

CLINICAL ASSESSMENT OF PATIENTS WITH HEPATITIS B VIRUS INFECTION

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Darrell HG Crawford School of Medicine, University of Queensland, Greenslopes Private Hospital; Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane, QLD.
Rebecca J Ryan School of Medicine, University of Queensland, Greenslopes Private Hospital; Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane, QLD.
Nghi Phung Department of Addiction Medicine, Department of Gastroenterology and Hepatology, Westmead Hospital, Westmead, NSW.

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KEY POINTS

- The assessment of a patient should be considered in the context of the natural history of hepatitis B infection.
- Transmission risks, lifestyle modification, cultural factors and long term complications associated with chronic hepatitis B infection are important elements for patient education.

Introduction

Following acute hepatitis B virus (HBV) infection, 95% of adult patients will mount an immune response adequate to clear the virus. Furthermore, only one third of adult patients experience symptoms of acute hepatitis following exposure, while the remaining patients usually have subclinical disease. In contrast, 90% of infants born to HBsAg-positive mothers and 30% of infants exposed before five years of age will develop chronic HBV infection (CHB), but symptomatic acute infection occurs very infrequently in this age group.¹

Therefore, the majority of patients with HBV infection who are encountered in primary care will have CHB. Such patients are usually asymptomatic until they develop features associated with hepatic decompensation. As a consequence of the silent clinical course of CHB, the management for the majority of

affected patients is not centred upon symptom relief but rather, care is primarily aimed at preventing disease progression to cirrhosis and hepatocellular carcinoma (HCC).¹⁻³

Assessment of patients with chronic HBV infection

History and physical examination

The assessment of patients with CHB should commence with a thorough clinical history and physical examination. Aspects of the clinical history that deserve close attention are risk factors for acquisition of CHB, such as ethnic background, a family history of CHB, and a family history of HCC; and host or viral factors that are associated with an increased risk of cirrhosis, including older age (related to a longer duration of infection), heavy alcohol consumption, cigarette smoking and co-infection with other viruses, e.g. hepatitis C virus (HCV), hepatitis

D virus (HDV), and human immunodeficiency virus (HIV). Hepatitis A vaccination should be offered to patients with chronic hepatitis B. 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

Extra hepatic manifestations of CHB occur in 10–20% of patients for which effective antiviral therapy is pivotal. Such manifestations include polyarteritis nodosa with multiple organ systems involvement, such as the gastrointestinal tract (colitis), kidney (glomerulonephritis), neurological (neuropathy), and dermatological systems (vasculitic skin rashes, palpable purpura). Conversely, approximately 50% of patients with polyarteritis nodosa are HBsAg positive. HBV infection-associated glomerulonephritis usually presents with nephrotic range proteinuria, which may progress to renal failure in the absence of effective antiviral therapy.

Transmission risk

An evaluation of the patient's risks for transmission to contacts is essential. The risk of transmission is proportional to the level of viraemia. However, all HBsAg-positive patients should be considered infectious. Patients should be counselled regarding vaccination of household members and sexual contacts, and the use of barrier protection for sexual contact with partners who are not completely immunised. Occupational risk of transmission is important—particularly for health care workers who should be counselled regarding the legislative restrictions on performing exposure-prone procedures. Hepatitis A vaccination should be offered to patients with CHB in the absence of hepatitis A immunity.

Laboratory investigations

Complete HBV serology—hepatitis B surface antigen (HBsAg), antibody to surface antigen (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), hepatitis B envelope antigen (HBeAg), antibody to hepatitis B e antigen (anti-HBe)—and measurement of HBV DNA level should be performed initially to evaluate

HBV replication status¹ (see Table 3.1, Chapter 3: Hepatitis B virus testing and interpreting test results). HBsAg is the first serological marker to appear and its presence for more than six months indicates CHB infection. HBsAg appears in serum 4–10 weeks after exposure, preceding the onset of symptoms of acute hepatitis and elevated alanine aminotransferase (ALT). HBsAg will become undetectable 4–6 months after acute exposure in those patients who achieve successful immune clearance^{2,3} (Table 6.1).

Table 6.1: Hepatitis B serology

Serological marker	Interpretation
HBsAg	Hepatitis B infection
Anti-HBs	Immunity to HBV infection
Anti-HBc	Previous exposure
HBeAg	Viral replication and infectivity*
Anti-HBe	Immune control phase (if HBV DNA negative)*
HBV DNA	Viral replication

*Except in HBeAg-negative chronic hepatitis B where there may be viral replication as evidenced by detectable HBV DNA, despite negative HBeAg and positive anti-HBe

Anti-HBs indicates immunity to HBV when it emerges following the disappearance of HBsAg. Anti-HBs usually persists for life, conferring long-term immunity.

