

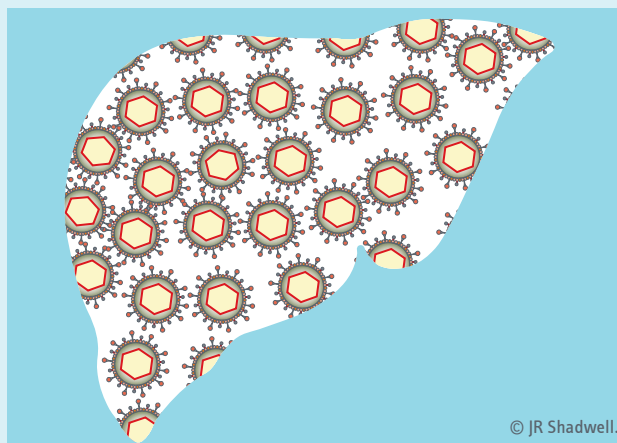
Mistakes in chronic hepatitis B management and how to avoid them

Upkar S. Gill and Patrick T.F. Kennedy

Hepatitis B virus (HBV) infection is the most common chronic viral infection in the world. Despite the availability of a preventative vaccine, more than 250 million people worldwide are chronically infected with HBV. The complications of chronic HBV infection—cirrhosis and hepatocellular cancer (HCC)—account for more than 850,000 deaths per year.¹ HBV is transmitted haematogenously and sexually, with the majority of HBV infections being transmitted vertically (or perinatally) in high prevalence regions.² HBV infection acquired at birth or in early childhood results in chronicity in >95% of cases, whereas only 5–10% of those who are infected in adulthood will progress to chronic infection.

Treatment options for chronic hepatitis B (CHB) are mostly non-curative. Although antiviral therapy can provide adequate viral suppression, cases of functional cure (or hepatitis B surface antigen [HBsAg] loss) are limited and therefore long-term therapy is required. CHB is a dynamic disease, which means that all patients with CHB require long-term monitoring to inform treatment and management decisions. The treatment paradigm in CHB is undergoing rapid change—a number of novel agents are entering the clinical trial pipeline with the therapeutic goal of HBsAg loss or functional cure. It will be important to optimise patient management in advance of these clinical trials, and maintaining viral suppression will be an important prerequisite for many of them. In addition, viral suppression is mandated in a number of patient groups, especially those with advanced disease and cirrhosis, to prevent the complications of CHB.

Here we highlight some of the mistakes frequently made by clinicians when managing CHB and provide an evidence and experience-based approach to its management.



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Mistake 1 Misinterpretation of serological test results

One of the most frequent errors in the management of CHB revolves around the interpretation of laboratory test results. Screening tests (e.g. tests for deranged liver function [liver function tests; LFTs]) include serological testing for HBsAg. The detection of HBsAg in the serum on two occasions at least 6 months apart is diagnostic of CHB. HBsAg positivity should trigger the performance of a broad panel of investigations, including viral serology coupled with biochemical tests, to profile the disease and facilitate management. HBV DNA (measured via quantitative polymerase chain reaction [PCR]), hepatitis B e antigen (HBeAg) serology and the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are key markers of disease, reflecting the presence of replicating virus and liver inflammation and/or injury, respectively. In addition, a full chronic liver disease screen and baseline imaging should be performed as part of formal disease assessment.³ A single positive HBsAg test that is

negative on subsequent testing could indicate that a patient has acute hepatitis B, and these patients do not usually require long-term follow-up if antibodies against HBsAg (HBsAb⁺) develop.

Mistakes in the interpretation of serological test results often include the referral of patients who are HBsAg[−], but hepatitis B core antibody positive (HBcAb⁺). This profile is in keeping with individuals who have previously been exposed to HBV and cleared the virus, but carry the hallmark of prior exposure (HBcAb⁺). These patients do not require monitoring or referral to secondary care, unless immunosuppression is being considered (discussed further in mistake 10). Vaccination in HBsAg[−], HBcAb⁺ patients is also not required. Individuals who have previously been vaccinated against hepatitis B will be HBsAg[−], HBsAb⁺ and HBcAb[−], whereas those who have not been vaccinated will be HBsAg[−], HBsAb[−] and HBcAb[−]. All individuals at risk of contracting HBV infection should be vaccinated (i.e. healthcare professionals, household or sexual contacts of individuals with CHB).

