Hepatitis B and D

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Abstract

Chronic hepatitis B (CHB) remains a major global healthcare challenge with changing epidemiology and increasing morbidity and mortality from the complications of liver cirrhosis and hepatocellular carcinoma (HCC). Hepatitis B virus infection can be broadly categorized into four disease phases: (1) hepatitis B e antigen (HBeAg)-positive chronic infection; (2) HBeAg-positive chronic hepatitis; (3) HBeAg-negative chronic infection; and (4) HBeAg-negative chronic hepatitis. After hepatitis B surface antigen loss, patients do not require any specific follow-up but they carry a risk of reactivation in the event of immunosuppression. The primary treatment goal in CHB is to improve survival and quality of life by preventing disease progression and the development of HCC. Current treatment regimens are non-curative and, once initiated, treatment is usually of indefinite duration. Treatment decisions are made on the basis of disease assessment and risk stratification. All CHB patients, including those on treatment, should be monitored for disease progression and HCC development. Hepatitis B virus/D virus co-infection represents the most severe form of chronic viral hepatitis because of more rapid disease progression and increased risk of cirrhosis and HCC; thus it requires special consideration. In the present review, we summarize the guidance on hepatitis B and D diagnosis and treatment.

Keywords Chronic hepatitis B; hepatitis B virus infection; hepatitis D virus infection

Key points

- Chronic hepatitis B is an important global healthcare problem, with significant morbidity and mortality secondary to disease progression to cirrhosis and development of hepatocellular carcinoma
- Hepatitis D virus infection occurs simultaneously or as a superinfection with hepatitis B virus
- Chronic hepatitis B treatment is based on disease assessment and risk stratification
- The current therapeutic options for chronic hepatitis B include pegylated interferon and nucleot(s)ide analogues, which are usually non-curative
- The mainstay of hepatitis D treatment remains pegylated interferon, but there are suboptimal therapeutic outcomes
- Several novel therapeutic strategies are under evaluation, including combination treatment with currently available drugs, as well as new agents

Introduction

Human hepatitis B virus (HBV) belongs to the Hepadnaviridae family of small, enveloped, primarily hepatotropic DNA viruses. When HBV enters the human hepatocyte, viral DNA is converted into covalently closed circular DNA (cccDNA) that is integrated into the host's genome and serves as a template for the transcription of four viral mRNAs by host RNA polymerase.[1]

HBV infection remains a major healthcare burden, characterized by increasing morbidity and mortality. Chronic hepatitis B (CHB) is characterized by the presence of hepatitis B surface antigen (HBsAg), and an estimated 257 million people are chronically infected globally.[1] HBsAg positivity classically demonstrates regional variation, with areas of low <2% (Western Europe, North America) and high >8% (Sub-Saharan Africa, East Asia, southern parts of Central and Eastern Europe) endemicity. However, there have been shifts in both the incidence and prevalence of CHB over the recent decades, mainly because of population movement, with migrants accounting for >90% of new diagnoses.[1]

Morbidity and mortality from CHB mainly result from disease progression and the complications of chronic infection, i.e. cirrhosis and hepatocellular carcinoma (HCC). The number of HBV-related deaths significantly increased between 1990 and 2015, to >880,000 in 2015.[1] The 5-year cumulative incidence of cirrhosis varies from 8% to 20% in untreated CHB patients and, among those with cirrhosis, the 5-year cumulative risk of disease decompensation is 20%. Moreover, the annual risk of HCC development in individuals with cirrhosis is reported to range from 2% to 5%.[1]

Hepatitis D virus (HDV) is a small spherical enveloped virusoid that, upon entry into the hepatocyte, recognizes its receptor via the N-terminal domain of the HBsAg. HDV infection can occur simultaneously (co-infection) or as a superinfection with HBV. At least 5% of patients with CHB are co-infected with HDV, resulting in a total of 15–20 million HDV-infected individuals worldwide. Data presented by the World Health Organization suggest that, since the 1980s, the overall number of individuals with HDV infection has gradually declined, owing to effective global vaccination programmes against HBV. However, HDV–HBV co-infection still represents the most severe form of chronic viral hepatitis because of more rapid disease progression and the development of HCC.[2]

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Diagnosis and serology

HBV infection is diagnosed using serum assays that can detect viral antigens and antibodies. These same serum markers are used for disease stratification and to determine candidacy for treatment, and are also used to guide treatment endpoints. HBV serology and interpretation of HBV markers are summarized in Tables 1 and 2.

