

## IN-DEPTH REVIEW

# Hepatitis B prevention, diagnosis, treatment and care: a review

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**Abstract** Hepatitis B virus (HBV) infection is a major cause of morbidity and mortality worldwide. Chronic hepatitis B (CHB) infection is associated with an increased risk of cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC). The likelihood of developing CHB is related to the age at which infection is acquired; the risk being lowest in adults and >90% in neonates whose mothers are hepatitis B e antigen positive. Treatment of CHB infection aims to clear HBV DNA and prevent the development of complications. There are currently seven drugs available for the treatment of CHB: five nucleos(t)ide analogues and two interferon-based therapies. Long-term treatment is often required, and the decision to treat is based on clinical assessment including the phase of CHB infection and the presence and extent of liver damage. A safe and effective HBV vaccine has been available since the early 1980s. Vaccination plays a central role in HBV prevention strategies worldwide, and a decline in the incidence and prevalence of HBV infection following the introduction of universal HBV vaccination programmes has been observed in many countries including the USA and parts of South East Asia and Europe. Post-exposure prophylaxis (PEP) with HBV vaccine +/- hepatitis B immunoglobulin is highly effective in preventing mother to child transmission and in preventing transmission following sharps injuries, sexual contact and other exposures to infected blood and body fluids. Transmission of HBV in the health care setting has become an increasingly rare event in developed nations. However, it remains a significant risk in developing countries reflecting the higher prevalence of CHB, limited access to HBV vaccination and PEP and a lack of adherence to standard infection control precautions.

**Key words** Hepatitis B; hepatitis B vaccines; occupational health.

## Introduction

Hepatitis B virus (HBV) infection is a major cause of morbidity and mortality worldwide. The World Health Organisation (WHO) has estimated that ~2000 million people worldwide have been infected with HBV and that 350 million of these are chronically infected. Of those chronically infected, it is estimated that 65 million will die from liver disease due to their HBV infection [1]. This article provides an overview of the epidemiology and natural history of HBV infection and its prevention, diagnosis, treatment and care.

## Methods

Using the combination of search terms shown in Box 1, we searched MEDLINE for articles relating to HBV epidemiology, prevention and occupational health (published between January 2000 and December 2010) and HBV diagnosis, treatment and care (published between

January 2005 and December 2010). The search was limited to review articles in the English language. Relevant papers were selected from review of abstracts and consensus reached between three reviewers (G.H., E.J.A. and D.G.). We also searched the websites of various expert organizations, including Centers for Disease Control (CDC), National Institute for Clinical Excellence (NICE), European Association for Study of Liver Disease (EASL) and American Association for the Study of Liver Disease (AASLD). The reference lists of selected articles and reports were also reviewed.

## Epidemiology

Hepatitis B is an infection of the liver caused by the HBV, a double-stranded DNA virus of the hepadnaviridae family. The virus is transmitted via percutaneous or permucosal exposure to infected blood or body fluids and has an incubation period ranging from 40 to 160 days (average 60–90

**Box 1. MEDLINE search strategy**

A standardized search strategy for hepatitis B was used as follows:

- Hepatitis B/
- Hepatitis B antibodies/
- Hepatitis B antigens/
- Hepatitis B, chronic/
- Hepatitis B e antigens/
- Hepatitis B surface antigens/
- Hepatitis B vaccines/
- Hepatitis B virus/
- Hepatitis B core antigens/
- 'HBV'.tw.

This search was then combined with four searches relating to epidemiology, prevention, occupational health and diagnosis, treatment and care as follows:

**Epidmiology**

- Prevalence/
- Incidence/
- Morbidity/
- Mortality/
- Disease transmission, infectious/
- Infectious disease transmission, patient-to-professional/
- Infectious disease transmission, professional-to-patient/
- Infectious disease transmission, vertical/
- (or/1–8)

**Prevention**

- Vaccination/
- Primary prevention/
- Contact tracing/
- Communicable disease control/
- (or/1–4)

**Occupational health**

1. Occupational Health/

**Diagnosis, treatment and care**

1. Diagnosis/
2. Therapeutics/
3. Treatment.tw.
4. Management.tw.
5. Treatment Outcome/
6. Prognosis/
7. (or/1–6)

Results were limited to human articles and reviews published in the English language between January 2000 and December 2010 (January 2005 and December 2010 for diagnosis, treatment and care).

days) [2]. Transmission can occur vertically from infected mother to child, horizontally (e.g. child-to-child transmission within a household), sexually or parenterally (e.g. via injecting drug use, sharps injury or contaminated blood products).

