

# Clinical assessment of patients with hepatitis B virus infection

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## KEY POINTS

- Determining the phase of hepatitis B virus (HBV) infection is essential to the clinical assessment of the patient with HBV.
  - HBV DNA, HBeAg status and liver function testing are all vital 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.
  - Fibrosis assessment to determine the stage of liver disease is also important (non-invasive tests, imaging with or without biopsy)
  - Non-invasive methods of assessing hepatic fibrosis such as transient elastography (FibroScan®) are becoming available.
  - Normal alanine aminotransferase (ALT) ranges are being revised downwards (< 19 U/L for females and < 30 U/L for males), and normal liver function tests (LFTs) 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 people are diagnosed with hepatitis B, testing, assessment and vaccination should be offered to their household and sexual contacts.
  - All patients with CHB require regular monitoring for liver damage and disease progression.
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## Initial assessment of patients with chronic hepatitis B virus infection

Table 6.1 provides a summary of acute hepatitis B virus (HBV) infection.

**Table 6.1** Acute hepatitis B virus infection

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

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 1000–2000 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 a 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.

### History and physical examination

The assessment of patients with chronic hepatitis B (CHB) should commence with a thorough clinical history and physical examination. 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, (e.g. spider naevi), portal hypertension (splenomegaly) or decompensation (jaundice, hepatic encephalopathy, 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 6.2) – 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: [Hepatitis B virus testing and interpreting test results](#)) (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 6.2** Tests used in the initial assessment of patients with chronic hepatitis B

Test	Why the result is important
HBeAg / anti-HBe HBV DNA	Quantify replication, identify phase of infection and consider treatment
Anti-HAV, anti- HCV, anti- HDV, HIV Ag/Ab	Ascertain co-infection (with HCV, HDV or HIV) and evidence of immunity to HAV (need to offer vaccination)
LFT FBC PT, INR AFP	Necroinflammatory activity, synthetic function Thrombocytopenia may indicate cirrhosis Assessing the liver's synthetic function 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; AFP: alpha fetoprotein

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 exclude 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 or immune escape). For a discussion of the definition and preferred terminology of CHB see Natural history of hepatitis B virus infection.

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 2000 IU/mL was found to be a strong predictor of increased risk of cirrhosis and HCC (5). 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 (immune escape) 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 levels of at least 20,000 IU/mL, and in HBeAg-negative patients with HBV DNA of at least 2000 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 (AFP) 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) are also recommended (1, 2, 4).

## Fibrosis assessment

### Liver biopsy

Liver biopsy should only be performed on the recommendation of a specialist clinician and is now uncommonly needed in assessing viral hepatitis. 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 stages F0 to F4 (F0=no fibrosis; F1=minimal fibrosis;

F2=periportal fibrosis; F3=septal fibrosis linking portal tracts or central vein; and F4=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 (6-8).

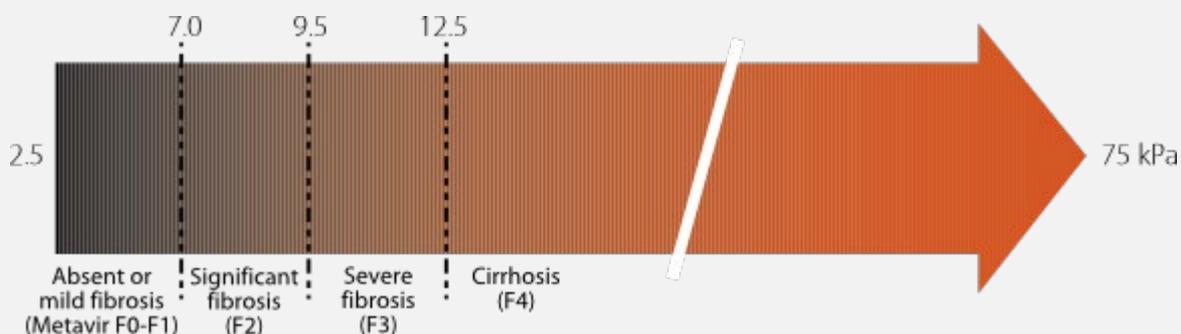
The development of significant fibrosis (stage 2 or greater) implies progressive disease and the need for treatment. Inflammation is graded using necroinflammatory scores.