HBsAg is the hallmark of HBV infection, which is first detected during the very early phase of an acute infection. HBsAg persistence and detection on two distinct occasions 6 months apart defines chronicity. Hepatitis B surface antibody (anti-HBs) can appear weeks after the acute insult. Its presence defines immunity, through either vaccination or natural immunity after resolution of HBV infection.

Hepatitis B core antibody (anti-HBc) appears 1–2 weeks after HBsAg detection (anti-HBc IgM) and is used to define an acute infection, whereas (anti-HBc IgG) is associated with chronicity. Detection of anti-HBc IgG in the absence of HBsAg, with or without detectable anti-HBs, indicates prior exposure, formally referred to as 'occult' HBV. This disease phase is usually associated with undetectable HBV DNA and does not require any follow-up; however, increased awareness is required as these patients are 'at risk' of HBV reactivation during biological, immunosuppressive and chemotherapy treatment regimens, and may thus require prophylactic antiviral treatment.[1] Hepatitis e antigen (HBeAg) and antibody (anti-HBe) determine disease phase; the presence of HBeAg is classically associated with a high replicative phase and increased infectivity. HBV DNA serum level is essential for diagnosis and disease stratification, and is a key determinant in the 'decision to treat' and subsequent monitoring of patients.

The initial evaluation of an individual with CHB should include a complete history, physical examination and assessment of liver disease activity and severity. Relevant co-aetiologies including alcohol and autoimmune and metabolic liver disease should be excluded. All first-degree relatives and sexual partners of patients should be tested for HBV serology (HBsAg, anti-HBs, anti-HBc) and vaccinated if negative.

Alanine aminotransferase (ALT) and aspartate aminotransferase should be measured during the initial assessment and regularly during the follow-up, as they are considered to be a surrogate of disease activity. Serum γ-glutamyltransferase, serum albumin, total bilirubin, serum immunoglobulins, full blood count and prothrombin time also provide important information and comprise an important part of the clinical work-up. Hepatitis A, C and D virus serology, as well as testing for

Definition of serological tests in hepatitis B virus infection

Markers	Clinical interpretation
HBsAg	• Hallmark of infection • Positive in the early phase of acute infection • Persistently positive in chronic infection
Anti-HBs	• Recovery from acute (or chronic) infection • Immunity after vaccination
HBeAg	• HBeAg positivity associated with high replicative state • HBeAg negativity reflects a change in disease phase • Usually associated with emergence of anti-HBe
Anti-HBe	• Marker of HBeAg seroconversion • Associated with immune control in low-viraemia states
Anti-HBc (IgM)	• Positive in acute infection • Can be positive during reactivation of HBV
Anti-HBc (IgG)	• Exposure to infection, and present in association with HBsAg in chronic infection • HBsAg negativity and anti-HBc positivity usually indicative of past exposure to virus • Anti-HBs may or may not be positive; if anti-HBs-negative, a false-positive anti-HBc should be considered (e.g. after intravenous immunoglobulin infusion) • HBV DNA must be checked to exclude occult infection

For abbreviations, see text.

Table 1

Interpretation of serological tests in hepatitis B virus infection

Tests	Clinical interpretation
HBsAg (–) Total anti-HBc (+) Anti-HBs (+)	Indicative of past infection Clinically relevant in the context of immune suppression
HBsAg (–) Total anti-HBc (–) Anti-HBs (+)	Indicative of previous hepatitis B vaccination
HBsAg (+) Total anti-HBc (+) Anti-HBc IgM (+) Anti-HBs (–)	Indicative of acute HBV infection
HBsAg (+) Total anti-HBc (+) Anti-HBc IgM (–) Anti-HBs (–)	Chronic HBV infection
HBsAg (–) Total anti-HBc (+) Anti-HBs (–)	Several potential clinical interpretations: • Past HBV infection • False-positive anti-HBc • Occult chronic hepatitis B if HBV DNA is detectable • Resolving acute infection

For abbreviations, see text.