The majority of acute HBV infections are asymptomatic. In adults, ~30% will present with jaundice and hepatitis and 0.1–0.5% develop fulminant liver failure [3]. During acute infection, hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) can be detected in the serum and there are high levels of IgM antibodies to the viral core antigen (IgM anti-HBc) [4]. A successful host immune response to the virus leads first to clearance of HBeAg (and appearance of antibody to HBeAg) and subsequent clearance of HBsAg (and appearance of antibody to HBsAg). The appearance of antibodies to HBsAg indicates recovery from acute infection [4]. The persistence of HBsAg for >6 months from its first detection denotes chronic hepatitis B (CHB) infection. The likelihood of developing CHB varies with the age at which the infection is acquired, the risk being lowest in adults (<5%) and greatest in neonates whose mothers are HBeAg positive (~90%) [5,6].

The prevalence of HBV infection varies geographically and can be categorized into areas of high (>8%), intermediate (2–8%) and low (<2%) endemicity [7] (see Box 2). The principal mode of HBV transmission also varies geographically. In low prevalence areas such as Northern Europe and North America, HBV infection is primarily acquired in adulthood through sexual contact or injecting drug use, whereas in high prevalence areas, HBV infection is most commonly acquired perinatally or in early childhood [5].

In a recent review conducted by the European Centre for Disease Prevention and Control [8], population prevalence of CHB was found to vary widely between European countries ranging from 0.1% in Ireland and the Netherlands to >7% in the eastern part of Turkey. The review also found that in all the countries for which data were available, the estimated prevalence of CHB infection was higher among migrant groups than in the general population. Similarly, immigration of individuals with CHB from countries of intermediate and high HBV prevalence has been estimated to account for >95% of the estimated annual incidence of CHB infections in England [9].

HBV virus can be subdivided into different genotypes. To date, eight HBV genotypes (A–H) have been identified and these have distinct geographical distributions. For example, Genotype A is prevalent in northwestern Europe and the USA, Genotypes B and C in Asia and Genotype D in the Mediterranean Basin, Middle East and India. Epidemiological studies suggest that HBV genotype may influence disease progression, with Genotypes A and B associated with more favourable outcomes than Genotypes C and D [10–12].

## Box 2. Geographical distribution of HBV infection

High prevalence areas include: China, South East Asia, sub-Saharan Africa, parts of South America and Alaska.

Intermediate prevalence areas include: parts of South America, North Africa, Eastern Europe, parts of Southern Europe, the Eastern Mediterranean area and the Indian subcontinent.

Low prevalence areas include: most of North America, Australia, Northern Europe and most of Western Europe.

## Natural history of CHB infection

The natural history of CHB can be divided into five phases. Not all patients experience every phase, and the duration of each phase can be highly variable. Reversion or reactivation between different phases can occur seemingly without warning, and therefore, clinical management can be challenging [13]. The five phases are summarized below and in Table 1 and Figure 1:

### Phase 1: immune tolerant phase

The ‘immune tolerant phase’ is typically the first phase of infection and is characterized by host immune tolerance despite active HBV replication. The lack of host immune response means that liver histology and alanine aminotransferase (ALT) levels are usually normal. Active HBV replication releases HBV DNA, HBeAg and HBsAg, which are detectable in the serum [15]. The immune response is limited to anti-HBc antibody production (initially IgM and then IgG), but this does not act to neutralize infection.

### Phase 2: HBeAg-positive CHB (immune reactive phase)

The ‘HBeAg-positive CHB phase’ starts once the host mounts an immune response to the viral infected hepatocytes. Serum ALT is raised (higher levels indicating a more vigorous response and therefore more hepatocyte damage), and chronic active hepatitis is visible on liver ultrasound (USS) or biopsy [15]. During this phase, the immune response reduces (but does not eliminate) HBV replication and begins to clear HBeAg and HBsAg (which occurs at a rate of 10–15% and 0.5–1% per year, respectively) [16].

