



Fighting liver disease



A professional's guide
to hepatitis B

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The British Liver Trust works to:

- support people with all kinds of liver disease
- improve knowledge and understanding of the liver and related health issues
- encourage and fund research into new treatments
- lobby for better services.

All our publications are reviewed by medical specialists and people living with liver disease.

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Introduction

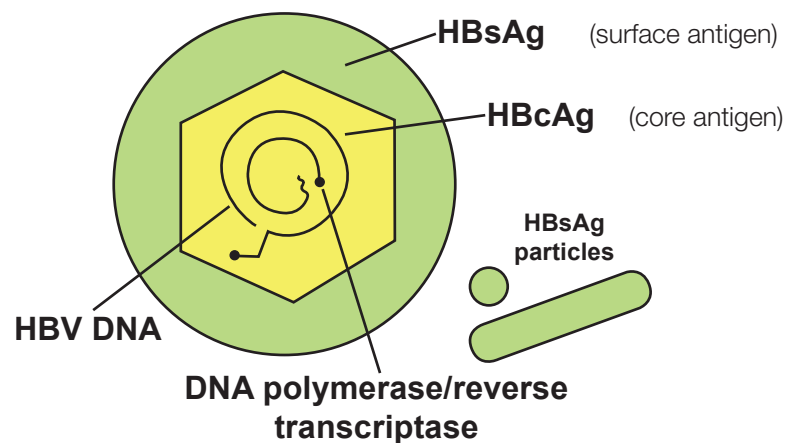
The hepatitis B virus is classified by the World Health Organisation (WHO) as the world's second greatest carcinogen after tobacco.

Type B hepatitis is caused by the hepatitis B virus (HBV), a small enveloped DNA virus that infects the liver causing hepatocellular necrosis and inflammation. HBV can cause either an acute illness or chronic, persistent infection. Acute or chronic infection can lead to severe liver damage and is therefore potentially fatal.

After the identification in 1965 of the hepatitis B surface antigen, called HBsAg, hepatitis B was clearly linked to the development of cirrhosis and primary liver cancer. The virus and subviral particles were identified in serum and the genome of the virus was isolated and characterised as a small circular molecule of DNA

Structure of the hepatitis B virus

(Acknowledgement: Baruch S. Blumberg)



The identification of HBV led to the development of vaccines using HBsAg particles isolated from the serum of chronic carriers and later, after the genome of the HBV had been cloned, recombinant DNA vaccines.

HBV has been classified into eight genotypes, each with a distinct geographical and ethnic distribution:

Genotypes A and D	Africa, Europe and India
Genotypes B and C	Asia
Genotype E	West Africa
Genotype F	Central and South America
Genotype G	France, Germany and the USA
Genotype H	Central America

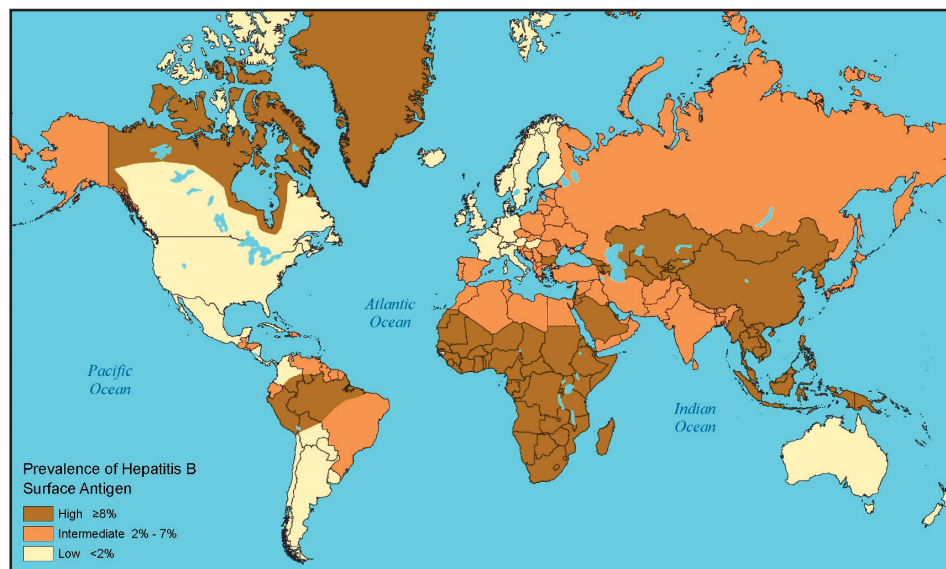
Hepatitis B presents clinical staff with many difficult challenges. Disease management is still developing, influenced by the introduction of new drugs and the evolution of new data. Treatment is complicated, may be costly and time consuming. While there is an effective vaccination for HBV, it is not universally available. Dealing with patient uncertainties about therapy and the social and occupational implications arising from this may present further problems.

This publication reviews current understanding about hepatitis B and provides a framework for optimal management of the disease by health professionals.

How prevalent is HBV?

HBV is 50 to 100 times more infectious than HIV. Morbidity and mortality statistics are significant. About two billion people worldwide have been infected with the virus and about 350 million live with chronic infection. An estimated 600,000 die each year due to the acute or chronic consequences of hepatitis B.

Areas with high prevalence of HBV (South-East Asia, the Indian subcontinent, the Middle and Far East, Southern parts of Eastern and Central Europe and Africa) are also regions with the highest rates of hepatocellular carcinoma (HCC), one of the most common forms of cancer.



Map of global prevalence of chronic hepatitis B virus infection

(Acknowledgement: U.S. Centers for Disease Control and Prevention)

With 75% of the global population currently living in areas of high infection, it is clear that hepatitis B is a major international health problem.

In the UK, hepatitis B has a low prevalence but there is significant variation across the country. It is higher in those born in high endemicity countries, many of whom will have acquired infection at birth or in early childhood. Overall, less than 1% of the population is HBsAg positive, with an estimated pool of 180,000 to 320,000 cases.

Since 1992, laboratory reports of confirmed acute hepatitis B have fluctuated between 600 and 800 cases per year. Although reliable recent data is not available, estimates suggest that only a small proportion of chronic infections are established as a result of infection acquired in the UK (around 200 per year) but an estimated 7,000 chronic cases of hepatitis B come to the UK every year as a result of immigration to the UK from high prevalence areas. The majority of this group may not present with symptoms to health workers until disease is advanced. As a result, screening of recent immigrants from high prevalence areas should be considered when they register with a GP. More formal approaches to identifying migrants with chronic infection have been suggested, as this could allow for early treatment and for vaccination of close contacts, but as yet no national recommendation exists.

Acute hepatitis B

usually a self-limiting disease marked by inflammation in the liver in association with a transient HBV infection

Chronic hepatitis B

persistent HBV infection accompanied by ongoing liver injury and resulting risk of cirrhosis and HCC

Transmission of HBV

Transmission of HBV is by parenteral exposure to infected blood or body fluids.

Globally, the major mode of HBV infection is **perinatal transmission** although patterns of transmission are shifting due to the introduction of universal vaccination programmes in many countries.

In countries with low endemicity the spread is caused predominantly by sharing contaminated equipment during injecting **drug use** and through **sexual contact**.

In the UK, the most reported risk factor, for new cases among adults with a known likely source of infection, is injecting drug use followed by sexual contact.

Many patients, perhaps up to one third, will not know how they acquired the infection.

