Clinical assessment of patients with hepatitis B virus infection

KEY POINTS

- Determining the phase of hepatitis B virus (HBV) infection is essential in the clinical assessment of the patient with HBV.
- HBV DNA, HBsAg, and liver function testing are all vital components of this assessment.
- HBV DNA is an important parameter in inferring treatment decision. Testing is widespread and increasingly used for treatment monitoring.
- Risk factor 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 now available.
- Normal platelet counts and prothrombin time (PT) have been reversed downward (< 15%, for males and < 20%, for females), and normal liver function tests (ALT) do not rule out significant hepatic disease.
- Transmission risks, lifestyle modification, and 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>
<thead>
<tr>
<th>Table 6.1: Acute hepatitis B virus infection</th>
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<tr>
<td>ALT: alanine aminotransferase, anti-HBs: antibodies to core antigen; anti-HBC: antibodies to surface antigen; AST: aspartate aminotransferase; CHB: chronic hepatitis B; HBeAg: hepatitis B envelope antigen; HBcAg: hepatitis B core antigen; HBV: hepatitis B virus; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; I numer: immunoglobulin</td>
</tr>
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History and physical examination

The assessment of patients with chronic hepatitis B (CHB) should commence with a thorough clinical history and physical examination. Important points to consider are:

- Any risk factors for the acquisition of hepatitis B, for example, ethnic background, family history of CHB, and history of hepatocellular carcinoma (HCC).
- Host or viral factors that are associated with an increased risk of chronicity, for example, older age, gender, duration of infection, heavy alcohol consumption, cigarette smoking, and coinfection 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 assessed by examining for peripheral signs of chronic liver disease.

Laboratory investigations

Complete blood count, – ALT, AST, total protein, albumin, total bilirubin, alkaline phosphatase, gamma-glutamyltransferase, and lipase. Consider measuring ferritin and inflammatory markers, and, if indicated, serologic tests for other viral infections and malignancies.

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.

ALT is inversely associated with liver function test and is therefore useful in monitoring viral hepatitis. ALT is a measure of serum transaminase activity.
Table 6.2: Tests used in the initial assessment of patients with chronic hepatitis B

<table>
<thead>
<tr>
<th>Test</th>
<th>Why the result is important</th>
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<tbody>
<tr>
<td>HBSAg/anti-HBs HBV DNA</td>
<td>Quantitative replication; identify phase of infection and consider treatment</td>
</tr>
<tr>
<td>Anti-HBc, anti-HBc, anti-HDV, anti-HAV, HAV Ag antibodies</td>
<td>Ascertain co-infection with HCV, HDV or HAV and evidence of immunity to HAV need to offer vaccination</td>
</tr>
<tr>
<td>LFT</td>
<td>Immuno-inflammatory activity; synthesis function</td>
</tr>
<tr>
<td>ALT</td>
<td>Assessing the liver's synthetic function</td>
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<tr>
<td>RFT, INR, albumin</td>
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</table>

HbsAg is considered a marker of HBV replication and infectivity. Seropositivity and development of anti-HBs often signals transition from an active phase (immune clearance of the disease) to an immune control phase (HbsAg negative, anti- Hbs positive, low HBV DNA level). Patients can fluctuate between the active (HbsAg positive, anti-HBs negative, high HBV DNA level) and immune control phases of the disease over time. The absence of HbsAg, however, does not necessarily exclude active viral replication, since specific mutations in the HBV genome can prevent HbsAg synthesis - the so-called low HbsAg and core promoter mutants. Patients with these HbsAg mutants have elevated HbsAg and ALT despite the absence of HBV DNA and negative HbsAg 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 2,000,000 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 8.8, 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 hybridization assays. An earlier version of the hybridization assay, used commonly until a few years ago, has a threshold of detection greater than 20,000 IU/mL (1.4 x 10^6 copies/mL). Hence, the clinical status for some patients may need to be reinterpreted using the results obtained with the newer assay. In particular, patients with HBV DNA below the threshold of detection of the previous assay might be erroneously diagnosed as inactive or being in the immune control phase, because of the inability of older assays to demonstrate viremia below the assay detection threshold.

The threshold of HBV DNA level associated with liver disease is unknown. However, treatment is usually considered in HBsAg-positive patients with HBV DNA levels of at least 20,000 IU/mL, and in HBsAg-negative patients with HBV DNA levels of at least 200,000 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 profiles), and liver ultrasound and alpha-fetoprotein (AFP) estimation. A complete laboratory screen for other causes of liver dysfunction and testing for coinfection with other viruses (e.g., hepatitis C and D) are also recommended [1.2.4].

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Fibrosis assessment

Liver biopsy

Liver biopsy should only be performed on the recommendation of a specialist clinician and is now unnecessary 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. The two histological features of liver biopsy used in the assessment of fibrosis stage are necroinflammation and degree of fibrosis. Liver biopsy is usually graded from 0 to 4 (F0-F4: fibrosis). F1-F4 is subdivided into F1 (minimal fibrosis), F2 (moderate fibrosis), F3 (severe fibrosis), and F4 (cirrhosis). Liver biopsy also suffers from sampling bias, because fibrosis and necroinflammation may be heterogeneous distributed in the liver. The absolute requirement for a biopsy before commencing treatment was removed by the Pharmacological Benevolents 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 and its use only considered when it influences management.