The immune response to HBV tends to be episodic, with flares of ALT up to five times the normal limit and flares of anti-HBc IgM production, which may be confused with acute HBV infection. Active hepatitis occurring during this phase may lead to cirrhosis, in some cases complicated by hepatic decompensation and hepatocellular carcinoma

(HCC) [15]. If patients clear HBeAg, they pass into the ‘low replicative phase’, although their infection may subsequently reactivate [10,15].

### Phase 3: low replicative phase

Patients in the low replicative phase have minimal HBV replication and HBV DNA is low or undetectable. HBeAg is negative, but HBsAg remains positive. Previously known as the ‘Inactive Carrier State’, this term is now thought to be misleading, given the ongoing risk of reactivation to active disease. Around 10% of patients in this phase will reactivate at some point to HBeAg-positive CHB and 10–20% will reactivate to ‘HBeAg-negative CHB’ [17].

### Phase 4: HBeAg-negative CHB

HBeAg-negative CHB occurs due to a variant of the HBV virus that is unable to produce HBeAg. This is due to a mutation in the precore or core promoter region of the genome, although the virus is still actively replicating. HBeAg-negative CHB may occur following periods in the low replicative or HBeAg-positive CHB phases and normally represents a later stage in disease progression.

### Phase 5: HBsAg-negative phase

Progression to clearance of both HBsAg and HBeAg is known as the ‘HBsAg-negative phase’. HBV viral replication may persist but is unlikely to be detectable in serum [3]. Once in the HBsAg-negative phase, there is an improved outcome and a reduced risk of liver complications, although HBV may reactivate in individuals receiving immunosuppressive therapy and still represents a risk for organ donation [18].

## HBV infection following vertical transmission

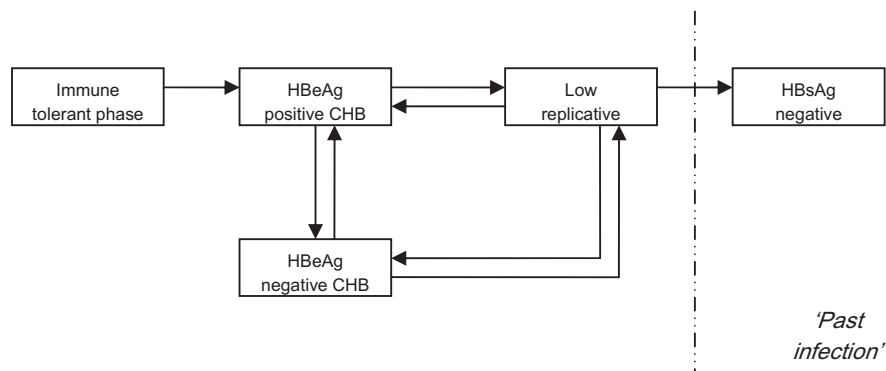
In neonates infected by mother to child transmission (MTCT), the risk of developing CHB depends on the HBeAg status of the mother. Neonates whose mothers were HBeAg positive during the perinatal period have a 90% chance of developing chronic infection, whereas this risk is <15% in neonates with HBeAg-negative mothers [13]. Neonatal vaccination can be effective in reducing the risk of MTCT and is discussed below. Both the immune tolerant phase and the HBeAg-positive CHB phase are prolonged in individuals infected in the neonatal period, with HBeAg clearance typically occurring during the third or fourth decade [16]. This longer course of infection increases the risk of developing HBV-related liver complications.

## HBV infection in childhood (horizontal transmission)

Children infected between 1 and 5 years of age have a 20–50% chance of developing chronic infection. The

**Table 1.** Phases of HBV infection [14]

Phase of infection	ALT	HBV DNA	HBeAg	HBsAg	Liver histology	Comment
1. Immune tolerant	Normal	High	Positive	Positive	Normal or mild inflammation	May be short or absent in infections acquired during adulthood
2. HBe antigen-positive CHB (immune reactive)	High	Moderate/high	Positive	Positive	Chronic inflammation	May last from several weeks to several years
3. Low replicative phase ('inactive carrier')	Normal	Low/undetectable	Negative	Positive	Depends on complications incurred in previous phases	Reactivation into Phase 2 or 4 possible
4. HBe antigen-negative CHB	Periodically high	Moderate/high/fluctuating	Negative	Positive	Chronic inflammation	Can be difficult to distinguish from Phase 3 due to fluctuating viral load
5. HBsAg-negative phase ('past infection')	Normal	Low/undetectable	Negative	Negative	Depends on complications incurred in previous phases	Immunosuppression may lead to reactivation



**Figure 1.** Schematic diagram of phases of chronic HBV infection.

immune tolerance phase in these children is usually fairly short, with features of immune response to HBV sometimes present by the time of the first clinic review, and nearly always by adolescence or early adulthood [16].

