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# Assessment and management of chronic hepatitis B


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Hepatitis B virus (HBV) infection is one of the most common viral infections in humans. It is estimated that more than two billion people worldwide have been exposed to the virus. Approximately 350 million people are chronic carriers of HBV[1,2], of whom 15–40% will develop serious liver complications during their lifetime[3]. Chronic HBV infection remains a leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). The distribution of patients with hepatitis B varies greatly throughout the world. It is thought to be uncommon in the UK, but the real prevalence of chronic hepatitis B surface antigen (HBsAg) carriers in the general population or amongst patients with chronic liver diseases is not known because only cases of acute hepatitis B infections are reported. Importantly, it is a preventable disease for which a safe and effective vaccine has been available for nearly 20 years.

## Definitions and terminology in hepatitis B virus infection

Chronic infection with HBV is defined as persistence of HBsAg in a patient's serum for more than six months[4]. These patients, colloquially referred to as 'chronic HBsAg carriers', represent a heterogeneous group. Their precise characterisation includes three components:

1 *Virological:* detection of hepatitis B e antigen (HBeAg) or antibody to HBeAg (anti-HBe) in serum. The level of HBV replication is determined by quantification of serum HBV DNA.

2 *Biochemical:* serum alanine aminotransferase (ALT) levels.

3 *Liver histology:* assessment of the grade of hepatic inflammation and the stage of fibrosis (Table 1).

**Table 1. Standardisation of terminology in chronic hepatitis B virus (HBV) infection (based on ref 4).**

| Terms | Diagnostic criteria |
|---|---|
| Chronic hepatitis B | 1 Serum HBsAg positivity longer than 6 months<br>2 Persistent or intermittent elevation of ALT/AST levels<br>3 Serum HBV DNA >$10^5$ copies/ml<br>4 Liver biopsy with a necroinflammatory score O 4 |
| Inactive HBsAg carrier | 1 Serum HBsAg positivity longer than 6 months<br>2 HBeAg(-); anti-HBe(+)<br>3 Serum HBV DNA <$10^5$ copies/ml<br>4 Persistently normal serum ALT/AST levels<br>5 Liver biopsy* showing absence of significant inflammation (necroinflammatory score <4) |
| Resolved hepatitis B | 1 Serum HBsAg(-); anti-HBc(+)<br>2 Normal serum ALT levels<br>3 History of known acute or chronic hepatitis B<br>4 Undetectable serum HBV DNA (hybridisation assays)** |

* In these circumstances liver biopsy is optional.
** HBV DNA may be detectable using sensitive polymerase chain reaction assays.

ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e antigen (HBeAg); anti-HBc = antibody to hepatitis B core antigen; AST = aspartate aminotransferase; HBsAg = hepatitis B surface antigen.