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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). It measures liver stiffness via ultrasound technology. These 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%) [11]. A more recent meta-analysis of TE in CHB supports these findings, with similar sensitivity and specificity in the detection of fibrosis ≥S0 and S3 [26]. The authors of the meta-analysis noted that the results were consistent with the evidence for other non-invasive tests, such as Fibro Sen and APRI [3]. Australian and international consensus guidelines now include TE as an acceptable alternative to biopsy for fibrosis staging [27.28.29.30.31]. Currently, Fibroscan is available in a wide variety of settings, although it is not universally available. 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®
A number of other ways 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 biomarkers, such as those used to derive the separate non-invasive fibrosis score (NIFS) by plakoglobin (APRI), fibrosis-4 (Fib-4), and non-invasive tests such as the current Australian guidelines [15]. Predicting cirrhosis in hepatitis B with an APRI score greater than 1.5 has a sensitivity of 56% and specificity of 78%. With a 0.5 cut-off value, the APRI has a sensitivity of 29% and a specificity of 85%. For predicting fibrosis more than 2, and a cut-off of 1.5, the sensitivity is 29% and the specificity is 91%, with a 1.5 cut-off value, the sensitivity is 10% and the specificity is 98% [19]. The APRI score is currently recommended by the WHO for evaluation of cirrhosis in China and middle-income countries using a threshold of 1.5 but defects only one-third of patients with cirrhosis [17]. Further research into non-invasive assessment of hepatic fibrosis is required.

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DETERMINING THE NEED FOR TREATMENT

The need for treatment is based on assessment of HBeAg and liver function tests (to determine the phase of infection), and assessment of fibrosis. Candidates for treatment are those with HBeAg-positive or negative chronic hepatitis B (previously known as immune tolerance) and all patients with cirrhosis. Pharmacological benefits of the different 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 (Table 6.3).

<table>
<thead>
<tr>
<th>Table 6.3 Monitoring patients with chronic hepatitis B</th>
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<tbody>
<tr>
<td>Indication</td>
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<tr>
<td>HBsAg-positive chronic infection (previously referred to as immune tolerance)</td>
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<tr>
<td>HBsAg-negative chronic infection (previously referred to as immune tolerance)</td>
</tr>
<tr>
<td>On treatment</td>
</tr>
<tr>
<td>HBsAg-positive chronic hepatitis (previously referred to as immune clearance)</td>
</tr>
<tr>
<td>HBsAg-negative chronic hepatitis (previously referred to as immune clearance)</td>
</tr>
</tbody>
</table>

Monitoring for those not on treatment consists of LFTs 6-monthly and HBV DNA annually (incorporating four sequential results every 12 months). The monitoring is needed to determine if and when the disease phase has changed and when treatment may be indicated.

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MANAGEMENT OF PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION

CHB can be a lifelong 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 [15]. It is important to ensure that counseling about CHB is done in a culturally appropriate and safe manner. Health practitioners need to be sensitive to 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 333 400 which is free, available 24 hours a day, 7 days a week. For more information on TIS, and links to TIS information packages in other languages, see: health professional resources.

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).

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Table 6.4 Clinical situations and the need for referral

<table>
<thead>
<tr>
<th>Seroconversion (or acute HBV)</th>
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</thead>
<tbody>
<tr>
<td>• Potential fulminant disease – how to recognize?</td>
</tr>
<tr>
<td>• Read more on natural history of ACUTE HBV in Chapter 4</td>
</tr>
</tbody>
</table>

Reactivation during immunosuppression/chemotherapy

<table>
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<tr>
<th>One situation where urgent antiviral therapy required</th>
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</thead>
<tbody>
<tr>
<td>• Read more on immunosuppression in Chapter 12</td>
</tr>
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</table>

Cirrhosis: suspicion where suggestion of decompensation

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<tr>
<th>Needs immediate discussion, imaging prioritisation with specialist advice</th>
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Possible HCC found on surveillance
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 6.3). Screening is recommended every 6 months using ultrasound (with or without AFP estimation) (1, 2, 4, 13, 14, 21).

The incidence of HCC is lower in patients receiving nucleoside analogues based mainly on data from treatment with lamivudine or entecavir (or interferon) than in untreated patients, even though without cirrhosis (8, 23). However, screening for HCC needs to continue, regardless of treatment outcome, because the risk is not completely eliminated.

Table 6.3: Recommended screening for hepatocellular carcinoma (HCC) screening in patients with chronic hepatitis B (adapted from Australian consensus recommendations for the management of hepatitis B (2022))

- People with cirrhosis
  - Asian men older than 40 years
  - Asian women older than 50 years
  - Sub-Saharan Africans older than 20 years
  - Indigenous and Torres Strait Islander people older than 50 years
  - With co-infection with hepatitis delta virus
  - With family history of HCC (first-degree relative)
  - Observed HBeAg loss with prior indication for HCC surveillance

- Other high-risk groups in whom screening can be considered
  - Persons of European ancestry according to risk scores (e.g., PAGE-B)
  - African and Pacific Islander men older than 40 years and women older than 50 years

HbsAg: hepatitis B surface antigen; HCC: hepatocellular carcinoma; PAGE-B: HCC predictive score based on age, sex and platelet count (22).

Not available data not available, but HCC incidence is likely to be increased.

1 Based on Northern Territory Linkage data (21).

Identified with permission from the Hepatocellular Carcinoma Consensus Statement Steering Committee. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement (20).

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, as current knowledge is particularly relevant because current migration patterns suggest that the prevalence of disease in Australia will continue to increase.

References


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