-term follow up of chronic hepatitis B & C

Web: www.hepfoundation.org.nz

**Hepatitis B Virus Fact Sheet**
Web: http://www.hepfoundation.org.nz/hepatitisb.html

**Liver Fact Sheet**
Web: http://www.hepfoundation.org.nz/liver.html

**Hepatitis B – B Positive Support Programme**

Web: http://www.adhb.govt.nz/hepbfree/

**Hepatitis C Resource Centres** – provides and resources and information on viral hepatitis and liver disease

Web: www.hepcnz.org/en/resource-centre

## OTHER ONLINE RESOURCES

**Australian Indigenous Health Info Net Infectious conditions** – Hepatitis– provides information and facts on hepatitis

Web: www.healthinfonet.ecu.edu.au/infectious-conditions/hepatitis

**Hepatitis B Bear – Understanding Hepatitis B**

Video for use with patients, explaining the phases of Hepatitis B, using the 'Hepatitis B Bear'

**Understanding Hepatitis B (part 1)**
Web: www.youtube.com/watch?v=2JZzpbtutKo

**Understanding Hepatitis B (part 2)**
Web: www.youtube.com/watch?v=pxhl3RjRPDo

**LAB Tests Online**

**Liver Disease** – provides information on liver complications

Web: www.labtestsonline.org.au/understanding/conditions/liver_disease-2.html

**Teen Health – Child and Youth Health**

**Hepatitis B Fact Sheet** – provides information and facts on hepatitis B

Web: www.cyh.com/HealthTopics/HealthTopicDetails.aspx?p=243&np=292&id=2177

**'The Hepatitis B Story' –** an educational tool in plain English, designed for use by healthcare workers with clients with limited health literacy who are newly diagnosed

Web: www.svhm.org.au/gp/Documents/The%20Hepatitis%20B%20Story.pdf

## INTERNATIONAL

**American Association for the study of liver diseases (AASLD)** – provide practice guidelines, educational conferences, training programs and professional publications

Web: www.aasld.org

**American Gastroenterological Association (AGA)** – provides resources and information on liver disease to health professionals and consumers

Web: www.gastro.org

**American Liver Foundation (ALF)** – provides resources and information on liver disease to health professionals and consumers

Web: www.liverfoundation.org/

**Asian Pacific Association for the study of the liver (APASL)** – produce guidelines and hold scientific educational symposia/conferences periodically

Web: http://apasl.info/

**Centers for Disease Control and Prevention** – National Centre for HIV, Viral Hepatitis, STD, and TB Prevention

Web: www.cdc.gov

**European Association of the study of the liver (EASL)** – produce guidelines, promotes research, supports wider education, and provides input to European liver policies

Web: www.easl.eu

**Hepatitis B Foundation** – is dedicated to finding a cure and improving the quality of life for those affected by hepatitis B worldwide

Web: www.hepb.org

**'Living with Hepatitis B'** – information and resources on hepatitis B

Web: http://www.hepb.org/living/index.htm

**New Zealand Society of Gastroenterology** – provides resources and information on liver disease to health professionals and consumers

Web: www.nzsg.org.nz

**The Hepatitis B Information and Support List** – is a worldwide information and support group, dedicated to providing timely information and support to all those living with hepatitis B

Web: http://hblist.net/

**The Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP)** – was established as a multidisciplinary body to advocate for public policy reforms that aim to reduce the burden of viral hepatitis in Asia-Pacific

Web: www.cevhap.org

**World Health Organisation (WHO) hepatitis B fact sheet**

Web: http://www.who.int/mediacentre/factsheets/fs204/en/

**World Hepatitis Alliance** – is composed of over 170 organisations who work in the field of viral hepatitis, representing every region of the world. They are patient-led and patient-driven; the global voice for the 500 million people worldwide living with viral hepatitis

Web: http://www.worldhepatitisalliance.org/en/

# ABBREVIATIONS

| | |
|---|---|
| AASLD | American Association for the Study of Liver Diseases |
| ACCHS | Aboriginal Community Controlled Health Services |
| ACE | angiotensin converting enzyme |
| ADF | Australian Defence Force |
| ADV | adefovir |
| AFP | alpha-fetoprotein |
| AIDS | acquired immune deficiency syndrome |
| ALT | alanine aminotransferase |
| anti-HBc | antibodies to core antigen |
| anti-HBe | antibodies to envelope antigen |
| anti-HBs | antibodies to surface antigen |
| APASL | Asian Pacific Association for the Study of Liver |
| APP | Australian privacy principles |
| BCLC | Barcelona Clinic Liver Cancer |
| BCP | basal core promoter |
| CALD | culturally and linguistically diverse |
| cART | combined antiretroviral therapy |
| ccc DNA | covalently closed circular DNA |
| CHB | chronic hepatitis B |
| CM | complementary medicine |
| CT | computed tomography |
| DNA | deoxyribonucleic acid |
| eAg | envelope antigen |
| EASL | European Association for the Study of Liver |
| eGFR | estimated glomerular filtration rate |
| ETV | entecavir |
| FBC | full blood count |
| HAI | Histological Activity Index |
| HAV | hepatitis A virus |
| HBcAg | hepatitis B core antigen |
| HBeAg | hepatitis B envelope antigen |
| HBIg | hepatitis B immune globulin |
| HBIG | hepatitis B immunoglobulin |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCC | hepatocellular carcinoma |
| HCV | hepatitis C virus |
| HDV | hepatitis D virus |
| HIV | human immunodeficiency virus |
| IFN | interferon |
| IgM | immunoglobulin M |
| IRIS | immune reconstitution inflammatory syndrome |
| IU | international unit |
| INR | international normalised ratio |
| LAM | lamivudine |
| LdT | telbivudine |
| LFT | liver function test |
| MDR | multidrug resistant |
| MELD | Model of End-Stage Liver Disease |
| MHR | major hydrophilic region |
| MRI | magnetic resonance imaging |
| MSM | men who have sex with men |
| NA | nucleoside or nucleotide analogue |
| NAFLD | non-alcoholic fatty liver disease |
| NSAID | nonsteroidal anti-inflammatory drug |
| NSW | New South Wales |
| nt | nucleotide |
| OLT | orthotopic liver transplantation |
| ORF | overlapping reading frame |
| PBS | Pharmaceutical Benefits Scheme |
| PCR | polymerase chain reaction |
| PEG-IFN | pegylated interferon |
| pg | pregenomic |
| Pol | polymerase |
| PSE | portal systemic encephalopathy |
| PVT | portal vein thrombosis |
| RC | relaxed circular |
| RCT | randomised controlled trial |
| RFA | radiofrequency ablation |
| RNA | ribonucleic acid |
| rt | reverse transcriptase |
| SBP | spontaneous bacterial peritonitis |
| SSRI | selective serotonin reuptake inhibitor |
| TACE | transcatheter arterial chemoembolisation |
| TAE | transcatheter arterial embolisation |
| TCM | Traditional Chinese medicine |
| TDF | tenofovir disoproxil fumarate |
| TE | transient elastography |
| TGA | Therapeutic Goods Administration |
| TIPS | transjugular intrahepatic portosystemic shunt |
| TIS | Translating and Interpreting Service |
| ULN | upper limit of normal |
| USA | United States of America |
| VIDRL | Victorian Infectious Diseases Reference Laboratory |
| WHO | World Health Organization |

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