Hepatitis B is not spread by casual contact such as touching hands and kissing, or sharing towels and eating-utensils. Faeces of chronic HBsAg carriers do not appear to harbour the virus.

Exposure to blood

The source of most HBV infection is probably exposure to blood and secretions from chronic carriers.

Highest amounts of HBV are present in blood. HBsAg carriers vary considerably in their infectivity from less than 10 to greater than 10^8 virions/ml of plasma.

Patients with HBeAg (Hepatitis B e-antigen) in addition to HBsAg generally have more than 10^6 virions/ml in serum, which explains why transmission of hepatitis B usually occurs from exposure to an HBeAg-positive person.

The introduction of HBsAg screening of blood donations in the UK and viral inactivation of blood products has all but eliminated these as a source of infection in this country since 1991.

Drug paraphernalia is often shared and is thus at risk of being HBV-contaminated. This includes not only needles but also barrels, filters, spoons, citric or water. The virus is able to persist in dried blood on

implements and surfaces for at least one week. Tattooing, body-piercing and acupuncture may also pose a risk if unsterilised equipment is used.

Patients should always avoid sharing needles and syringes, razors and shaving equipment, and toothbrushes.

Other body fluids

HBsAg can also be detected in other bodily secretions such as saliva, semen and vaginal fluid, even without blood contamination. However, the amount of virus is always 100 to 1000-fold less than in blood.

While HBsAg can occasionally be found in urine, breast milk, cerebrospinal fluid, sweat, tears and bile, the amounts are low and have not proved infectious.

Sexual transmission

The virus can be spread by sexual contact. Transmission usually occurs through exposure of mucous membranes to infected blood or body fluids during vaginal or anal intercourse.

Young adults engaging in high-risk sexual behaviours such as unprotected sex (penetrative or oral) and with multiple partners are at greatest risk of infection.

Perinatal transmission

Maternal to infant spread is an important means by which the virus is sustained in worldwide populations. This has been reduced by the universal infant vaccination programmes recommended by the WHO. In 1992 just 31 countries vaccinated infants against hepatitis B during national immunisation programmes. By 2007 this had increased dramatically to 171 countries.

In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) recommends targeted rather than universal infant vaccination. Pregnant women are offered antenatal screening for hepatitis B infection and babies born to infected mothers are immunised at birth. Infants of mothers who are known to be very infectious from antenatal screening are offered both

hepatitis B immunoglobulin and immunisation. The cost effectiveness of universal immunisation of infants or teenagers is currently being re-assessed as part of the continual review of immunisation policy in the UK.

Although breast milk of HBsAg positive mothers has been found to be positive for the virus, there have not been any reports of HBV transmission through breast-feeding, even before the availability of hepatitis B vaccine for infants. Any residual risk of transmission would be almost completely abolished by ensuring that the infant is vaccinated on time. Mothers who breast-feed are advised to take good care of their nipples to avoid cracking and bleeding which may increase the risk of other unrelated problems. Clinicians should promote the importance of timely vaccination and discuss the risks and benefits of breast-feeding to reassure pregnant women.

The acute phase of the infection in children and newborns is typically mild and not associated with apparent illness. However, infection during the neonatal period almost always leads to chronic infection.

Interfamilial transmission

Non-sexual interfamilial spread is not commonplace but may occur. It becomes common when the first family member to be infected is an infant or child and is seen most clearly amongst adoptive parents of chronic HBsAg carrier children.

Travel

Travel to endemic regions accounts for around 12% of cases in the UK.

The risk to travellers to high or intermediate prevalence areas is increased with certain activities such as high risk sexual activity, injecting drug use, medical or dental procedures, undertaking relief aid work and/or participating in contact sports.

Around a half of travel-related cases in England, Wales and Northern Ireland reported heterosexual exposure as a risk factor.

Individuals likely to need medical or dental treatment should be vaccinated before they travel; these include those remaining for lengthy periods, children or others who may need medical care while visiting families or relatives, those with chronic medical conditions and those travelling for medical care. It is particularly important to ensure that individuals

who may require dialysis are aware of the risks of blood-borne virus acquisition whilst overseas and are fully vaccinated and the response to vaccination documented.

Occupational risks

Hepatitis B is an important occupational hazard for healthcare workers via accidental needle sticks, injury from sharp objects, or direct exposure to blood and body fluids to breaks in the skin or to mucous membranes (eyes, inside of the mouth and nose). This risk can be virtually eliminated by pre-exposure vaccination of individuals at risk of needlestick accidents and by appropriate post-exposure risk assessment and management of those not fully protected.

Similarly an infected health care worker may present a risk to patients. It is vital that healthcare workers are vaccinated and, if injured at work with sharp objects or needles, have appropriate tests and follow-up checks for hepatitis. Without this there is also the unnecessary risk of developing chronic infections, hepatitis B, C or HIV.

Other professions may also be at risk due to exposure to blood or body fluids, such as laboratory staff, staff in accommodation caring for those with learning difficulties, the prison service, police, social work, parks and funeral workers. Vaccination is recommended for anyone at occupational risk and it is a requirement for the employer to ensure that the risk to staff is assessed and all reasonable measures taken to reduce this risk, including providing vaccination.

Diagnosis of acute hepatitis B

Signs and symptoms

The average incubation period is 60 to 90 days (range is 40 to 160 days). In the initial stages of HBV infection the symptoms are vague and ill-defined. The onset of hepatitis B is typically insidious, with nonspecific symptoms of malaise, poor appetite and nausea, with pain in the right upper quadrant. Fever, when present, is usually mild.

Roughly 30 to 50% of adult patients will develop jaundice. As jaundice sets in, the urine becomes darker and the stools paler.

The disease generally lasts from one to six weeks but may be prolonged and can be fulminant. Acute hepatitis B resembles other forms of acute hepatitis clinically and cannot easily be distinguished by history, physical examination or routine serum biochemical tests.

Unusually, fulminant hepatitis B can occur during acute infection. This occurs in approximately 2 to 3% of cases. Fulminant hepatitis can lead to the rapid onset and development of acute hepatic failure with encephalopathy, coma and death.

Interpreting laboratory results

Various classifications of antibody indicate the stages of the immune response.

The three main HBV antigens are:

- **HBcAg** Hepatitis B core antigen (HBcAg is not found in serum)
- **HBsAg** Hepatitis B surface antigen
- **HBeAg** Hepatitis B e-antigen (denotes active viral replication)

HBcAg can stimulate IgM and IgG antibodies:

- immunoglobulin 'M' (IgM) indicating that HBV infection has occurred within the last six months
- immunoglobulin 'G' (IgG) indicating that HBV infection occurred more than six months earlier

The diagnosis of acute hepatitis B generally rests upon the finding of hepatitis B surface antigen (HBsAg) and IgM antibody to hepatitis B core (anti-HBc) in the serum of a patient with clinical and biochemical evidence of acute hepatitis.