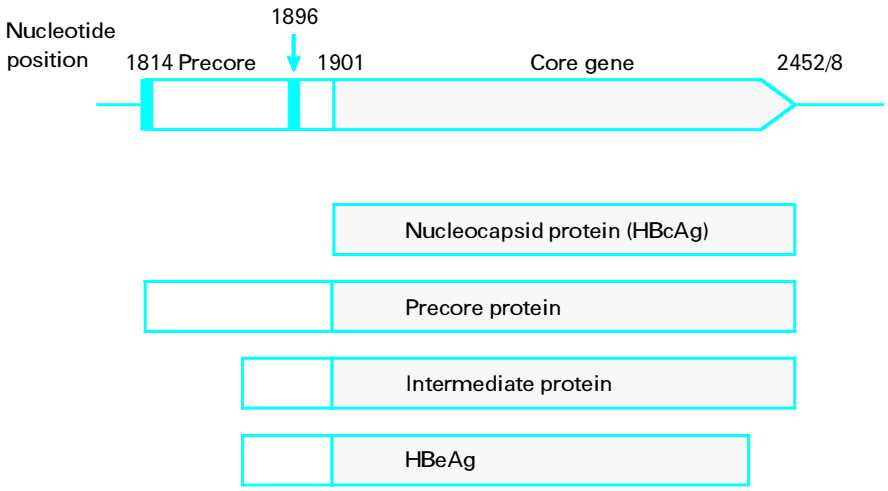


**Fig 1. Frequent precore mutations in patients with antibody to hepatitis B e antigen (anti-HBe)(+) chronic hepatitis B.** Translation from the start codon of the HBV core gene (nucleotide position 1901) produces hepatitis B core antigen (HBcAg). Translation from the precore start codon (1814) produces a transient precore protein which, following two proteolytic cleavages, is secreted as hepatitis B e antigen (HBeAg). The stop codon mutations at position 1896 or position 1814 block the translation of HBeAg but not that of the nucleocapsid protein.

Quantification of serum HBV DNA is essential to define the level of viral replication in a patient with chronic HBV infection. The National Institutes of Health conference chose the value of $10^5$ viral DNA copies/ml as a level of HBV replication below which there are no significant necroinflammatory changes in the liver[4]. However, this is not an absolute cut-off value and should be interpreted in conjunction with the results of other investigations performed on more than one occasion.

Seven genotypes of HBV have been identified, designated A to G. These naturally occurring variants of the virus differ in approximately 10% of their nucleotide sequences. The distribution of HBV genotypes worldwide shows a distinct geographic pattern:

- *genotype A:* prevalent in Northern Europe and USA
- *genotypes B and C*: exclusively found in the Far East
- *genotype D:* predominant in Southern Europe and the Middle East.

Genotype E is mainly found in Africa, while genotypes F and G have been described in individual patients.

The impact of different genotypes on the severity of chronic hepatitis B and the treatment response is currently under investigation.

Although the terms HBV 'variant' and 'mutant' are often used interchangeably, there are important differences. Any variation from published wild-type HBV sequences can be considered as a 'variant' of HBV[3]. HBV 'mutants' have specific changes in the amino acid sequences which emerge under a selection pressure: for example, the surface antibody escape mutant or lamivudine-associated HBV mutants[5]. The presence of HBV mutant strains does not imply a more severe hepatitis B, but they alter the clinical course of HBV infection as they escape the specific pressure which has led to their selection. Furthermore, HBV mutants are usually replaced by the wild-type virus if the selection pressure is removed. Precore mutations which create a stop codon prevent the translation of HBeAg but do not stop viral replication (Fig 1). The most common mutation is a guanine to adenine change at position 1896. The development of this mutation depends on HBV genotype, occurring in HBV genotypes B, C, D and E but not A.

## Key Points

**Spontaneous control of HBV replication can take place, either after resolved acute hepatitis B or in chronic HBV carriers; however, hepatitis B virus (HBV) DNA usually persists in the host**

**The characterisation of patients with chronic HBV infection involves virological, biochemical and histological assessment. This provides the basis for selection of patients who would benefit from antiviral treatment and for longitudinal monitoring**

**Treatment of chronic hepatitis B aims to achieve sustained inhibition of HBV replication. When successful, this results in improvement of liver histology and patient survival**

**Molecular diagnostic tests (quantitative polymerase chain reaction, genotyping, mutation detection) are important for optimising the treatment monitoring of patients with chronic hepatitis B**

**Hepatitis B is a preventable disease for which a safe and effective vaccine is available**

**KEY WORDS: CPD, hepatitis B, hepatitis B treatment, hepatitis B virus, hepatitis B virus mutants, immunopathogenesis**

## Immunopathogenesis and natural history of chronic HBV infection

The diversity of clinical manifestations and the outcome of HBV infection depend primarily on the host immune response to the virus[6]. The dominant cause of viral persistence in patients with chronic HBV infection is weak or undetectable T cell reactivity to viral antigens. Over the last five years the traditional concept of virus-host interaction in HBV infection has significantly changed. First, it has been shown that interferon-gamma and tumour necrosis factor-alpha, released from virus-specific cytotoxic T lymphocytes, can abolish viral gene expression and replication without destroying the target cells. Rather than direct killing of infected hepatocytes this cytokine-mediated, non-cytolytic inhibition of viral gene expression represents the dominant mechanism for HBV inactivation and control of viral replication[7].