Table 2

HIV co-infection, should always be undertaken. Negative anti-HAV should prompt vaccination against hepatitis A virus.[1]

Patients with CHB should also be offered abdominal hepatic ultrasonography. Liver biopsy or a non-invasive test, such as transient elastography, should also be performed to determine disease severity, especially in cases where biochemical and HBV markers are inconclusive. Transient elastography has been widely studied and appears to yield a higher diagnostic accuracy for detecting advanced disease and cirrhosis, rather than low-grade fibrosis. Notably, however, the results of transient elastography can be confounded by severe inflammation and elevated ALT levels; therefore liver biopsy retains its status as the gold standard for evaluating liver disease in the presence of biochemical activity in CHB.[1]

HDV infection is diagnosed on the basis of high titres of IgG and IgM anti-HDV, and confirmed by detecting HDV RNA in serum.[2]

Natural history of HBV infection

HBV is transmitted haematogenously and sexually. In high-prevalence regions, most new infections are through vertical (or perinatal) transmission. Similarly, HDV is also transmitted either haematogenously or through other body fluids of infected individuals.[1,2] After acute HBV infection, the course of the disease largely depends on age at the time of acquisition. Infection in adulthood is associated with clinical and virological resolution of the infection in >95% of cases, whereas >95% of infections acquired vertically or in early childhood progress to chronicity.[1]

CHB is a dynamic disease that classically progresses through four distinct disease phases. HBV serology, serum ALT and HBV DNA in addition to the degree of fibrosis, based on liver biopsy or non-invasive modalities, assist in establishing disease phase and consequently informing decisions on when and who to treat. Traditionally, the four disease phases of CHB have been as follows: immune tolerant, immune active or immune clearance, inactive carrier and immune escape. In general, treatment has been reserved only for the immune active and immune escape disease phases, which were associated with increased disease activity and likelihood of disease progression.

Historically, the immune tolerant phase has been considered a 'benign', disease-free phase; hence these patients were excluded from therapy. However, the perception that this disease phase is not associated with events potentially causing liver damage, including initiation of HCC, has been challenged by recent data. Results from large studies demonstrate that this is in fact a low-inflammatory, high-replicative state where factors associated with tumorigenesis may be already present.[1,3]

In light of these findings, the European Association for the Study of the Liver (EASL), in its latest guidelines published in 2017, proposed a novel clinical categorization of CHB, based on the two main characteristics of chronicity: chronic infection versus active inflammation. HBeAg-positive chronic infection, formerly called immune tolerant, is a low-inflammatory, high-replicative disease phase, more frequently seen in younger patients infected perinatally. These patients are highly infectious and have very little chance of spontaneous HBeAg seroconversion.

HBeAg-positive chronic hepatitis, previously referred to as immune active disease, can occur many years (or even decades) after the first phase of the disease. It is characterized by necroinflammation and accelerated progression of fibrosis. The outcome of this disease phase varies. Patients can progress to HBeAg-negative chronic infection, formerly termed the inactive carrier disease phase, which is defined by HBeAg loss and seroconversion (appearance of anti-HBe). Necroinflammation is minimal and risk of disease progression is low.

Finally, it is now proposed that the 'immune escape' phase should be termed HBeAg-negative chronic hepatitis, typically demonstrating necroinflammation and fibrosis with low rates of spontaneous disease remission.[1,3] Clinical categorization is summarized in Table 3.