- The first serological marker to be detectable in the serum is **HBsAg** which appears during the incubation period and rapidly rises in titre. In about 10% of patients HBsAg is cleared early and may not be detectable when the patient is first seen by the physician.
- Concurrent with or shortly after the appearance of HBsAg in serum, **HBeAg** and **HBV DNA** are detectable. Disappearance of HBeAg, seroconversion to anti-HBe and a decline in HBV DNA indicates resolution of viral replication and predicts resolution of acute hepatitis B.
- In patients who develop chronic hepatitis B, by contrast, HBeAg and HBV DNA remain high. **HBcAg** is not found in the serum.
- The first antibody to arise during the course of typical acute hepatitis B is **anti-HBc. IgM anti-HBc** is positive in acute hepatitis B and is used to document the acute disease, rather than an exacerbation of disease. It generally persists for only a few months, making it a useful marker for the diagnosis of acute hepatitis B. **IgG anti-HBc**, indicative of chronic infection, generally persists for life. A proportion of patients with active chronic hepatitis B may also develop IgM anti-HBc, detected by sensitive tests.
- Antibodies to HBsAg (**anti-HBs**) usually appear during convalescence following the surface antigen's disappearance. Anti-HBs alone is also a marker of immunisation.

Diagnosis of chronic hepatitis B

Symptoms of uncomplicated chronic hepatitis B

Some patients with acute hepatitis B do not clear the virus (less than 5%) and will progress to chronic hepatitis. Chronic hepatitis B is defined as persistence of HBsAg in the circulation for more than six months.

The disease can cause mild to serious liver damage as well as active hepatitis, cirrhosis and primary liver cancer.

The persistence of abnormal alanine aminotransferase levels for more than six months after the onset of acute hepatitis B indicates disease progression and is usually accompanied by serological evidence of continued infection.

Chronic hepatitis B is more likely to follow infections acquired in childhood than those acquired in adult life. 90% of neonates infected at birth will develop chronic hepatitis B unless vaccination is given.

Only a small percentage of patients with chronic infection give a history of acute hepatitis or jaundice. Physical examination in chronic hepatitis B may show no physical abnormalities and many patients show no symptoms of liver disease. If symptoms are present, they are usually non-specific and mild.

With more advanced disease there may be spider naevi and hepatomegaly (enlarged liver). Muscle wasting, ascites, oedema, palmar erythema, encephalopathy and bruising, suggest advanced disease with cirrhosis. The symptoms of portal hypertension, such as ascites and bleeding oesophageal varices, are late features of hepatitis B and cirrhosis.

There are several signs to look out for:

- **Fatigue** is the most common symptom, variously described as a lack of energy, lassitude or the feeling that one is ageing.
- With the development of cirrhosis, **weight loss, weakness, muscle wasting, abdominal swelling, encephalopathy, oedema, dark urine and jaundice** may become progressive problems. Many carriers may be detected through routine screening for HBsAg e.g. in pregnancy.
- Older patients may present with complications of **active hepatitis** and **cirrhosis** or with **HCC**.

- A small proportion of patients may present with extrahepatic manifestations of HBV infection – **glomerulonephritis, vasculitis, or polyarteritis**, for example.

Interpreting laboratory results

The following liver function tests (LFTs) are used to determine the presence of liver disease.

- **ALT** – tests usually show an increase in ALT although young carriers with high levels of hepatitis B may have normal ALT levels. Recording single measures of ALT is less useful in a disease as dynamic as hepatitis B as aminotransferases may fluctuate over time.
- **AST** – tests will usually show an increase in AST.
- **Serum bilirubin and albumin tests** – usually normal unless the disease is severe and advanced.
- **Prothrombin time** – usually normal length unless the disease is severe and advanced.

The utility of HBV genotypes is still being determined but there is a suggestion that response to interferon is higher in genotypes A and B versus genotypes C and D. In comparison with genotype C, genotype B is associated with spontaneous HBeAg seroconversion at a younger age, less active liver disease, slower progression to cirrhosis and less frequent development of HCC. Genotype D is associated with HBeAg-negative chronic hepatitis B.

The terms used to describe the pathology of chronic hepatitis are being reappraised. More emphasis is now placed on grading the degree of inflammation and staging the extent of fibrosis.

Reporting cases

Hepatitis B, like all viral forms of hepatitis, is a notifiable disease and doctors have a statutory duty to notify their 'proper officer' of the local authority, who is usually the consultant in communicable disease in the local health protection unit, of suspected and confirmed cases. They will pass on the information to the national centres. This information is used to help plan local services for prevention and treatment.

Classification of HBV infections

The clinical outcome of HBV is a result of a combination of the level of replication attained by the virus and the nature of the patient's immune response.

Patients with persistent hepatitis B generally exhibit one of four major clinical patterns of infection:

1. **Profound immunotolerance and mild hepatitis B** despite high levels of replication of the virus (HBeAg-positive immunotolerant chronic hepatitis B).
2. **Active infection** (sustained high levels of replication of HBV and raised ALT) in which the 'wild-type' HBeAg-positive HBV is predominant (chronic HBeAg-positive hepatitis B).
3. **Active infections** in which variant forms of HBV unable to secrete HBeAg are predominant (chronic HBeAg-negative or 'precore mutant' chronic hepatitis B).
4. **Inactive HBV infection** (HBeAg-negative inactive disease).

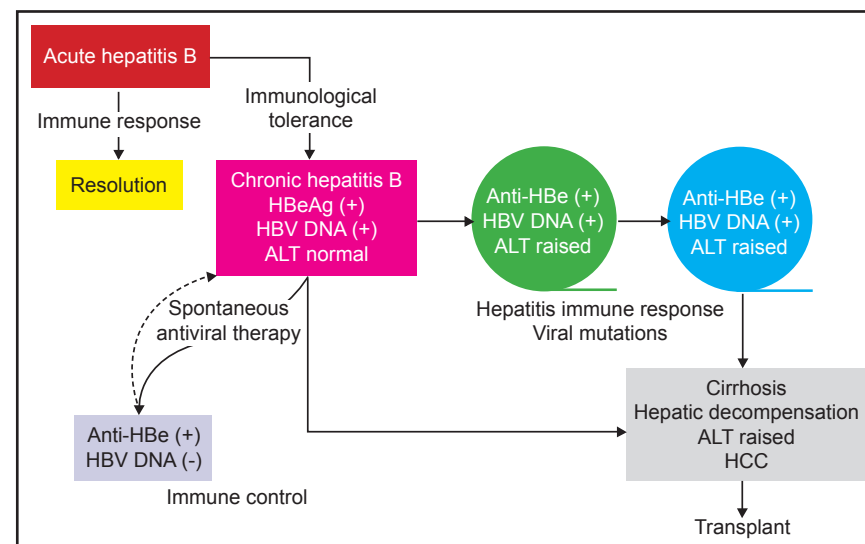
A fifth profile, of uncertain clinical significance, is occult HBV infection which is characterised by the persistence of HBV DNA in liver tissue in HBeAg-negative patients.

It is important to note that these phases are by no means static and can change from one to the other.

The virological pattern of chronic hepatitis B is changing in many parts of the world. A few decades ago the disease was characterised primarily by wild-type (HBeAg-positive chronic hepatitis B) infection. In recent years the prevalence of HBeAg-positive relative to HBeAg-negative infection has diminished. A substantial proportion of HBV infection is now characterised by HBV variants unable to secrete HBeAg.

Natural history of chronic hepatitis B

Natural history and serological markers: acute and chronic hepatitis B



The subsequent course of chronic hepatitis B is variable. Perhaps 15% to 20% of patients who acquire chronic infection in adulthood ultimately develop cirrhosis. Furthermore, the development of cirrhosis is usually slow, occurring over five to twenty years. Up to 9% may go on to develop HCC. The risk of complications of hepatitis B is in part related to ongoing active HBV replication.