**HBV infection in adulthood**

Individuals infected in later childhood or adulthood have a 5% risk of developing chronic infection. Progression through the phases of infection is very rapid, and the immune tolerant phase is sometimes absent [3,15].

**Complications of chronic HBV infection**

Patients with CHB are at increased risk of cirrhosis, hepatic decompensation and HCC [11]. Longitudinal studies of patients with CHB indicate that, after diagnosis, the 5 years cumulative incidence of cirrhosis is from 8 to 20%, and

once cirrhosis has developed, the annual risk of HCC is 2–5% [14]. It has been estimated that HBV infection is responsible for 50–80% of HCC cases worldwide [19]. Table 2 shows the risk of liver complications in relation to the various phases of CHB infection. The risk of cirrhosis is highest in those with chronic active hepatitis (HBeAg-positive CHB or HBeAg-negative CHB), whereas the risk in those who remain in the low replicative or HBsAg-negative phase approaches that of the background uninfected population. The majority of cases of HCC occur in individuals who have already developed cirrhosis, although recent studies have shown that HCC can still occur in the low replicative and the HBsAg-negative phases in patients with seemingly normal liver architecture [11,21]. The risk of cirrhosis and HCC is increased in males, older age, family history of HCC, high viral load, persistently raised ALT, co-infection with HCV or HIV and HBV Genotypes C and F [3,11].



**Table 2.** Incidence of liver cirrhosis and HCC depending on phase of infection [5,20]

Phase of infection	Liver cirrhosis <sup>a</sup> (per year)	HCC <sup>a</sup> (per year)
1. Immune tolerant	Rare	Rare
2. HBeAg-positive CHB (immune reactive)	2.4–3.5%	3–6% in those with cirrhosis
3. Low replicative	Rare if remain in this phase	0.06% <sup>b</sup>
4. HBe antigen-negative CHB	2.1–2.9%	3–6% in those with cirrhosis
5. HBsAg negative	Rare	0.02% <sup>b</sup>

<sup>a</sup>Assuming no co-existent liver pathology.

<sup>b</sup>Substantially higher than in background uninfected population.

## Testing for HBV infection

Testing for HBV offers the opportunity to provide treatment and prevention advice to those who are positive (and their contacts) and recommend vaccination to those who are negative but at continuing risk [18]. The NICE are in the process of developing guidelines on promoting and offering HBV testing, but there are currently no UK or European guidelines. The CDC recommends testing for individuals in the groups shown in Table 3 [22].

## Further investigation

Further investigation of HBsAg-positive individuals is indicated to establish the phase of infection. Initial investigations should include HBeAg, HBV DNA viral load, liver function tests and abdominal USS (Figure 2).

## Testing for co-existent infection

Patients should be screened for hepatitis C, hepatitis D and HIV, given that co-infection confers a poorer prognosis than HBV infection alone [4].