Secondly, in patients with resolved hepatitis B, a low level of viral replication, accompanied by strong HBV-specific cell reactivity has been shown to persist for 10–20 years, demonstrating that HBsAg clearance following HBV infection does not imply viral eradication. Instead, HBV DNA usually persists as a latent infection, while the efficient host immune responses control HBV replication.

This concept is supported by clinical examples of hepatitis B reactivation in patients with lymphoma after withdrawal of chemotherapy, or individual cases of *de novo* HBV infection in transplant recipients of a liver graft from antibody to hepatitis B core antigen positive donors[8].

There are two forms of chronic hepatitis B–HBeAg positive and anti-HBe positive – and they have a different clinical course (Fig 2). An important event in the natural history of HBeAg positive chronic hepatitis B is the seroconversion to anti-HBe positivity. This is associated with a transient ALT flare followed by biochemical and histological remission[9]. The annual rate of spontaneous HBe seroconversion is 5–15% of patients[4]. Both spontaneous and treatment-induced transition to the 'inactive carrier state' are usually favourable outcomes associated with improved patient survival[10]. Fluctuations in ALT and HBV DNA levels are common during the course of chronic HBV infection. Therefore, serial testing must be performed to define an 'inactive carrier state' and to monitor the patient subsequently[3]. For patients with compensated HBsAg positive cirrhosis, the survival is 84% and 68% at five years and 10 years, respectively[11], and for patients with decompensated HBsAg positive cirrhosis the five-year survival is 14%[3]. Importantly, effective control of HBV replication in patients with cirrhosis, either spontaneously or after antiviral treatment, reduces the risk of decompensation and improves survival[11].

HBeAg-negative chronic hepatitis B is usually due to precore mutant HBV. This form is increasingly common in areas where HBV genotypes B, C and D are prevalent, such as the Far East and Mediterranean basin. The clinical course is characterised by low HBV DNA levels, which usually fluctuate and are mirrored by fluctuating ALT levels (Fig 2).

Both forms of chronic hepatitis can lead to cirrhosis depending on the duration and severity of hepatic inflammation. Although HCC is more common in cirrhotic patients, 30–50% of HBsAg positive patients with HCC do not have cirrhosis[12].

## Assessment of patients with chronic HBV infection

In addition to history and physical examination, the initial assessment should include virological markers, liver function tests, alpha-fetoprotein and ultrasound scan[3]. A liver biopsy is performed