Infection in childhood may have a different prognosis. Typically, the infection is mild and associated with few symptoms and only minimal elevations of serum aminotransferases. The disease may change once adulthood is reached, with marked fluctuations in its activity and the development of cirrhosis in up to 40% of patients.

A pattern of recurrent reactivation with multiple remissions and recurrences is a particularly severe form of disease which frequently leads to cirrhosis and ultimately to liver failure.

Chronic hepatitis B can lead to HCC. The majority of patients with this cancer also have cirrhosis. In endemic areas of HBV infection, HBV positive patients frequently have silent disease until the development of HCC.

People with active inflammation and cirrhosis (high ALT), where there is a rapid cell turnover, are at increased risk of developing HCC. Ultrasound examinations and regular determinations of alpha fetoprotein can be used to screen for HCC in high-risk populations and in individual patients, particularly those over the age of 40 who acquire HBV infection during childhood and who have cirrhosis. Integration of the HBV genome into hepatocyte DNA may be an important initiating factor in this.

Progressive disease is associated with persistence of viral replication

Remission is associated with loss of active viral replication

Treatment of acute hepatitis B

Most adult icteric (jaundiced) patients with acute hepatitis B resolve their infection and do not require treatment. **Subacute hepatic necrosis** is characterised by a more protracted acute course and transition to chronic hepatitis with ongoing HBV replication.

Patients with **fulminant hepatitis**, including acute and subacute forms, should be considered for liver transplantation if appropriate. Nucleoside analogue antiviral therapy (see 'Current antiviral therapies', page 23), should be given as soon as possible; interferons are not useful for the treatment of acute or fulminant hepatitis.

Although there are no controlled trials of lamivudine or adefovir for patients with acute hepatitis, uncontrolled reports suggest some efficacy in these patients.

Therapy of chronic hepatitis B

Treatment remains complex with somewhat unpredictable responses. Currently used antiviral agents either inhibit HBV replication or invoke immune responses which may be necessary but not sufficient to effect viral control.

Most treatment regimes involve either one potent drug (such as tenofovir or entecavir) or a combination of drugs (such as tenofovir plus lamivudine). For many patients treatment may need to be continued for many years. Poor compliance can lead to drug resistance.

General management principles

- The patient should be encouraged to understand the **natural history** of hepatitis B.
- The patient should be educated about their **laboratory tests** (including the significance of the serum aminotransferases, HBeAg, anti-HBe or HBV-DNA levels) and their **liver biopsy** findings (if done).
- It will help if the patient retains a copy of their **blood test results**.
- Patients must be made aware of their **infectivity**. Methods of preventing transmission should be emphasised (for example, practising safe sex).
- **Vaccination** should be offered to sexual partners, other household members and children.
- Reassure the patient that **close, ongoing observation** will be maintained. It is important to explain the indications for treatment so that patients understand why they may not require immediate therapy.
- Advise patients to carefully consider **who they should disclose their illness to** outside of their healthcare team.
- Practical **support networks** for the patient should be encouraged and **counselling services** where possible should be made available to them.
- Ensure that the patient will be **referred for medical or specialist supervision**. Specialists may recommend ongoing primary care management.

- Severe acute hepatitis B should be **immediately referred to a hospital with a liver unit or facilities for transplant assessment**. Measurement of the prothrombin time is important to ascertain the severity of acute hepatitis.
- Patients with chronic hepatitis B should be **referred to specialist services** in a timely fashion. **Severe chronic hepatitis B requires rapid treatment**.
- Patients with chronic hepatitis B are recommended to **avoid alcohol**.

Indications for treatment

Several difficulties remain in formulating treatments for hepatitis B. There are areas of disagreement on management of the disease, for example regarding the level above which HBV DNA concentrations are indicative of active disease or the threshold for initiating treatment. Thus, patients with mild disease may not require immediate treatment but careful monitoring.

Substantial health care resources are frequently required to manage patients with hepatitis B. Most clinicians consider that therapy should be considered only if there is evidence of moderate to severe activity or fibrosis. NICE guidance on the indications for treatment should be followed.

Indications and considerations

- Treatment is indicated for **chronic progressive disease**, although there is a role for rapidly acting nucleoside analogues in fulminant acute hepatitis B or subacute hepatic necrosis.
- Many clinicians would consider a **liver biopsy** helpful to ascertain the degree of necroinflammation and fibrosis. However, the limitations of biopsy (including sampling error, subjectivity and reproducibility) will mean risks and discomfort to the patient as well as costs. Assessment of fibrosis is necessary to measure how far the disease has progressed, although progression of disease in hepatitis B may not be linear and may be influenced by periods of activity.
- **The European Association for the Study of the Liver (EASL) guidelines** suggest that patients should be considered for treatment when HBV DNA levels are above 2000 IU/ml (i.e. approximately 10,000 copies/ml) and/or the serum ALT levels are above the upper limit of

normal (ULN) for the laboratory, and liver biopsy (or non-invasive markers when validated in HBV-infected patients) shows moderate to severe active necroinflammation and/or fibrosis using a standardised scoring system (for example at least grade A2 or stage F2 by METAVIR scoring).

- **Patients with mild chronic hepatitis B:** patients with slightly elevated ALT (less than two times ULN) and mild histological lesions (less than A2F2 with METAVIR scoring) may not require immediate therapy. Follow-up is mandatory.
- **Immunotolerant patients:** most patients under 30 years of age with persistently normal ALT levels and a high HBV DNA level (usually above 10^7 IU/ml), without any suspicion of liver disease and without a family history of HCC or cirrhosis, do not require immediate liver biopsy or therapy. Follow-up is mandatory.
- Patients with severe, advanced hepatitis B and cirrhosis should receive rapid treatment.

It may also be necessary to monitor patients carefully to ascertain the change in the pattern of disease evidenced by the elevation of ALT. HBeAg-positive patients with greater disease activity are more likely to seroconvert on antiviral treatment – whether interferon or a nucleoside.

Goals of treatment

The major goals of therapy for hepatitis B are to prevent progression of the disease to cirrhosis and end stage liver disease.

The immediate objectives depend upon the stage of the disease and the level to which the disease has progressed.

Patients may request treatment to reduce viral replication and their own potential infectivity. If decompensated disease is already present, it is important to reduce viral load and stabilise the disease. Patients with decompensated hepatitis B cirrhosis may need liver transplantation and early treatment with appropriate antiviral therapy. Nucleoside analogues such as lamivudine, have been used in decompensated cirrhosis.

Other more potent nucleosides including tenofovir or entecavir are preferable. Interferon is contraindicated in decompensated cirrhosis.

Although it may be possible to reduce the cumulative incidence of decompensated cirrhosis by treating patients with cirrhosis, it is not clear whether suppression of HBV replication will reduce the incidence of HCC. Moreover, suppression of HBV replication in patients with advanced liver disease may not improve synthetic function in time. Exacerbations can occur as viral load is reduced.

End points of treatment

HBeAg-positive patients

The end points of treatment are not clearly defined and differ in HBeAg-positive versus negative disease. Ideally, patients will clear HBsAg by developing anti-HBs. This is, however, relatively infrequently achieved.