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 fibrosis 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 comorbidities 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 available and used. The most commonly used technique is transient elastography (TE) or FibroScan<sup>®</sup>. It measures liver stiffness via ultrasound elastography. Shear waves are generated and measured in kilopascals (kPa), which correlate with fibrosis score as determined by biopsy. Cut-off values 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%). (9). A more recent meta-analysis regarding the use of TE in CHB support these findings, with similar sensitivity and specificity in the detection of cirrhosis (sensitivity 86% and specificity 88%) and better sensitivity and specificity in the detection of significant fibrosis ( $\geq$  F2/F3, sensitivity 81-82%, specificity 82-87%) (10). In the detection of cirrhosis in patients with CHB, TE has greater sensitivity and specificity when compared to other non-invasive tests, such as FIB-4 and APRI (11). Australian and international consensus guidelines now include TE as an acceptable alternative to biopsy for fibrosis staging (1,2,12-14). Currently, FibroScan<sup>®</sup> is available in 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.

**Figure 6.1** Clinical significance of liver stiffness cut-off values in chronic liver diseases using FibroScan® (18)



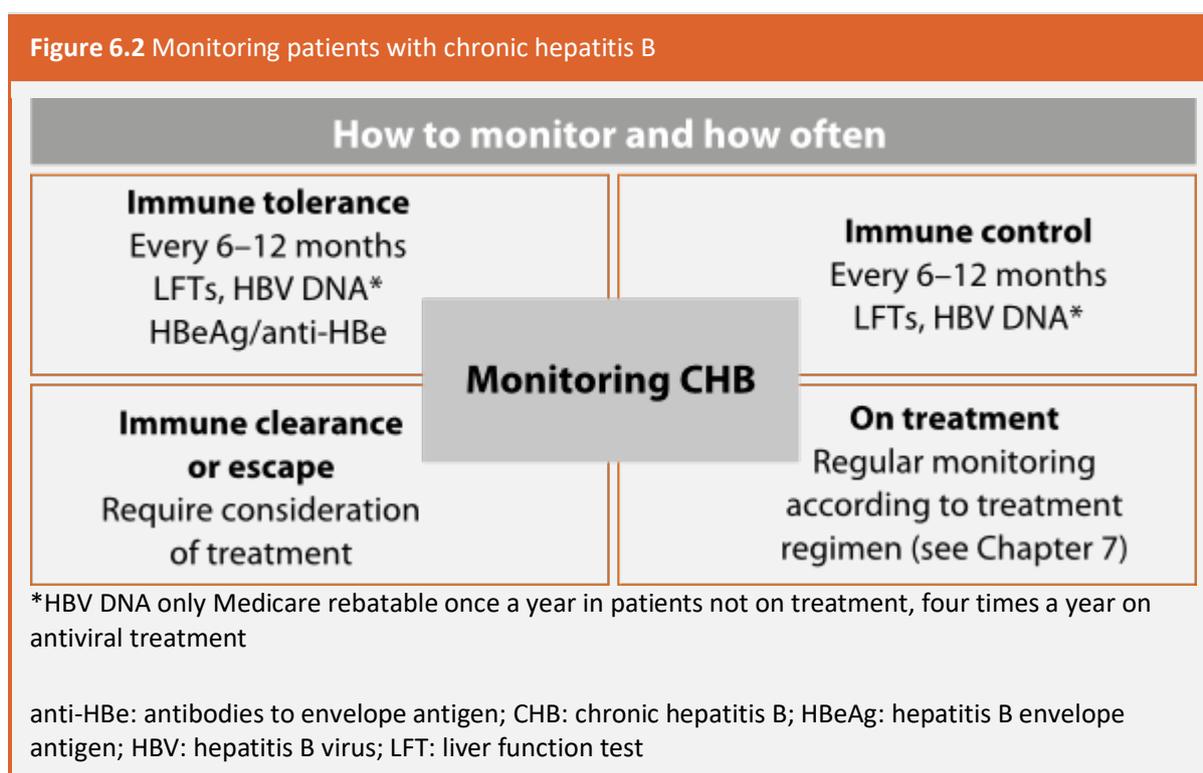
Used with permission: Castera L, Fornis X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol* 2008;48:835-47.