HBeAg is only expressed in liver tissue and therefore not used in routine clinical practice. Anti-HBc is a marker of exposure. Anti-HBc IgM is seen in high titres in acute HBV infection and at lower levels in patients with CHB undergoing a flare in disease activity. Anti-HBc is not found in subjects with anti-HBs who are immune through HBV vaccination.

HBeAg is considered to be 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 of the disease to the immune control phase (HBeAg negative, anti-HBe positive, low HBV DNA level). Over time patients can fluctuate between the active (HBeAg positive, anti-HBe negative, high HBV DNA level) and immune control phases of the disease. The absence

of HBeAg, however, does not necessarily preclude active viral replication, since specific mutations in the HBV genome can prevent HBeAg synthesis—so-called precore and core promoter mutants. Patients with these HBV mutants have elevated HBV DNA and ALT levels, despite the absence of HBeAg (HBeAg-negative CHB). The frequency of HBeAg-negative CHB is increasing, representing 20–40% of CHB infection in Australia.^{2,3}

HBV DNA is a measure of viral replication, often used as a criterion for commencing antiviral therapy in patients with CHB. Furthermore, in population studies, a HBV DNA level greater than 2000 IU/mL is found to be a strong predictor of increased risk for cirrhosis and HCC.⁴ Levels of HBV DNA were previously expressed as copies/mL, but these should be converted to the accepted standard of international units (IU)/mL. The conversion factor is 1 IU/mL = 5–6 copies/mL (the range from 5.2–5.8 depends 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 a hybridisation assay, used commonly until a few years ago, had 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 with results from newer assays. In particular, patients with HBeAg-negative CHB might be erroneously diagnosed as in the immune control phase, due to the inability of older assays to demonstrate viraemia below the level of the assay detection threshold.²

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 \geq 20,000 IU/mL, and in HBeAg-negative patients with HBV DNA \geq 2000 IU/mL.¹

HBV DNA levels may fluctuate widely in CHB, so a more accurate assessment of the patient's clinical status requires serial HBV DNA measurements over time.

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

Liver biopsy should be only performed on the recommendation of a specialist clinician. Liver biopsy provides an accurate assessment of the degree of necroinflammatory activity and the extent of hepatic fibrosis, as well as the exclusion of other liver diseases. Such results can be vital in informing the need for antiviral therapy. However, some patients resist liver biopsy because of its invasive nature and risk of complications, such as haemorrhage and gall bladder perforation. Further research into non-invasive assessment of hepatic fibrosis is required (see Chapter 3: Hepatitis B virus testing and interpreting test results).

Acute HBV infection

The incidence of acute HBV infection has been decreasing in Western countries for a number of years, probably due to widespread vaccination. 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 symptoms of anorexia, nausea, jaundice, and right upper quadrant pain. Symptoms usually disappear after 1–3 months, but some patients have prolonged fatigue even after the liver function tests have normalised.

Elevated alanine and aspartate aminotransferase (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, thus 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. This is believed to be due to the massive immune-mediated lysis of infected hepatocytes and therefore, 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 (< 2g/day) or codeine may be cautiously administered for abdominal pain or fevers. Since most patients recover, antiviral therapy is not usually recommended. However, case reports and small series of patients suggest some benefits of early therapy. Current recommendations support the use of nucleoside 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, signs of encephalopathy, or if the illness is uncharacteristically lengthy (Table 6.2). Continued serological assessment following recovery from the icteric illness is important to identify the small proportion of patients who develop CHB.

Managing patients with chronic HBV infection

Chronic HBV 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 and natural history of HBV suggest that the vast majority of patients will come from culturally and linguistically diverse (CALD) backgrounds. Indigenous Australians also have a high prevalence of CHB. A number of issues inherent in the ethnic diversity arise when counselling patients about CHB. Apart from language difficulties, health practitioners have to be sensitive to the cultural beliefs of specific patient groups and be aware of the implications of a diagnosis of CHB in various patient populations. It is often important to provide consultation in the presence of other family members or with an interpreter. HBV information packages in various languages are usually available in major tertiary hospitals.