Although it is reasonable to infer improvement in liver disease if HBV replication is suppressed with an accompanying improvement in serum ALT, the absolute or relative decreases in serum ALT and HBV DNA that will alter the disease outcome have yet to be categorically defined.

HBeAg-positive disease

The most potent antivirals with the highest barrier to resistance, in particular tenofovir or entecavir are recommended. Patients may also respond to pegylated interferon.

Currently, antiviral therapy for HBeAg-positive disease is directed to attaining loss of HBeAg and, ideally, durable seroconversion to anti-HBe. This represents the transition from chronic hepatitis B to the inactive HBsAg state. A proportion of patients may go on to lose HBsAg.

Although this is a potential stopping point, treatment with nucleoside analogues should be prolonged for six months to one year after loss of the HBeAg. The durability of this response requires assessment in the future. Finite courses of treatment are possible in only a minority of HBeAg positive patients and the majority still require longterm maintenance suppressive therapy.

Ideally profound and rapid reductions in HBV DNA are critical for long-term therapy, to reduce the risk of development of resistance to antiviral therapies. Loss of HBsAg, in the setting of low HBV DNA levels is the ideal end point but is attained in only a minority.

Anti-HBe positive disease

For patients who are already HBeAg-negative, reduction in ALT and HBV DNA and the accompanying histological improvement are the endpoints. Ideally successful treatment is characterised by a decline in HBV DNA to less than 15 IU/ml or levels undetectable by sensitive real time PCR. However, as there is no agreed threshold to define response, maintaining the response should be the objective.

In anti-HBe positive therapy, stopping points and finite courses of treatment are less commonly achieved because of higher rates of relapse in these patients. It is not clear if treatment can be halted even if HBV DNA remains suppressed and resistance or relapse does not occur. While maintaining the response is the objective, the absolute definitions of these remain elusive.

Current antiviral therapies

Once a decision is made that a patient with HBV infection needs therapy, two major groups of antiviral therapies are currently utilised.

These are **interferon** therapy (interferon alpha or 'pegylated' interferon alpha) or an oral **nucleoside** or nucleotide agent such as tenofovir, entecavir, lamivudine, adefovir or telbivudine.

The patterns of response observed with nucleotides are broadly similar although these agents have different structures, inhibit different phases of hepatitis B replication and have variable mechanisms of action. Their pharmacokinetics, inhibitory capacity, onset of action, resistance patterns and rates of HBeAg seroconversion vary during the first year of treatment.

There are also a number of therapeutic vaccines in the early stages of clinical development designed to produce a specific cellular immune response against HBV.

Interferon alpha

Interferon alpha is a naturally occurring protein which supports the host's immune system. The main advantages of interferon alpha (or 'alfa') over nucleoside analogues are the theoretical absence of resistance and the possibility of a finite treatment course (48 weeks). Also, pretreatment factors predictive of response to interferon alpha therapy have been partially defined. Treatment requires self-injection three times a week over an extended period – usually six months.

Pegylated forms of interferon alpha (peginterferon alfa-2a) with improved pharmacokinetic profiles (pegylation increases the persistence of the interferon in the blood) and more convenient once-weekly administration are now licenced and may be preferable to interferon alpha. Treatment is given for a year. Peginterferon alfa-2a (PEG IFN alfa-2a) is recommended as a possible first treatment for adults with chronic hepatitis B, as long as it is suitable for the person and the stage of hepatitis B.

Studies in HBeAg-positive and anti-HBe positive patients indicate that the addition of lamivudine to PEG IFN alfa-2a does not improve seroconversion rates when compared to PEG IFN alfa-2a alone. The use of peginterferon alfa-2a and interferon alpha is limited by a response rate of 30–40%. Although rules for stopping treatment have not been absolutely defined, treatment should be discontinued if little change in HBV DNA concentrations has occurred after four to six months. In anti-HBe positive patients, relapse rates remain high after stopping 48 weeks of peginterferon treatment.

Interferon is contraindicated in decompensated cirrhosis. This drug, which has to be injected, causes more side effects than nucleoside analogues and requires a high level of monitoring. Treatment stopping points at present have been only tentatively defined.

Nucleoside analogues

Overall, nucleoside analogues are the most frequently used primary therapeutic agents for all stages of HBV infection, including wild-type and precore/core mutation variants. The goal of therapy is achieved with the currently approved agents in this category. Current guidelines suggest the use of potent agents with high barriers to resistance as first line therapy.

Tenofovir – Tenofovir is a potent agent and has a high barrier to resistance. It can be used alone as a first line *de novo* treatment for chronic hepatitis B in accordance with NICE recommendations (treatment of chronic HBeAg-positive or HBeAg-negative hepatitis B where antiviral treatment is indicated).

Some experts consider that lamivudine and tenofovir or possibly tenofovir with emtricitabine (Truvada) should be prescribed to patients with cirrhosis and/or high rates of HBV replication. However this policy will require substantiation.

The combination of tenofovir and emtricitabine is licenced for HIV. If patients infected with both HIV and chronic hepatitis B require only treatment for chronic hepatitis B, they should receive antivirals that are not active against HIV, such as peginterferon alfa-2a or adefovir, but this situation is becoming rare. Management of these patients should be co-ordinated between HIV and hepatology specialists. The drug is cleared by the kidneys. Renal tubular disease may occur and requires appropriate monitoring. Osteopaenia has been reported in HIV positive patients.

Entecavir – NICE has recommended entecavir as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.

Studies suggest that entecavir, which inhibits all three activities of the HBV polymerase/reverse-transcriptase, is a potent inhibitor of hepatitis B virus replication. However, although the mean change from baseline was almost 7 log in HBeAg-positive patients, HBeAg seroconversion occurred in just 21% of entecavir-treated patients after one year of treatment. Genotypic resistance has been reported in 1.2% of naïve patients after five years. Dose adjustments are required in cases of renal impairment.

Entecavir is effective in patients not previously treated with nucleoside analogues. Entecavir should not generally be used to treat patients with lamivudine resistance, as high rates of both lamivudine and entecavir resistance results. Post marketing surveillance for the risk of malignancy (reported in preclinical studies) is in place.

Lamivudine – Lamivudine is effective in those who have failed interferon alpha therapy (HBeAg-negative patients, for example) and in improving decompensated disease.

Although a relatively inexpensive drug with few side effects, even in patients with advanced disease, the major disadvantage of lamivudine is the high rate of resistance seen in both HBeAg-positive and anti-HBe positive patients. The virus becomes resistant in about 20% of cases after one year of lamivudine treatment and 70% after five years. Resistance has typically been managed by sequential treatment with adefovir or entecavir but the advantage of the strategy compared to more recent combination therapy is questionable. Elimination of the drug occurs mainly by renal clearance and dosages need to be adapted to creatinine clearance. The other clinical concerns during lamivudine therapy are withdrawal or initiating hepatitis flares.

Adefovir – The efficacy of adefovir has been assessed in patients with HBeAg-positive and negative disease and other settings. In HBeAg-positive patients seroconversion rates at one year are low but can increment with time. Recent data have shown that adefovir is a less potent agent than tenofovir and has a relatively low barrier to resistance. Patients with a slower decrement in HBV DNA have been observed to have relatively high rates of resistance.

Adefovir pharmacokinetics are substantially altered in patients with marked and severe renal impairment.

Combination therapy of adefovir with lamivudine may be used first line or second line in the case of lamivudine resistance. Adefovir is likely to be replaced by the more potent tenofovir.