A number of other means of assessing fibrosis non-invasively have been reported. They include acoustic radiation force impulse (ARFI), shear-wave elastography (SWE), magnetic resonance imaging (MRI)-based elastography and serum blood algorithms, such as those used to derive the aspartate aminotransferase (AST) to platelet ratio index (APRI), Fibrotest and Hepascore results. APRI can be calculated from AST and platelet count and is used to evaluate the presence of cirrhosis in hepatitis C in the current Australian consensus guidelines (15). Predicting cirrhosis in hepatitis B with an APRI score greater than 1.5 has a sensitivity of 54% and specificity of 78%. With a 2.0 cut-off value, the APRI has a sensitivity of 28% and a specificity of 87%. For predicting fibrosis more than F2 and a cut-off 1.5, the sensitivity is 49% and the specificity is 84%. With a 0.5 cut-off value, the sensitivity is 84% and the specificity 41% (16). The APRI score is currently recommended by the WHO for evaluation of cirrhosis in CHB in low- and middle-income countries using a threshold over 2.0 but detects only one-third of patients with cirrhosis (17). 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 (see: [Treatment of chronic hepatitis B virus infection](#)). All patients with CHB require some form of monitoring, the frequency of which is determined by their clinical state ([Figure 6.2](#)).

**Figure 6.2** Monitoring patients with chronic hepatitis B



Monitoring for those not on treatment consists of LFTs 6-monthly and HBV DNA annually (Medicare rebatable once every 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, up to four times higher than non-Indigenous Australians (19). 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 National) has a number of services, including the Doctors Priority Line 1300 131 450 (which is freely available, 24 hours a day, 7 days a week). For more information on TIS (National), and links to HBV information packages in other languages, see Appendix 2.

Various lifestyle issues need to be addressed: alcohol consumption should be at safe levels and avoided (20) in people with fibrosis or cirrhosis, 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: Primary prevention of hepatitis B virus infection).

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 that influence the decision to commence treatment, including the role of liver biopsy. Table 6.3 provides some examples of when to seek urgent advice or referral.

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

<p><b>Severe acute exacerbation (or acute HBV)</b></p> <ul style="list-style-type: none"><li>▶ Potential for fulminant disease – how to recognise/react</li><li>▶ Read more on natural history of ACUTE HBV in Chapter 4.</li></ul> <p><b>Reactivation during immunosuppression/chemotherapy</b></p> <ul style="list-style-type: none"><li>▶ One situation where urgent antiviral therapy required</li><li>▶ Read more on immunosuppression in Chapter 11.</li></ul> <p><b>Cirrhosis (especially where suggestion of decompensation)</b></p> <ul style="list-style-type: none"><li>▶ Needs immediate discussion, triage prioritisation with specialist service</li></ul> <p><b>Possible HCC found on surveillance</b></p> <ul style="list-style-type: none"><li>▶ Read more on hepatocellular carcinoma in Chapter 9.</li></ul>
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HBV: hepatitis B virus; HCC: hepatocellular carcinoma

#### 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 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 contractures).

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

ALT: alanine aminotransferase; AST: aspartate aminotransferase

## 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 6.4). Screening is recommended every 6 months, using ultrasound and AFP estimation ([1](#), [2](#), [4](#), [13](#), [14](#), [21](#)).

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](#), [22](#)). However, screening for HCC needs to continue, regardless of treatment outcome, because the risk is not completely eliminated.

**Table 6.4** Recommended screening for hepatocellular carcinoma (HCC) screening in patients with chronic hepatitis B

**Ongoing surveillance, including 6-monthly ultrasound tests and alpha fetoprotein (AFP) level tests, is recommended for the following patients with chronic hepatitis B**

- 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
- People with a family history of HCC.

## 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 (see: [Treatment of chronic hepatitis B virus infection](#)). 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 current migration patterns suggest that the prevalence of disease in Australia will continue to increase.

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