## Treatment and care

### Lifestyle advice

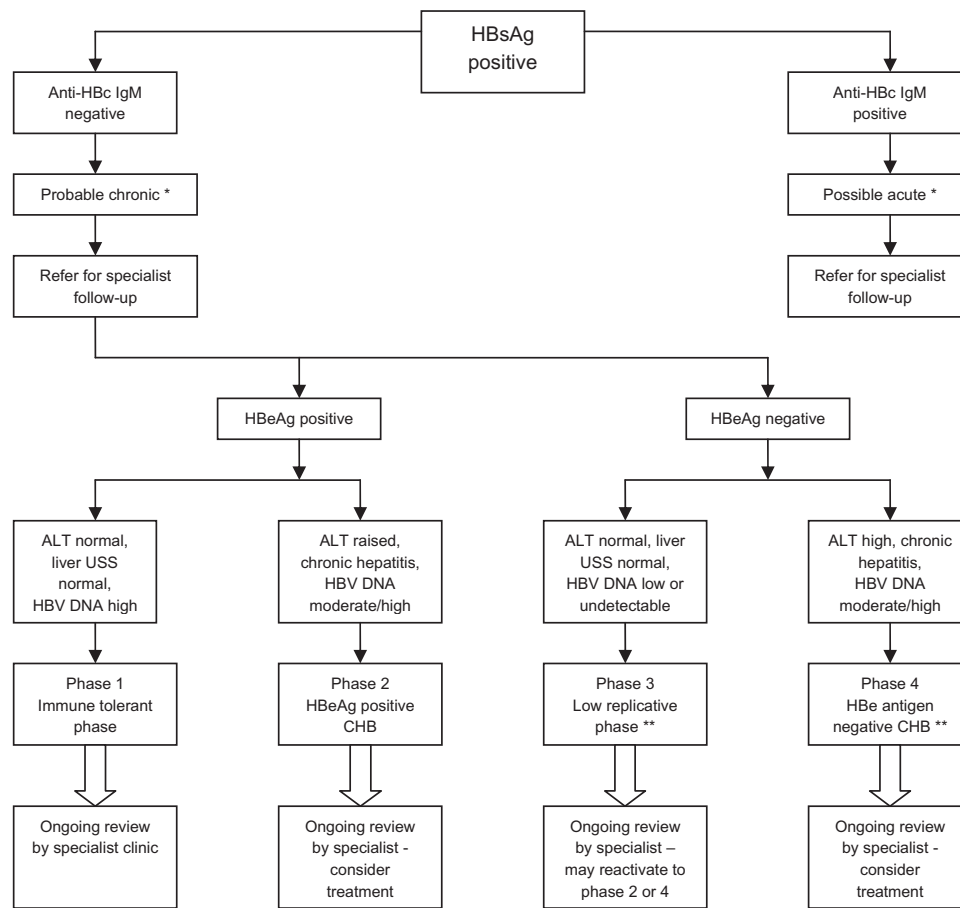
Smoking and excessive alcohol consumption are associated with a poorer prognosis in chronic HBV infection, and patients should be offered lifestyle advice accordingly. Patients should be advised on the prevention of other blood-borne viruses, and vaccination against hepatitis A should be offered to those not already protected as a result of previous immunization or infection [2]. Ongoing review of patients in Phases 1–4 is required in order to monitor changes in disease phase or the development of liver complications (Table 2).

**Table 3.** Recommended testing regimes [22]

Screening group	Recommended test	Comment
Individuals with chronically elevated ALT or AST	HBsAg	These individuals should be screened regardless of their risk history
Individuals at increased risk of HBV infection: Persons born in high/intermediate prevalence areas and their children Household contacts of HBsAg-positive individuals Persons who have ever injected drugs, had multiple sexual partners or history of sexually transmitted disease Men who have sex with men Prison inmates Those infected with HCV or HIV	HBsAg	A negative HBsAg does not rule out previous infection but provides adequate screening for groups at risk
Pregnant women	HBsAg	If HBsAg positive, check HBeAg and HBV DNA viral load in order to differentiate between high and low risk of mother to child transmission and chronic infection in the neonate.
Candidates for blood/tissue/organ donation	HBV DNA	High risk of HBV transmission from donor with previous HBV infection, even if HBsAg negative
Individuals undergoing immunosuppressive therapy	Anti-HBc IgG	High risk of HBV reactivation in individuals with previous infection. Therefore important to detect past infection that may reactivate.

## HCC screening

The AASLD recommends HCC screening with abdominal USS every 6–12 months for some individuals (see Box 3) [22].



**Figure 2.** Further investigations to establish HBV status. Notes: \*Persistence of HBsAg for 6 months denotes chronic infection. \*\*These two phases can be difficult to distinguish unless full assessment has been performed. Phase 3 patients may reactivate to Phase 4 and should therefore be kept under active review. Liver biopsy may be indicated.