Mistake 2 Incorrect and/or inappropriate referral to secondary care

As indicated above, all patients testing HBsAg⁺ require referral to secondary and/or specialist care. Two positive HBsAg tests 6 months apart confirms a diagnosis of CHB and these patients will need long-term monitoring and close follow-up. The dynamic nature of CHB means

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Upkar Gill is an Academic Clinical Lecturer & Honorary Specialist Registrar in Gastroenterology & Hepatology and **Patrick Kennedy** is a Reader & Honorary Consultant Hepatologist at Barts Liver Centre, Blizard Institute, Barts and The London, School of Medicine & Dentistry, Queen Mary University of London, London, United Kingdom.

Correspondence to: p.kennedy@qmul.ac.uk

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that liver enzymes (e.g. ALT) and HBV DNA levels may fluctuate over time and can result in liver inflammation. Patients with CHB are at risk of disease progression and require specialist monitoring. At initial diagnosis, laboratory tests (including HBeAg status and measurement of HBV DNA and liver enzyme levels) should be performed every 3 months to establish the disease phase. The disease phase will also determine disease stratification and indications for treatment. At initial diagnosis, patients require a full disease work-up including liver imaging and assessment of liver damage, (e.g. with noninvasive tests such as transient elastography or by histological assessment of liver biopsy samples).

In cases where treatment is not indicated, an individualised management plan is still required to ensure there is an appropriate level of monitoring and supervision, including screening for HCC.⁴ Current guidelines recommend specialist follow-up of patients with CHB (HBsAg⁺), therefore discharging them back to primary care is a mistake.

Mistake 3 Assuming that a normal alanine aminotransferase level means there is no significant liver disease

The 2017 EASL guidelines for the management of CHB have modified the nomenclature used to describe its disease phases.⁴ Fluctuations in ALT will often occur during the course of the disease and they may not be accounted for at the time of testing, thus liver damage may ensue and formal evaluation of the liver be required.

The threshold for the upper limit of normal (ULN) for ALT is also controversial. Mistakes are often made when an ALT level is considered 'normal', but may in fact be elevated. For example, the Prati criteria define the ULN for ALT as 19 IU/L and 30 IU/L for women and men, respectively,⁵ yet most laboratories use levels of 35 or 40 IU/L as the ULN. Even small elevations in ALT levels may lead to liver damage over time, and it is noteworthy that studies have confirmed the presence of liver damage even in disease phases considered benign (e.g. HBeAg⁺/– chronic infection).⁴ To avoid disease progression, a more circumspect approach to management is required in these patients.^{6,7}

Mistake 4 Assuming that a low level of HBV DNA means there is no significant liver disease

Patients with advanced disease often have a low level of both HBV DNA and ALT, having

been infected with HBV for many years. For this reason, it is critical that even for patients who have a low level of HBV DNA (and normal or near normal ALT levels) that markers of advanced liver disease are checked (i.e. platelet count, clotting screen, albumin).^{3,4}

Mistakes are often made with patients considered 'inactive carriers' (e.g. HBeAg[–] chronic infection with low ALT and HBV DNA levels), as clinicians associate this disease phase with no liver damage. Significant fibrosis can, however, be present in these patients, mandating formal disease assessment and, in some cases, treatment to prevent further disease progression or even decompensated liver disease from developing if cirrhosis is present.⁸

Mistake 5 Failing to exclude co-infection with HDV

Infection with hepatitis delta virus (HDV) can only occur in the presence of an HBV infection. HDV is a satellite RNA virus that causes a progressive and more aggressive form of liver disease than HBV and is often mistakenly missed. All patients who test positive for HBsAg should be checked for the HDV antibody—if positive, HDV RNA testing should then be undertaken.

In patients who are HBeAg[–], with low levels of HBV DNA, but significantly high levels of ALT and AST and established liver disease, it is imperative that HDV co-infection is excluded, as active HDV infection usually occurs in a setting where hepatitis B viraemia is low.

Although treatment options for hepatitis D are limited, it is critical that HDV co-infection is excluded so that patients can be appropriately managed and risk stratified.^{4,9}

Mistake 6 Failure to exclude a co-aetiology of liver disease

Patients with CHB may also have a coexisting aetiology that is contributing to, or causing, their liver disease. Co-factors and aetiologies therefore need to be excluded in all patients with CHB. A raised ALT level, for example, is common in patients who have nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH), the prevalence of which is increasing.¹⁰ Patients at risk of metabolic syndrome who have raised ALT levels or liver parameters out of proportion with their disease phase, should have other possible aetiologies excluded—in some cases a liver biopsy is indicated to determine appropriate management.