Various lifestyle issues should be addressed. Alcohol consumption should be ceased or minimised and cigarette smokers should quit. Weight reduction with sound nutritional advice for those with increased body mass index should be encouraged. Issues related to vaccination and transmission have been previously addressed.

Table 6.2: Referral guidelines for specialist review of patients with hepatitis B virus infection

Investigations to be performed before referral	Complete HBV serology (HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe) HBV DNA Liver function tests, full blood count, coagulation profile Hepatitis C antibody Hepatitis D antibody
Investigations for hepatocellular carcinoma surveillance	Alpha fetoprotein Abdominal ultrasound
Criteria for referral of patients with acute hepatitis B	Elevated prothrombin time, international normalised ratio or serum bilirubin concentration Signs of decompensated liver disease (encephalopathy, ascites) Uncharacteristically lengthy illness
Criteria for referral of patients with chronic hepatitis B	All HBsAg-positive patients: particularly if HBV DNA > 2000 IU/mL, elevated ALT levels or features of significant liver damage
Criteria for referral of anti-HBs-positive patients	If considering immunosuppression (including corticosteroids) Annual monitoring by GP for all other anti-HBs-positive patients (consider inactive cirrhosis in the older patient)

Irrespective of language difficulties, patients should understand the aims of treatment, namely:

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

It is important that patients have an understanding of the key factors, including the role of liver biopsy, which influence the decision to commence treatment.

Pegylated interferon, lamivudine and entecavir are approved for reimbursement by the Pharmaceutical Benefits Advisory Committee (PBAC) for initial antiviral treatment in patients with CHB. Patients should be advised that the selection of the most appropriate antiviral therapy depends on many factors, including safety, efficacy and cost. Pegylated interferons are administered for a defined duration—but patients require pre-treatment education and ongoing support while on therapy, due to the adverse events associated with their use.

Nucleoside analogues (NA), e.g. lamivudine and entecavir, are generally very well tolerated, with a limited number of side effects. A major concern with their long-term use is the emergence of antiviral resistant mutations.

The emergence of antiviral resistant mutants is related to previous exposure to NAs, the duration of therapy, the pre-treatment HBV DNA level and the rate of decline of HBV DNA levels after therapy has commenced. Adefovir, while effective in suppressing wild type and lamivudine-resistant HBV, is only available under the Pharmaceutical Benefits Scheme (PBS) in Australia for the treatment of resistant HBV. Entecavir is also available for the treatment of lamivudine-resistant HBV, but a higher dose (1.0 mg) is recommended than for treatment-naïve patients (0.5 mg).⁵

HBeAg-positive patients are treated until they establish HBeAg seroconversion and maintain the immune control phase (HBeAg negative, HBsAg positive and low HBV DNA). HBeAg-negative patients often need to be treated

indefinitely, as relapse is common. For this reason, the decision to use NAs needs to be considered carefully because of the risk of viral resistance. Treatment is often deferred until later for patients in their twenties or younger, unless there are indicators of significant liver disease or a family history of HCC.²

Combination antiviral therapy has proved to be highly beneficial in preventing antiviral resistance in HIV and it is likely that a similar scenario will emerge in HBV treatment (see Chapter 2: Virology: viral replication and drug resistance).

Patients interested in starting a family should consider the safety profile of various treatment options and the restricted access to treatment under PBS Section 100 criteria. The management decision for patients initiated on treatment who later become pregnant must be individualised. There are abundant safety data for lamivudine in HIV-treated patients that may facilitate a discussion on the risks and benefits of treatment cessation, including a potential flare of disease activity during pregnancy. Initiating a patient prior to family planning with pegylated interferon may be an alternative option, as interferon treatment is limited to a defined duration.

Treatment of chronic hepatitis B is discussed in more detail in Chapter 7: Treatment of chronic hepatitis B virus infection.

Screening for hepatocellular carcinoma

An important element in the assessment of a patient with CHB is the issue of HCC screening. HCC screening is recommended for patients with CHB at high risks for HCC (Table 6.3). Screening is recommended every six months using ultrasound or a combination of ultrasound and alpha fetoprotein estimation.²

Table 6.3: Recommendations for hepatocellular carcinoma screening in patients with chronic hepatitis (adapted from Sherman M.)⁶

Any patient with cirrhosis
Asian men over 40 years of age
Asian women over 50 years of age
Africans over 20 years of age
Family history of hepatocellular carcinoma

Conclusion

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

References

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