### Box 3. Individuals at increased risk of hepatocellular carcinoma for whom HCC screening is recommended

Individuals who are HBsAg positive and:

- Asian males aged >40 years
- Asian females aged >50 years
- Africans aged >20 years
- Aged >40 years with persistent or intermittent ALT elevation and/or high HBV DNA level
- Any age and confirmed liver cirrhosis

### Treatment

The goal of treatment is clearance of HBV DNA (and, if possible, clearance of HBeAg and HBsAg) to prevent the development of cirrhosis, liver failure and HCC [23]. Long-term treatment is often required, although some individuals maintain a low or undetectable HBV DNA level >6 months after stopping treatment, which is

classified as a 'sustained virological response' (SVR). Complete eradication of HBV infection does not occur, due to the persistence of HBV DNA within the nuclei of host hepatocytes [24].

Treatment should be considered for patients in either the HBeAg-positive CHB or the HBeAg-negative CHB phases and those with cirrhosis, irrespective of eAg status [23]. Treatment is not indicated for individuals in the immune tolerant phase, where liver damage has not yet occurred. The phase of infection or extent of liver damage may be difficult to assess, in which case a liver biopsy can be helpful. Patients and clinicians are often keen to avoid liver biopsy, and new non-invasive tests, including serum markers and transient elastography (fibroscanning<sup>®</sup>), may avoid the need for biopsy in the future.

### Available treatments

There are currently seven drugs available for the treatment of CHB: five nucleos(t)ide analogues (NUCs) (lamivudine, adefovir, entecavir, tenofovir and telbivudine) and two interferon-based therapies (conventional interferon and pegylated interferon alpha). NUCs suppress viral replication by inhibiting HBV viral polymerase,

whereas interferon therapy works by enhancing the host immune response. The two main treatment strategies are finite therapy with interferon or NUC therapy (for those who maintain an SVR off treatment), or long-term therapy with one or more NUCs, for those with cirrhosis or who do not maintain an SVR [24].

### NUC therapy

NUC therapy has a good side-effect and safety profile but there is a considerable risk of viral resistance [15]. Long-term studies of lamivudine therapy have shown that treatment reduces the incidence of cirrhosis and HCC compared to untreated controls. However, long-term data on the effects of other NUCs are limited due to their relatively recent introduction into clinical practice [11].

The EASL currently recommends either entecavir or tenofovir as first-line monotherapy, given their antiviral potency (67–90% and 60–88% have undetectable HBV DNA at 1 year respectively), and a much more favourable resistance profile compared with the previous first-line treatment, lamivudine [14]. Lamivudine can still be used for the prevention of HBV reactivation in those undergoing immunosuppressive therapy [25]. Adefovir can be used (sometimes in tandem) in patients already on lamivudine who are showing signs of antiviral resistance [25]. Telbivudine has not been recommended in the UK for the treatment of chronic HBV due to unacceptably high levels of viral resistance [14,26–28]. There is currently a lack of evidence for the superiority of *de novo* combination NUC therapy over monotherapy in treatment naïve patients. However, some experts recommend the use of *de novo* combination therapy in those with a high risk of viral resistance, or in patients with cirrhosis, for whom the development of resistance may have life-threatening consequences [14].

### Interferon therapy

The advantages of interferon therapy are the absence of viral resistance, the finite course of treatment (normally 48 weeks) and an increased chance of SVR and HBeAg and HBsAg clearance compared with those taking NUC therapy [25]. Long-term studies have demonstrated that interferon treatment is associated with a significant reduction in the risk of cirrhosis and HCC, even in those who fail to clear HBeAg [11]. However, interferon has a poor side-effect profile (including persistent flu-like symptoms and psychiatric complications) compared with NUC therapy, requires subcutaneous injection and is not recommended for patients with decompensated cirrhosis. The use of interferon is therefore restricted to patients who are most likely to benefit; in particular, younger patients who have more potential years in which to develop complications from their CHB and thus have more to gain from achieving an SVR [3,15].

### Treatment in children

Treatment should be considered as soon as there is evidence of the immune reactive phase, regardless of the patient's age [16]. Interferon therapy, lamivudine and adefovir are approved for use in children, but the newer antivirals (tenofovir and entecavir) have not yet been fully evaluated in younger children and are only recommended for individuals >15 years of age [16].