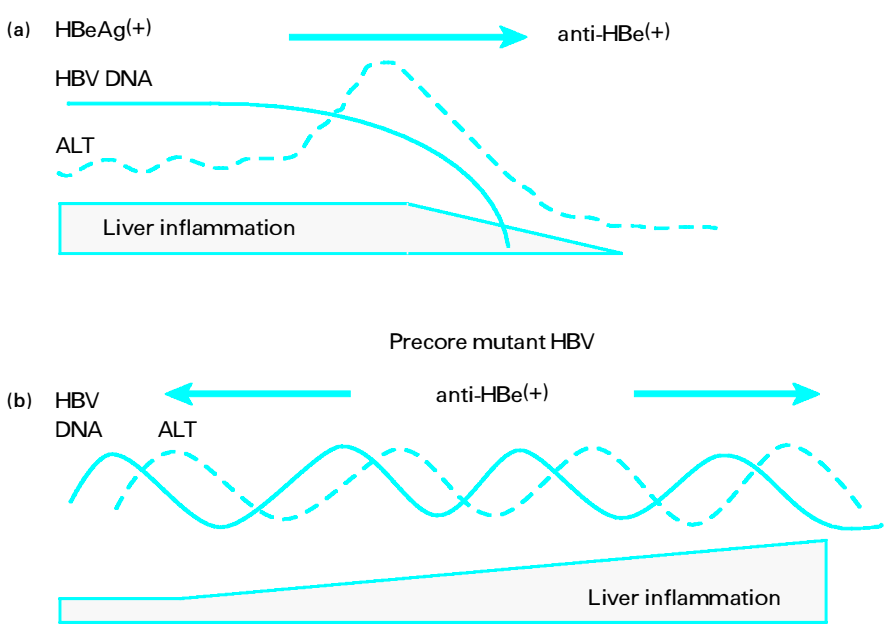


**Fig 2. The different clinical course of the two forms of chronic hepatitis B: (a) the seroconversion of hepatitis B e antigen (HBeAg)(+) to antibody to HBeAg (anti-HBe) is usually associated with a sustained inhibition of hepatitis B virus (HBV) replication and remission of liver disease; (b) chronic hepatitis B due to precore mutant HBV is characterised by a fluctuating pattern of serum HBV DNA and alanine aminotransferase (ALT) levels.**

in patients with elevated ALT, but this is not necessary for inactive HBsAg carriers. The follow-up monitoring differs in HBsAg positive patients (Table 2).

## Treatment of chronic hepatitis B

### *Interferon-alpha and lamivudine*

Not all patients with chronic HBV infection require antiviral treatment (Fig 3). Treatment aims to achieve sustained inhibition of HBV replication and remission of liver disease. The end-point of treatment in HBeAg positive chronic hepatitis B is serum HBV DNA less than $10^5$ copies/ml and seroconversion to anti-HBe. Interferon-alpha (IFN-α) and lamivudine are currently licensed for treatment of chronic hepatitis B. IFN-α (5 million units daily or 10 million units three times a week by subcutaneous injections) is given for a limited time, usually 16 weeks. Drug resistance does not occur, but the side effects and cost of IFN-α are major disadvantages. Lamivudine (100 mg tablet daily) was first licensed in 1998. Because of the ease of administration, excellent safety profile and potent antiviral activity, lamivudine has revolutionised the treatment of hepatitis B. The rate of HBeAg seroconversion after 12 months' treatment with lamivudine is 16–32%, rising progressively as treatment continues. Response rates to lamivudine and IFN-α treatment are proportional to the pretreatment ALT levels.

With longer treatment, lamivudine-resistant HBV is increasingly common. Genotypic resistance is detectable in 14–32% of patients after one year, increasing to 38%, 49% and 66% after two, three and four years, respectively[3,4]. The emergence of lamivudine-resistant HBV is not necessarily associated with phenotypic resistance (ie loss of clinical benefit). If it occurs, the decision whether to continue with lamivudine or stop treatment depends on the specific circumstances and treatment objectives in the individual patient.

Patients with anti-HBe positive chronic hepatitis B respond poorly to IFN-α. Treatment with lamivudine for at least 18–24 months is required. This leads to a marked improvement of liver histology, but most patients relapse after stopping therapy. There is no well defined end-point in this subgroup and treatment should be limited to patients with significant hepatic inflammation and fibrosis[4].

**Table 2. Laboratory tests for assessment of patients with chronic hepatitis B virus (HBV) infection (based on Ref 3).**

| Patient visit | Investigations |
|---|---|
| **Initial evaluation** | 1 Liver function tests; full blood counts; prothrombin time<br>2 HBeAg/anti-HBe; serum HBV DNA levels<br>3 Exclude other causes of liver disease<br>4 Serum AFP<br>5 Ultrasound scan<br>6 Liver biopsy, if chronic hepatitis B is suspected |
| **Follow-up monitoring:** | |
| Inactive HBsAg carrier | 1 Serum ALT every 6–12 months<br>2 If ALT >2 x ULN, check HBV DNA levels and exclude other possible causes of liver disease |
| Mild chronic hepatitis B HBeAg(+) | 1 Serum ALT every 6 months; if ALT <2 x ULN no treatment<br>2 Check HBeAg and HBV DNA levels annually |
| Moderate/severe hepatitis B or cirrhosis | 1 Serum ALT every 3 months<br>2 HBV DNA levels and HBeAg every 6 months<br>3 If standard treatments failed, consider experimental protocols to suppress HBV replication<br>4 Screening for HCC with ultrasound and AFP |

AFP = alpha-fetoprotein; ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e antigen (HBeAg); HCC = hepatocellular carcinoma; ULN – upper level of normal.