Viral suppression in patients with coexisting NAFLD/NASH would usually be required to remove HBV as an inflammatory propagating

factor. It is therefore critical to avoid the mistake of not considering comorbidities (e.g. CHB with coexisting NAFLD/NASH), a clinical scenario that puts patients at increased risk of disease progression.^{11,12}

Mistake 7 Failure to perform HCC surveillance correctly

CHB is the most common cause of HCC worldwide. Antiviral therapy may reduce the risk of HCC development, but does not completely eliminate it, thus patients require appropriate screening and surveillance. Inappropriate HCC surveillance, in terms of the timing of initiation and its frequency, is a mistake often made in the management of CHB.

Guidelines differ on HCC surveillance, but robust screening programs are mandated for the early detection of HCC, with early intervention if required. The risk of developing HCC is higher in patients with certain host-related factors, which include: cirrhosis; older age (>40 years), male sex, being of African or Chinese origin, a family history of HCC, coexisting liver disease, chronic coinfections (e.g. with other hepatitis viruses or HIV) and a high level of HBV DNA. Patients with any of these risk factors have an increased chance of developing HCC, so early treatment of their CHB should be considered and a more tailored surveillance program offered. HCC surveillance is usually undertaken at 6-monthly intervals, with a liver ultrasound scan (with or without measurement of serum alpha-fetoprotein) is considered the most cost-effective approach.⁴

Mistake 8 Mistiming the decision to treat

As mentioned, the treatment for CHB rarely leads to cure, unlike the situation for the majority of cases of hepatitis C. However, viral suppression can potentially halt progression of CHB and reduce the risk of developing advanced liver disease, cirrhosis and HCC. The timing of the 'decision to treat' remains the subject of debate in the management of CHB.

New treatment thresholds for CHB are now being considered, such that treatment could be initiated earlier in the course of chronic infection in order to avert the complications of CHB, for example, in those patients who have a low HBV DNA load or those previously considered immune tolerant.^{4,6,7} However, treating patients too early in the course of chronic infection may be problematic due to the potential long-term side effects of therapy, thus each patient must be considered on an individual basis.¹³ Delaying treatment until the later stages of chronic infection is another

mistake in the management of CHB. Cirrhotic patients require life-long treatment irrespective of their laboratory parameters, to prevent disease progression and reduce the risk of HCC development.

Notably, a multitude of novel therapies for CHB are now entering the clinical trial pipeline, which may further broaden treatment candidacy.^{2,14} It is important that patients be made aware that CHB treatment will change dramatically over the coming years.

Mistake 9 Thinking that patients not on treatment do not require close monitoring

Even patients who are not receiving treatment for CHB require regular monitoring. It is often thought these patients (especially those with low levels of ALT and HBV DNA or an HBeAg⁻ chronic infection) are not at risk of disease progression, which is inaccurate. It is imperative that such patients are appropriately monitored and a thorough disease assessment undertaken. The dynamic nature of CHB means that these patients are also at risk of disease progression, thus it is important to provide timely intervention should this be required.

Mistake 10 Failing to adequately screen for HBV infection prior to immunosuppressive therapy

The inadequate assessment of patients undergoing immunosuppressive therapy is a commonly made mistake in those with CHB or who have previously been exposed to HBV (HBcAb⁺). CHB patients (HBsAg⁺) will almost always require treatment when undergoing immunosuppressive therapy. The risk of HBV reactivating can be classified as high, moderate or low.¹⁵ All patients being considered for chemotherapy and immunosuppressive therapy require appropriate screening (see mistake 1) and those testing positive for HBcAb will potentially require antiviral prophylaxis to prevent reactivation of HBV. This is especially pertinent when administering B-cell-depleting agents and other novel biological agents. Vaccination of HBV seronegative patients is also recommended in this clinical setting.^{4,15}

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Your chronic hepatitis B briefing

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- 'The changing epidemiology of viral hepatitis' session at 25th UEG Week 2017 [<https://www.ueg.eu/education/session-files/?session=1817&conference=149>].
- 'Nucleos(t)ide analog (NUC) treatment of hepatitis B: Can we stop therapy?' presentation at 25th UEG Week 2017 [<https://www.ueg.eu/education/document/nucleos-t-ide-analog-nuc-treatment-of-hepatitis-b-can-we-stop-therapy/155932/>].
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