### Treatment monitoring

Ongoing review is recommended to monitor side-effects, alter treatment dosage and check adherence to the prescribed regimen. In compliant patients, a detectable HBV DNA following initial clearance (virological breakthrough) should raise the suspicion of viral resistance [14].

### Genotype and prediction of treatment success

Genotypes A and B may be associated with a better response to interferon therapy, although the clinical trials that showed this association were not designed to look at the effect of genotype and may be confounded by ethnicity [12]. The success of NUC therapy does not appear to be associated with genotype [12].

### Pregnancy

Treatment in women of childbearing age should take into account the likelihood of spontaneous reversion, the anticipated duration of treatment and the immediacy of pregnancy plans [23]. Treatment of pregnant women with antivirals is sometimes considered, but interferon therapy is contraindicated in pregnancy. The most recent EASL guidelines suggest testing the viral load in eAg-positive mothers and considering the use of antivirals in the mother in the third trimester to reduce the viral load and vertical transmission [14]. HBV infected women should be monitored closely after delivery as exacerbations of CHB may occur [29].

### Treatment of acute HBV

Most cases of acute HBV can be managed with supportive treatment, although there is some evidence that NUC therapy can improve prognosis in patients with severe or fulminant infection [14].

### Future developments

Valtorcitabine (a prodrug of telbivudine) and pradefovir (a prodrug of adefovir) are currently in Phase II clinical trials. However, there are no current developments that are likely to offer a significant improvement over existing regimens [10]. The limited treatment options emphasize the importance of starting treatment at an appropriate

time and encouraging patient compliance, in order to minimise the risk of antiviral resistance [30].

## Prevention of HBV infection

### Vaccination

Safe and effective hepatitis B vaccines containing inactivated HBsAg have been available since the early 1980s. The first vaccines were plasma derived; however, these have been replaced over the years by vaccines manufactured in yeast or mammalian cells using recombinant DNA technology [31,32]. In general, the vaccine is administered using a three-dose schedule. Vaccine efficacy (defined as anti-HBs concentration of  $\geq 10$  mIU/ml) is greatest in infants, children and young adults—with protective antibody levels achieved in  $\sim 95\%$  of those vaccinated [7]. After the age of 40 years, the proportion of persons who have a protective antibody response following vaccination declines to  $< 90\%$  and to  $\sim 75\%$  in those vaccinated over the age of 60 years [33]. Other factors associated with a reduced response to vaccination include immunosuppression, liver disease, renal failure, smoking and obesity [31,34]. Protection conferred by hepatitis B vaccination has been shown to be long lasting, with the risk of HBV infection significantly reduced even when anti-HBs concentrations decline to  $\leq 10$  mIU/ml over time [32].

### HBV vaccination programmes

In 1992, the WHO recommended that all countries should introduce universal HBV vaccination into their routine immunization programmes [1]. The impact of universal infant HBV vaccination has been reported in a variety of countries and settings. In general, studies in high endemicity areas have shown a decline in the prevalence of CHB infections in children to  $< 2\%$ , and a reduction in the incidence of HCC in children and young adults has also been reported in some South East Asian countries where universal infant vaccination programmes have been in operation for up to 20 years [35]. In the USA, the number of newly acquired HBV infections has declined substantially since the introduction of a national immunization strategy which includes the universal vaccination of infants beginning at birth and the identification and vaccination of adults at increased risk of infection [33]. Between 1990 and 2007, the annual incidence of HBV infection in the USA declined by  $> 80\%$  overall, and by  $98\%$  in children  $< 15$  years old [36]. In Europe, studies in Italy and Bulgaria have demonstrated a dramatic decline in the incidence of acute HBV infections and the prevalence of CHB following the introduction of universal HBV vaccination programmes [37].

As of 2008, 177 of 193 WHO member states ( $92\%$ ) had integrated HBV vaccination into their national infant

vaccination schedules [32]. In Europe, 22 of 29 EU/EEA countries have implemented a universal infant or adolescent HBV vaccination programme. The remaining seven countries, including the UK, have adopted a selective vaccination programme targeting at-risk groups based on the local epidemiology of HBV infection [38].

### Occupational HBV vaccination

Vaccination and post-vaccination testing of response is recommended for individuals at occupational risk of exposure to HBV. In the UK, vaccination is recommended for the following occupational groups [2]:

- health care workers (HCWs)
- laboratory workers
- staff of residential and other accommodation for those with learning difficulties:
- other occupational groups at increased risk, e.g. morticians, embalmers and prison service staff.