Telbivudine – Telbivudine is licenced for treatment of chronic hepatitis B infection but not recommended by NICE as it was not found to be cost effective.

Clevudine – Phase 3 studies of clevudine were stopped in April 2009 because of reports of myopathy and neuropathy.

Please refer to NICE.org.uk for the latest guidance releases.

Strategies and choices for treatment

Two different treatment strategies are applicable in both HBeAg-positive and HBeAg-negative chronic hepatitis B patients: treatment of finite duration with pegylated interferon alpha or nucleosides, and long-term treatment with nucleosides.

Finite-duration treatment (a 48-week course) with pegylated interferon alpha is mainly recommended for HBeAg-positive patients considered to have a good chance of HBe seroconversion.

Finite-duration treatment may be possible with nucleosides for HBeAg-positive patients who develop HBe seroconversion on treatment.

The EASL guidelines suggest that an attempt at finite treatment with nucleosides should use the most potent agents with the highest barrier to resistance (entecavir or tenofovir) to rapidly reduce levels of viremia to undetectable levels and to avoid resistance.

For most, long term treatment is required. Patients who cannot achieve a sustained virological response off-treatment require extended therapy, namely HBeAg-positive patients who do not develop HBe seroconversion and in HBeAg-negative patients. This strategy is also recommended in patients with cirrhosis irrespective of HBeAg status or HBe seroconversion on treatment. Again, the most potent drugs with the optimal resistance profile i.e. tenofovir or entecavir, should be used as first-line monotherapies.

There is, as yet, no data to indicate an advantage of *de novo* combination treatment with tenofovir or entecavir in naïve patients. Therapeutic trials are in progress. Some experts recommend a *de novo* combination therapy approach to prevent potential resistance in patients with a high likelihood of developing resistance.

Co-infection

Some people carry two or more different blood-borne viruses, such as hepatitis B, hepatitis C, and HIV as they share similar routes of transmission. Co-infection tends to lead to faster progression of liver damage and an increased risk of liver cancer and cirrhosis. It can make treatment more difficult, but co-infection is not a bar to any particular treatment option.

In agreement with recent HIV guidelines, it is recommended that most co-infected patients be simultaneously treated for both HIV and HBV *de novo*.

In addition, patients with hepatitis B can also become infected with hepatitis D virus (HDV), an incomplete virus that requires the presence of HBV to survive in the body. Super-infection with HDV of a patient with HBV is more likely to cause severe chronic hepatitis and cirrhosis. Around 5% of people with HBV also have HDV, which is seen mainly in central Africa, the Middle East and central South America but rare in Europe and the US. Interferon alpha (conventional or pegylated) is the only drug effective on HDV replication.

Hepatitis B prevention

The hepatitis B vaccine

HBV vaccine contains recombinant HBsAg particles adsorbed on to aluminium hydroxide adjuvant which induce antibodies to HBsAg.

A combined vaccine containing purified inactivated hepatitis A virus and purified recombinant HBsAg, separately adsorbed onto aluminium hydroxide and aluminium phosphate, is also available.

It should be pointed out that mercury-based Thiomersal is not used as a preservative in hepatitis B vaccines available in the UK. Thiomersal is still used in the production process for Engerix-B, Twinrix, Ambirix and Fendrix, and therefore residues are present in the final product.

Around 10 to 15% of adults do not respond to the three dose schedule of vaccine or respond poorly. Poor responses are identified with individuals older than 40 years, smokers and the obese. Patients with advanced liver disease, who are immunosuppressed or on renal dialysis, and patients with concomitant hepatitis C may also have lower seroconversion rates.

Individuals who are anti-HBs and anti-HBc positive are immune and do not require vaccination.

Vaccination can also provide high levels of protection when given shortly after exposure. In these situations it is important to commence vaccination as soon as possible (ideally within 24 hours) and to complete the vaccination schedule on time. Vaccination should not be delayed whilst awaiting further information or blood test results.

Specific hepatitis B immunoglobulin (HBIG)

HBIG provides passive immunity and thus can confer immediate, albeit temporary, protection after accidental exposure to HBV-infected blood.

HBIG is given concurrently with HBV vaccine as it does not alter the development of active immunity. HBIG gives rapid protection after exposure until the hepatitis B vaccine becomes effective. Both the vaccine and HBIG should be given as soon as possible, preferably within 12 hours, ideally within 24 hours, although it should be considered up to a week after exposure. Babies born to mothers known to be very infectious during antenatal screening should be given HBIG as well as vaccine immediately after birth.

HBIG is obtained from the plasma of immunised and screened human donors. The theoretical risk of transmission of variant CJD from plasma products means that HBIG used in the UK is now prepared from plasma sourced from abroad and as a result supplies are somewhat scarce.

Administration

HBV vaccine is routinely given intramuscularly in the upper arm or anterolateral thigh. The buttocks are not used, as absorption may affect the vaccine efficacy. Patients who have bleeding disorders should receive their vaccination by deep subcutaneous injection.

HBIG can be administered in the upper outer quarter of the buttock or the anterolateral thigh.

Where administration of both the vaccine and HBIG is required these should be at different sites.

Schedules for pre-exposure and post-exposure prophylaxis

Pre-exposure immunisation is used for individuals who, because of lifestyle, occupation or other factors, are at increased risk of hepatitis B.

Post-exposure prophylaxis is recommended for babies born to HBV-infected mothers and persons accidentally inoculated or contaminated by exposure to potentially infected blood or body fluids.

The schedule requires a minimum of three doses with or without a fourth booster dose. The exception is for children given adult strength vaccines where two doses are sufficient. Children aged one to 15 can receive two doses of Ambirix or children aged 11 to 15 can receive Engerix B, at zero and six months.

In most risk groups and for post-exposure prophylaxis, an accelerated schedule should be used. The vaccine is given at zero, one and two months. For those who are at continued risk, a fourth dose is given at 12 months. An alternative schedule of zero, one and six months can be used but only where rapid protection is not required and there is a high likelihood of compliance.

An extension to the product licence for Engerix-B has been granted to allow for a very rapid immunisation schedule of three doses given at zero, seven and 21 days. When this schedule is used, a fourth dose should be given 12 months after the first dose. This schedule is licensed for use on occasions where people over the age of 18 are at immediate risk and a faster induction of protection is necessary (persons travelling to areas of high endemicity, IDUs and prisoners).

Individuals at continuing risk of infection should be offered a single reinforcing dose after five years.

Those at risk of occupational exposure, such as healthcare and laboratory workers have the right to know if they have been protected under the Control of Substances Hazardous to Health (COSHH) regulations. Antibody titres should be checked one to four months after completion of the primary vaccination course. Anti-HBs levels above 100mIU/ml are desired. Those with levels of 10 to 100mIU/ml should receive one additional dose of vaccine at that time and a reinforcing dose at five years as recommended above. An antibody level below 10mIU/ml is classified as a non-response. They will need testing for current or past infection, and a repeat course of the vaccine is recommended followed by re-testing. Those who still do not respond will require HBIG protection if exposed to the virus.