Treatment of chronic hepatitis B

Sustained HBsAg loss with or without seroconversion defines functional cure and is considered an optimal treatment endpoint; however, it is rarely achieved with currently licensed therapies. Thus, persistent antiviral-mediated suppression of HBV DNA represents the goal of current therapies. The primary aim of treatment is to prevent morbidity and mortality from HBV-related cirrhosis and its clinical complications and/or the development of HCC.[1,3] As per guidance from the EASL and the American Association for the Study of Liver Diseases (AASLD), disease stratification and assessment should be performed to identify treatment candidates and determine the timing of therapy initiation.[1,3,4]

There are currently two treatment approaches in the management of CHB: nucleot(s)ide analogues (NAs) and pegylated interferon (Peg-IFN). The former are the treatment of choice, owing to their favourable adverse-effect profile, excellent tolerability and easy once-daily oral administration. The preferred NAs are the third-generation tenofovir disoproxil fumarate (TDF) 245 mg once daily, entecavir (ETV) 0.5 mg once daily and more recently tenofovir alafenamide (TAF) 25 mg once daily; these agents are superior to the older NAs owing to their high genetic barrier to resistance. NAs prevent viral replication through inhibition of HBV DNA synthesis.

Their main disadvantage is the requirement for long-term or indefinite administration, owing to viral rebound in most individuals after treatment withdrawal. Consequently, the likely life-long treatment requirement may be arduous for patients, alongside concerns over renal and bone toxicity.[1,3,4] In HBeAg-positive patients, eAg seroconversion can justify discontinuing treatment after a period of consolidation therapy. However, among those who seroconvert, around 50% ultimately relapse with higher levels of viraemia off-treatment. Similarly, treatment discontinuation can also be considered in HBeAg-negative patients provided viral suppression has been achieved and maintained for >2 years; however, viral remission off treatment is anticipated in 50% at 3 years, and there is a substantial risk of hepatic flares and potentially liver failure; therefore active monitoring is mandated.[1,3,4]

HBsAg loss during treatment with NAs is achieved in a minority of patients who were initially HBeAg-positive

Clinical parameters during disease phases of CHB

	Immune tolerant HBeAg-positive	Immune active or immune clearance HBeAg-positive	Inactive carrier HBeAg-negative	Immune escape HBeAg-negative	HBsAg negative, anti-HBc positive: 'occult'
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis	
Duration	20–30 years	Can be protracted	Many years	Variable if occurs	Awareness required in the context of immune suppression
Anti-HBe	Negative	Negative	Positive	Positive	Positive
HBV DNA (IU/ml)	$>10^6$	>20,000	<2000	2000–20,000	Usually not detected
Liver enzymes	Normal	Elevated (fluctuating)	Normal	Elevated	Normal
Liver histology	Absent/minimal fibrosis and/or inflammation	Moderate/severe fibrosis and inflammation	No fibrosis and inflammation	Moderate fibrosis and inflammation	Absent/minimal fibrosis and inflammation
HBsAg titre	High	High/Moderate	Low	Low/moderate	Absent

For abbreviations, see text.

Table 3

(approximately 10–12% after 5–8 years of therapy), while HBsAg loss is even rarer in HBeAg-negative individuals (<1–2% after 5–8 years of therapy).[1] Although uncommon with these newer NAs, should viral resistance emerge, rescue therapy should be introduced, with the most effective antiviral drug that does not share cross-resistance.[1]

At present, Peg-IFN given for 48 weeks is the only finite treatment option for CHB and should be considered in selected patients, especially younger patients with mild to moderate disease. Peg-IFN is thought to work by boosting the cellular immune response against infected hepatocytes.[3] Its use is limited by the high variability of response, poor tolerability and systemic adverse-effect profile, often leading to early discontinuation of treatment. It appears to be more effective in patients with active inflammation (elevated serum ALT), but even with careful patient selection overall efficacy remains suboptimal.[3] Early-stopping rules are now well established, allowing early cessation of treatment in patients with a low likelihood of long-term response.