Similar recommendations for occupational HBV vaccination have been made elsewhere [39,40].

### Post-exposure prophylaxis

Post-exposure prophylaxis (PEP) with HBV vaccination alone or a combination of HBV vaccination and passive immunisation with HBV immunoglobulin (HBIG) has been shown to be highly effective in preventing HBV transmission following exposure to infected blood or body fluids, e.g. via contaminated sharps injury, sexual contact or perinatal exposure [40]. In order to maximize efficacy, PEP should be initiated as soon as possible following exposure. The choice of PEP and dose regimen will depend on the timing and nature of the exposure, the vaccination status of the exposed person and the HBsAg status of the source [2,40,41].

### Prevention of mother to child transmission

PEP, initiated at birth, is recommended for all infants of HBV infected mothers [2,7,42]. PEP using a combination of HBIG and an accelerated course of HBV vaccine has been shown to be effective in preventing perinatal HBV transmission in  $\sim 90\%$  of cases [35,42]. Many countries, including the USA and the UK, have introduced routine antenatal screening of all pregnant women to identify HBsAg-positive mothers and maximize opportunities to prevent mother to child transmission of HBV infection [40,43].

### Other prevention measures

In addition to vaccination, the risk of HBV transmission can be reduced through other prevention measures including: routine testing of blood, organ and tissue donors,



screening of blood and blood products, harm reduction advice and provision of needle exchange programmes for injecting drug users and condom use to reduce the risk of sexual transmission.

### HBV infection and HCWs

The WHO has estimated that, worldwide, ~66 000 cases of HBV infection and 261 HBV-related deaths among HCWs are caused by contaminated sharps injuries each year [44]. In developed countries, HBV transmission from patient to HCW has become an increasingly rare event due to the introduction of HBV vaccination for HCWs, the implementation of standard infection control precautions (SICPs), the safe disposal of sharps waste and the use of safer needle devices [5,45]. However, in developing countries, there remains a significant risk of transmission of HBV from patient to HCW, reflecting the greater prevalence of CHB in the population, limited access to HBV vaccination and PEP, unsafe work practices and lack of adherence to SICPs [44,46].

HBV infected HCWs represent a potential risk to their patients and the transmission of HBV from HCWs to patients has been well documented [47,48]. The risk of transmission is greatest during exposure prone procedures (EPPs). EPPs have been defined by the UK Advisory Panel (UKAP) as:

invasive procedures where there is a risk that injury to the worker may result in the exposure of the patient's open tissues to the blood of the worker. These include procedures where the worker's gloved hands may be in contact with sharp instruments, needle tips or sharp tissues (e.g. spicules of bone or teeth) inside a patient's open body cavity, wound or confined anatomical space where the hands or fingertips may not be completely visible at all times [49]

In 2003, a European Consensus Group recommended that HBeAg-positive HCWs should not perform EPPs, that quantitative HBV DNA testing should be used to determine whether HBeAg-negative HCWs are allowed to perform EPPs and that each country should agree a cut-off level for HBV DNA above which exclusion from performing EPPs is mandatory [47]. In the UK, this level has been set at  $10^3$  genome equivalents/ml [50,51]. In the USA, HCWs who are HBeAg positive or those with HBV DNA levels of  $\geq 10^4$  genomes/ml are restricted from carrying out health care associated procedures associated with a definite risk for blood-borne virus transmission (Category III procedures) [48].

### Public health action in response to a case

HBV infection is a notifiable disease in the UK [52,53]. Following notification, public health action aims to reduce the risk of onward transmission by providing prevention advice to the case and by identifying close contacts of the case who

should be offered HBV testing and PEP as appropriate [2]. Similar recommendations for the identification and management of contacts have been made in the USA [54].

### Conclusions

Hepatitis B is a common infection that is associated with a considerable burden of liver-related morbidity and mortality worldwide. Recent advances in treatment have seen the introduction of drug therapies with the potential to have a significant impact on the incidence of liver-related complications. However, the existence of a highly effective vaccine means that primary prevention through well-organized immunization programmes remains a priority.

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