Vaccination of high-risk groups

Selective hepatitis B vaccination is followed in the United Kingdom, rather than universal vaccination. Many other countries in Western Europe have recently introduced universal vaccination of infants (using combination vaccines) or adolescents. The UK policy is under constant review and the cost-effectiveness of such a programme is currently being reassessed. Even if a universal policy was to be implemented in childhood, possibly with an adolescent catch up programme, it would take many years to cover all the people in high risk groups. It is therefore vital that all opportunities are taken to ensure that those at high risk are offered vaccination and that health care workers do not introduce any unnecessary barriers to vaccination of high risk individuals.

Selective hepatitis B vaccination of the following high risk groups is recommended:

- infants born to HBsAg carrier mothers should be vaccinated immediately after birth
- injecting drug users (IDUs)
- individuals who change sexual partners frequently, particularly men who have sex with men (MSM)
- male and female sex workers
- close family contacts of a case or carrier
- families adopting children from countries with high to intermediate prevalence of hepatitis B
- foster carers
- travellers to high prevalence areas
- individuals receiving regular blood or blood products (such as haemophiliacs) and their carers
- patients with chronic renal failure
- health care workers and laboratory staff
- staff and residents of residential accommodation for those with severe learning disabilities

- other occupational risk groups such as morticians and embalmers
- inmates and staff of custodial institutions
- patients with chronic liver disease.

Some of these groups are not well-defined and can be difficult to target. Vaccination coverage of intravenous drug users has been improving, however a large proportion of at risk groups are not receiving vaccine. Because of the high HBsAg carrier rates among ethnic minorities and the evidence that many carriers acquired infection during childhood prior to their emigration to the UK, high levels of vaccination in those at high risk will need to be maintained even if the incidence of infection in the UK declines markedly.

GP practices may choose not to provide vaccination services for those at travel or occupational risk or may impose a charge. Patients travelling can be referred to travel health clinics where appropriate. Those at occupational risk should be advised that their employers have a statutory obligation to arrange for and pay for the vaccine, if an employee is assessed to be at risk as a result of their work.

The Joint Committee on Vaccination and Immunisation is currently examining the feasibility and cost effectiveness of various additional strategies including maintaining the status quo, widening the current risk groups, or of introducing either universal infant or adolescent vaccination programmes or both.

A full discussion of hepatitis B vaccination, dosing and scheduling can be found in the updated version of the Green Book: http://www.dh.gov.uk/en/PublicHealth/HealthProtection/Immunisation/Greenbook/DH_4097254

Preventing perinatal transmission

Post-exposure prophylaxis is particularly recommended for babies born to HBsAg positive mothers, including mothers who have had acute hepatitis B during pregnancy. Hepatitis B infection can be transmitted from infected mothers to their babies by perinatal transmission, conferring a high risk of chronic disease.

Perinatal transmission can be effectively prevented in over 90% of cases by appropriate vaccination starting at birth of all infants born to HBsAg positive mothers. Department of Health guidelines recommend that all pregnant

women should be offered screening for hepatitis B infection during each pregnancy. If infection is found, confirmatory testing and testing for HBeAg or anti-HBe should follow. All babies born to these mothers should receive a complete course of vaccine.

Babies born to mothers who are HBsAg positive and HBeAg-positive (or with no confirmation of the presence of anti-HBe) should receive HBIG as well as active immunisation. Similarly, babies born to mothers with acute hepatitis B or known to have HBV DNA level equal to or above 1×10^6 IU/ml and babies weighing less than 1500g born to mothers who are HBsAg positive, should receive both hepatitis B immunoglobulin and immunisation.

HBIG should be given, immediately after delivery or within 24 hours and needs to be ordered well in advance of the birth. It may be given simultaneously with vaccine but at a different site.

For post-exposure prophylaxis in babies born to HBV-infected mothers, the accelerated immunisation schedule should be used.

Babies receive a dose of vaccine at birth followed by doses at one and two months of age and a fourth dose at 12 months.

Testing for HBsAg at one year of age, at the time of the fourth dose, is required to identify any children for whom the intervention has failed and who have become carriers. These children will require on-going assessment and further management.

Women with high viral loads (i.e. HBV DNA $> 10^7$ IU/ml) and in cases where transmission to a previous infant has occurred during childbirth, may be at risk of transmission despite HBV vaccination and HBIG use and can be considered for antiviral therapy from 32 weeks of pregnancy. There is some evidence that a short treatment can reduce viral load and therefore the risk of transmission. If the apparent safety and lack of teratogenicity of nucleoside analogues in pregnancy can be verified, treatment of the mother either throughout, or in the third trimester of pregnancy to reduce mother infant transmission may be recommended. Ongoing disease management in the mother has also to be taken into account.

However, the risks, benefits and limited evidence for this approach should be discussed with the patient.

Safety precautions for occupational exposure

All blood and body fluids should be treated as being potentially infectious. The following precautions are recommended:

- wash hands after each patient contact and after contact with blood or body fluids
- use appropriate personal protective equipment
- wear disposable gloves whenever working with blood or body fluids
- wear disposable plastic aprons/impermeable gowns when there is the possibility of splashing with blood or body fluids
- use eye protection (visors, goggles or safety spectacles) when blood, body fluids or flying contaminated debris/tissue might splash into the face
- cover any cuts or abrasions with waterproof plasters
- dispose of sharps immediately into appropriate, puncture-proof sharps bins
- do not overfill sharps containers and never re-sheath needles.

Many incidents of occupational exposure can be prevented with adherence to standard precautions for the safe handling and disposal of clinical waste.

Overview

Transmission of HBV is by exposure to body fluids, most commonly blood. Highest amounts of the virus are present in blood.

Globally, the major source of HBV infection is perinatal transmission. In the UK, infection is most commonly acquired through injecting drug use or sexual intercourse.

Prevalence in the UK is highest in those born in high endemicity countries, who are likely to have acquired the infection at birth or early in childhood.

Hepatitis B has a complex natural history and causes a range of disease. It has different clinical manifestations depending on the patient's age at infection, their immune status and the stage at which the disease is diagnosed. Substantial health care resources are usually required to

manage patients. In light of this, patients with mild disease may require monitoring rather than treatment, while treatment should be indicated for chronic progressive disease.

The goal of therapy is to prevent progression of the disease to cirrhosis and end stage liver disease.

Treatment may involve finite or long-term therapy, or a therapy course undefined at the beginning and dependent on the patient's initial response.

Treatment should be given only when indicated. This should be carefully explained to patients to avoid perceptions of mismanagement when therapy is not forthcoming. Patients should be educated regarding liver function tests and preventing transmission of their infection.

Pre-exposure immunisation should be aimed at those at increased risk of hepatitis B because of lifestyle, occupation or other factors.

Post-exposure vaccination is generally used to prevent infection in babies born to infected mothers, mothers infected during pregnancy, needlestick injuries, accidental inoculations or contaminations.

With the introduction of orally administered antiviral agents and newer pegylated interferons with sustained antiviral activity, a new era for the treatment of hepatitis B has begun. These therapies promise to improve the outcome of chronic HBV but will make further demands on still-evolving disease management and ascertainment, particularly when predicting the benefit of monotherapy against combination therapy.

Useful words

Albumin – a protein manufactured by the liver. Low albumin levels are an indication of liver damage.

ALT – alanine aminotransferase, a liver enzyme that enters the blood following liver damage. The test is used to monitor and assess the degree of damage in patients infected with chronic HBV.

Antigen – a protein manufactured by an invasive pathogen that can trigger the body's immune response, leading to the production of an antibody.

AST – aspartate aminotransferase, a liver enzyme but less liver specific than ALT.