A health economic analysis conducted in the UK concluded that interferon is the most cost-effective first-line treatment option for HBeAg-positive or HBeAg-negative chronic hepatitis. As a result, the National Institute for Health and Care Excellence (NICE), in its 2013 guidance, updated in 2017, recommended that patients with HBeAg-positive or HBeAg-negative chronic hepatitis should be offered treatment with a 48-week finite course of Peg-IFN as a first-line approach.[5] Among patients treated with Peg-IFN who achieve HBeAg seroconversion, approximately 30% clear HBsAg in the long term.[1]

Indications for treatment

All patients with HBeAg-positive or HBeAg-negative chronic hepatitis and/or moderate to severe liver necroinflammation or fibrosis should be offered antiviral treatment. Patients with HBV DNA >20,000 IU/ml and ALT over twice the upper normal limit should be offered treatment regardless of the degree of underlying necroinflammation or fibrosis. All patients with chronic HBV infection and a family history of HCC or cirrhosis, or extrahepatic manifestations, can be considered for treatment.[1,5] The EASL, as well as NICE, recommends that individuals >30 years old with HBeAg-positive chronic infection should also be considered for treatment, regardless of the severity of necroinflammation or fibrosis.[1,5] In contrast, the AASLD has a more restrictive policy on treatment of such patients; in its latest guidelines, it is recommended that treatment should be offered in such patients if they are >40 years and have moderate/severe necroinflammation or fibrosis on biopsy.[4]

HBV cirrhosis confers a significant risk of HCC so all patients with compensated or decompensated cirrhosis require life-long treatment, with any detectable HBV DNA level and regardless of ALT concentrations. As Peg-IFN is contraindicated in decompensated cirrhosis, NAs comprise the treatment of choice in these patients.[1,3,4]

All patients with cirrhosis, and those at increased risk of HCC owing to ethnicity or family history, should be followed-up with abdominal ultrasonography 6-monthly, regardless of treatment status. The PAGE-B score developed by Papatheodoridis et al. offers good predictability for white patients being treated with NAs, but also appears to be a promising HCC predictor for untreated patients with CHB.[1]

Monitoring untreated patients

Monitoring untreated individuals is mandated in order to respond in a timely manner to changes in disease status. The optimum monitoring of patients in the HBeAg-positive chronic

infection phase remains a subject of debate; however, quarterly or 6-monthly biochemical assessment can probably identify fluctuations in biochemical activity.[1,5] Patients in the HBeAg-negative chronic infection phase could have ALT and HBV DNA monitored 6-monthly or annually.[1,5] Recent studies have shown that quantitative HBsAg can be of value in this disease phase, as it enhances monitoring and could potentially identify those at greatest risk of disease reactivation or HCC development, prompting more rigorous monitoring in selected patients.[1]

Acute hepatitis B treatment: the great majority of immunocompetent adult patients (>95%) with acute HBV infection fully recover, both clinically and virologically, so do not require any specific treatment or intervention. The main treatment indication is preventing acute or subacute liver failure; shortening the duration of disease-associated symptoms may be regarded as an additional treatment target, especially in individuals with a protracted disease course, i.e. marked jaundice and coagulopathy for >4 weeks. Where indicated, the mainstay of treatment in acute hepatitis B is NAs, namely TDF, ETV (and even lamivudine from historical studies). Good treatment outcomes have been demonstrated with these drugs, especially when introduced early during the course of acute HBV infection. TAF is also likely to be effective, but limited data exist in this clinical setting.[1,4]

Management of HDV–HBV co-infection

In patients with HBV-HDV co-infection and compensated liver disease, a 48-week course with Peg-IFN remains the only therapeutic option available, demonstrating on-treatment virological response rates of 17–47%. This treatment is an independent factor associated with reduced disease progression.[1,2] A series of studies has shown that >50% of initial responders to Peg-IFN presented with a late relapse 24 weeks after completing treatment, highlighting the limitations of Peg-IFN as a therapeutic option for HDV. In view of these results, long-term follow-up of serum HDV RNA is mandated for as long as HBsAg remains detectable. HBsAg can have a role in monitoring treatment response if quantitative HDV RNA results are unavailable. HBsAg loss is considered a cure for HDV infection, and is estimated to develop in around 10% of patients treated with interferon during long-term follow-up.[1,2]