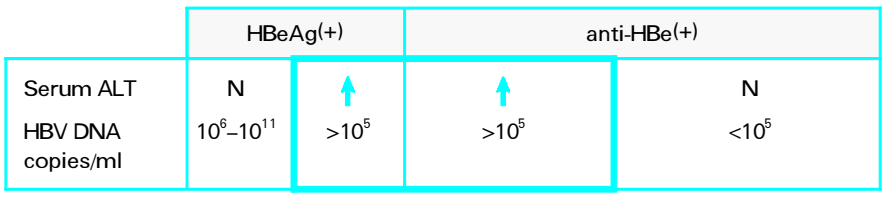


**Fig 3. Subgroups of patients with chronic hepatitis B virus (HBV) infection in whom antiviral treatment is indicated** (anti-HBe = antibody to hepatitis B e antigen; N = serum alanine aminotransferase (ALT) within the normal range).

### *New antiviral agents*

A number of new antiviral agents are currently being investigated in clinical trials. Adefovir dipivoxil, a nucleotide analogue effective against wild-type and lamivudine-resistant HBV, is expected to be available soon. Current efforts to improve treatment response are focused on designing combination regimens using different antivirals or antiviral and immunomodulatory agents.

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# Investigation and treatment of ascites

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## Investigation and management of ascites

Ascites is defined as the pathological accumulation of fluid in the peritoneal cavity. It arises as a consequence of liver disease in over 80% of cases, of cancer in 10% and the remainder from conditions such as heart failure, constrictive pericarditis, tuberculosis or pancreatic disease[1]. Over 4,000 people died from cirrhosis in the UK in 1999, and ascites is the most common and serious complication of cirrhotic liver disease[2]. The development of ascites is a poor prognostic sign, with only 50% of cases remaining alive at two years[3], and it is an indication for considering evaluation for liver transplantation. The pathogenesis of ascites is complex, but portal hypertension and sodium retention are key to its development.

The treatment of ascites depends on the cause. This review focuses on the investigations and management of patients with ascites secondary to chronic liver disease.

## Assessing patients with ascites

### *History*

Treatment depends on accurate distinction of cirrhotic from non-cirrhotic ascites. Questions about risk factors for liver disease must therefore be asked and diagnostic tests for causes of chronic liver disease performed. Sudden development of ascites in patients with previously stable cirrhosis raises the suspicion of an underlying hepatocellular carcinoma (HCC).

### *Physical examination*

Ascites can be detected clinically by the presence of shifting dullness which becomes clinically demonstrable when about 1,500 ml of fluid are present[4]. If the flanks are resonant, the probability of having ascites is less than 10%[4]. Ultrasound is useful if diagnostic doubt remains.

## Diagnostic ascitic tap

The history, physical examination and ascitic fluid analysis will almost always reveal the cause of ascites[5]. Abdominal paracentesis with careful analysis of the ascitic fluid should be performed early in the evaluation of patients with ascites. This can be safely performed at the bedside even in the presence of deranged clotting or reduced platelet count[5].

For a diagnostic tap, 20–50 ml of ascitic fluid is taken for the following investigations:

- *Cell count:* usually in an ethylene diamine tetraacetic acid (EDTA) (purple top) tube to prevent clotting
- *Microscopy:* separate sterile container
- *Ascitic fluid total protein/albumin:* separate sterile container
- *Culture:* sterile container or blood culture bottles
- *Cytology:* separate sterile container.

### *Appearance*

Ascitic fluid is usually straw coloured and clear. The presence of blood in a non-traumatic tap can indicate malignancy. Milky fluid (chylous ascites) is a feature of thoracic duct blockage or injury. Infected ascites can appear cloudy although it is frequently clear.

### *Cell count*

The white cell count with differential is the single most helpful test and should be requested on every specimen. Specimens can be sent in a full blood