Anti-HBc – anti-hepatitis B core antibody, an antibody to the core antigen HBc. It is found in acute infection, in chronic carriers and in those who have cleared the infection.

Anti-HBe – antibody to the hepatitis Be antigen, present in those recovering from acute hepatitis B infection, along with anti-HBc and anti-HBs. In patients with chronic hepatitis B, anti-HBe usually becomes positive when the virus disappears from the body.

Anti-HBs – antibody to the hepatitis B surface antigen, indicating recovery and immunity from HBV infection.

Bilirubin – a breakdown product of haemoglobin; increases can indicate liver disease, especially in disease of the bile ducts.

CccDNA – covalently closed circular DNA, the main host reservoir of HBV in the infected liver.

Compensated disease – treatment has counterbalanced damaged liver function.

Decompensated disease – treatment can no longer counterbalance severely damaged liver function, leading to failure.

De novo – from the beginning.

Fulminant – disease with rapid onset and following a short, severe course.

HBeAg – hepatitis B e-antigen, a marker detected in blood indicating early, active viral infection. Also can be used as a marker for a person's infectivity.

HBeAg-negative – chronic hepatitis B, appearing after lengthy infection where patients stop producing the 'e' antigen (HBeAg) but may continue to produce e-antibodies (anti-HBe).

HBeAg-positive – chronic hepatitis B characterised by presence of the hepatitis B e-antigen. Acquired during early infection, this is the most common form of the disease worldwide.

HbsAg – hepatitis B surface antigen, the earliest indicator of acute infection. HbsAg appears in the blood about six weeks following infection and usually disappears three months after acute illness.

Persistence for more than six months indicates carrier state/chronic infection.

HBV DNA – hepatitis B viral DNA in the host's blood, a marker for infection.

Hepatitis B anti-core IgM antibody – an antibody produced by the immune system indicating recent infection. It is later replaced by the IgG anti-core antibody which stays in the blood for life.

Hepatocyte – liver cell.

IDU – intravenous drug user.

Immunomodulatory – ability to modulate the immune response to a desirable level.

Immunoglobulins – proteins of animal origin with known antibody activity, synthesized by lymphocyte and plasma. Found in serum, other body fluids and cell tissues, they bind to invading organisms to destroy them.

Glomerulonephritis - inflammation of the small structures inside the kidneys that are known as glomeruli.

Osteopaenia – inflammation of the small structures inside the kidneys that are known as glomeruli.

Parenteral – injection via routes other than the alimentary tract, such as subcutaneous, intramuscular and intravenous.

Percutaneous injury – injury through the skin.

Perinatal transmission – transmission of the virus from mother to child during birth delivery.

Polyarteritis - an autoimmune disease characterised by spontaneous inflammation of the arteries (arteritis) of the body.

Polymerase Chain Reaction (PCR) – a test providing a numerical value for the viral load (the amount of virus present in blood).

Pre-core mutant – a form of the hepatitis B virus without the hepatitis B e-antigen.

Prothrombin time – a test that measures the clotting time of plasma.

Seroconversion – a change in the patient's antibody status from negative to positive. In HBV, this is the disappearance of the hepatitis B e-antigen (HBe-antigen, a marker of HBV replication) and the appearance of antibodies specific for this antigen (HBe-antibody).

HBsAg seroconversion is the ideal, but rarely achieved.

Vasculitis – inflammation of the blood vessels.

Viremia – presence of virus in the blood.

Who else can help?

DrugScope

Prince Consort House
Suite 204 (2nd Floor)
109/111 Farringdon Road
London EC1R 3BW
Tel: 020 7520 7550
Fax: 020 7520 7555
www.drugscope.org.uk

Drugscope is the UK's leading independent centre of expertise on drugs. Their aim is to inform policy development and reduce drug-related risk.

Health and Safety Executive (HSE)

Rose Court
2 Southwark Bridge
LONDON
SE1 9HS
Tel: 0845 345 0055
www.hse.gov.uk

HSE's job is to protect people against risks to health or safety arising out of work activities.

Health Protection Agency (HPA)

Health Protection Agency Central Office
7th Floor
Holborn Gate
330 High Holborn
London
WC1V 7PP
Tel: 020 7759 2700 / 2701
www.hpa.org.uk

The Health Protection Agency is an independent UK organisation that was set up by the government in 2003 to protect the public from threats to their health from infectious diseases and environmental hazards. It does this by providing advice and information to the general public, to health professionals such as doctors and nurses, and to national and local government.

Hepatitis B Foundation UK

The Great Barn
Godmersham Park
Canterbury
Kent CT4 7DT
Tel: 01227 738 279 (office) 07768 847545 (mobile) Monday to Friday
9.30am – 5.30pm
Helpline: 01243 673 388 Monday to Thursday 10.30am – 3pm
www.hepb.org.uk

A charity that raises awareness about the prevention, treatment and management of hepatitis B and offers advice, information and facilitates networking between patients, their families and professionals.

Macmillan Cancer Support

89 Albert Embankment
London SE1 7UQ
Tel: 0808 800 1234 Monday to Friday 9am – 8pm
Fax: 020 7840 7841
www.cancerbackup.org.uk

A leading cancer information service, giving cancer information, practical advice and support for cancer patients, their families and carers.

Mainliners

2nd Floor, Downstream Building
1 London Bridge
London SE1 9BG
Tel: 020 7022 1890
Fax: 020 7022 1893
Email: admin@mainliners.org.uk
www.mainliners.org.uk

Working to improve quality of life and prevent HIV, hepatitis and drug related harm through outreach, information and education.

NICE

Tel: 0845 003 7780
www.nice.org.uk

NICE is the NHS body responsible for producing national guidance on health technologies and treatments. NICE assesses technologies for their clinical and cost-effectiveness. Once it has recommended a medicine, the NHS is obliged to make it available for patients. NICE has issued guidance on adefovir and pegylated interferon alpha-2a and also on entecavir for hepatitis B, and is preparing guidance on telbivudine and also on tenofovir. More information is available on the NICE website.

Terrence Higgins Trust

Central Office
314-320 Grays Inn Road
London WC1X 8DP
Tel: 020 7812 1600
Email: info@ttht.org.uk
www.ttht.org.uk

A charity offering a wide range of support services for people affected by HIV. This website provides useful information about hepatitis B and HIV/ HBV co-infection. For further information about the three main types of viral hepatitis affecting gay men you can visit www.hepinfo.org, another site produced by the Terrence Higgins Trust.

Further information for patients

The British Liver Trust also publishes 'A professional's guide to hepatitis C and injecting drug use' and a large range of leaflets about the liver and liver problems written for the general public.

Leaflets that the general public may find particularly helpful include:

- *Alcohol and liver disease*
- *Cirrhosis of the liver*
- *Diet and liver disease*
- *Hepatitis B*
- *Hepatitis C*
- *Hepatitis D and E*
- *Liver cancer*
- *Liver disease tests explained*
- *Liver transplantation*
- *Life after liver transplant*

Information on hepatitis B is also available in the following languages which can be downloaded from the Trust website: Punjabi, Bengali, Gujarati, Polish, Chinese (Cantonese and Mandarin), Hindi and Urdu.

Contact us for more information:

Tel: 0800 652 7330

Email: info@britishlivertrust.org.uk

Web: www.britishlivertrust.org.uk

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