Although HDV is often the dominant virus in most patients with HDV co-infection, in cases where HBV DNA levels are >2000 IU/ml in serial measurements, treatment with NAs can be considered. Similarly, treatment with NAs should be considered for all patients with decompensated disease with any level of detectable HBV DNA in the serum.[1] All other patients with decompensated disease should be referred for liver transplantation, as Peg-INF is contraindicated and no other treatment alternatives are available.[1]

Novel treatment strategy in HBV and HDV hepatitis

We are on the cusp of major changes in the management of CHB and HDV co-infection, with multiple new agents in the developmental pipeline; there is no doubt that this will be an exciting and challenging time to work in the field of these complex viruses.

A number of novel approaches to the management of CHB are currently under evaluation, including early treatment and the use of currently available agents in combination or in sequence. Additionally, several novel promising agents are being evaluated, mainly in Phase I and II clinical trials; agents include viral entry inhibitors, targets against cccDNA formation and degradation, agents enhancing the host immune response against HBV and therapeutic vaccination.[1] Similarly, new drugs are also being evaluated for HDV co-infection, including HBV–HDV entry inhibitors, agents inhibiting the release of HBsAg and inhibitors of the prenylation of the large HDV antigen. These novel agents are likely to be combined with existing therapies in the first instance, with NAs remaining the backbone of therapy for the foreseeable future.[1] ◆

KEY REFERENCES

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 24-year-old man presented for review. He had recently been found to have chronic hepatitis B. He had no symptoms and there was no relevant family history. Clinical examination was normal.

Investigations

- Bilirubin 13 micromol/litre (1–22)
- Alanine aminotransferase 25 U/litre (5–35)
- Aspartate aminotransferase 28 U/litre (1–31)
- Alkaline phosphatase 65 U/litre (45–105)
- Hepatitis B surface antigen (HbsAg) detectable
- Hepatitis B core antibody (anti-HBc): IgG positive, IgM negative
- Hepatitis B e antigen (HbeAg) positive
- Hepatitis B virus DNA (HBV DNA) 3×10^7 IU/ml
- Transient elastography was normal

What is the most appropriate next step in his management?

A. Active monitoring
B. Nucleot(s)ide analogues for 48 weeks
C. Long-term treatment with nucleot(s)ide analogues
D. Pegylated interferon for 48 weeks
E. Long-term treatment with pegylated interferon

Question 2

A 29-year-old woman presented urgently for review. She had become ill with jaundice 5 weeks previously and had been found to have acute hepatitis B. She had no known co-morbidities and there was no family history of relevance. Clinical examination showed jaundice but no other abnormality.

Investigations

- Bilirubin 103 micromol/litre (1–22)
- Alanine aminotransferase 640 U/litre (5–35)
- Aspartate aminotransferase 368 U/litre (1–31)
- Prothrombin time 12.2 seconds (11.5–15.5)
- Activated partial thromboplastin time 25 seconds (30–40)
- Hepatitis B surface antigen (HbsAg) detectable
- Hepatitis B core antibody (anti-HBc): IgG negative, IgM positive

Which of the following can be regarded as an indication for treatment?

A. Young age at presentation
B. Anti-HBc IgM positivity
C. Elevated transaminases
D. Elevated bilirubin per se
E. Protracted course of disease

Question 3

A 47-year-old man presented for review. He had been found to have chronic hepatitis B infection and had been admitted to hospital a few weeks previously with decompensated liver disease and haematemesis, secondary to variceal bleeding. The rest of his medical history was unremarkable.

Investigations

- Hepatitis B surface antigen (HbsAg) detectable
- Hepatitis B core antibody (anti-HBc): IgG positive, IgM negative
- Hepatitis B e antigen (HbeAg) positive
- Hepatitis B virus DNA (HBV DNA) 106 IU/ml

What is the most appropriate next step in the management of the hepatitis B infection?

A. Active monitoring
B. Nucleot(s)ide analogues for 48 weeks
C. Long-term treatment with nucleot(s)ide analogues
D. Pegylated interferon for 48 weeks
E. Long-term treatment with pegylated interferon