

Treatment for hepatitis B

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Hepatitis B virus is estimated to have infected 350 million individuals globally, accounting for over 500 000 deaths each year.¹ An effective and widely available vaccine provides protection from infection, but treatment is rarely curative. Recent developments in antiviral treatment have brought the opportunity for greatly improved management of those chronically infected with hepatitis B virus, and for patients infected both with HIV and hepatitis B virus there is now the potential to treat both viruses with a simplified combination of drugs. This brief review discusses detection, referral, and management of patients with hepatitis B virus infection.

Who is at risk of acquiring hepatitis B virus infection?

Hepatitis B virus is endemic in many countries of the world (figure 1), particularly in South East Asia, Central Asia, the Amazon Basin, and Africa. Transmission occurs through contact with infected blood or body fluids.² The infection is commonly acquired from an infected mother at the time of birth (vertical transmission) or from infected family members during childhood (horizontal transmission). When exposure to the virus occurs early in life, the likelihood of chronic infection is high: 90% for vertical transmission, 8-15% for horizontal transmission.^{3,4} For those born or brought up in regions with a low prevalence of the virus, transmission through other routes is more common (box 1).⁵ Acquisition of infection in adult life is

Box 1 | Risk factors for hepatitis B virus infection in countries with low prevalence of the virus

- Migration from a country with a high prevalence of the virus
- Sexual intercourse (particularly for men who have sex with men)
- Intravenous drug use
- Contaminated blood products
- Occupational exposure

associated with a likelihood of chronic infection of less than 5%.⁶

Why should patients at risk be tested for hepatitis B?

The benefits to an individual of knowing their hepatitis B status are threefold. Firstly, there is the opportunity to prevent progression of their infection to the point of cirrhosis or hepatocellular carcinoma,⁷ an opportunity made more feasible by recent developments in treatment. About 700 000 people are estimated to die of hepatocellular carcinoma each year, and 54% cases are thought to result from hepatitis B virus.⁸ Secondly, treatment and other preventive measures can reduce the transmission of the virus to a sexual partner, household contacts, or unborn children.³ Finally, for those with no evidence of hepatitis B virus but who are at ongoing risk of infection, vaccination can be offered.

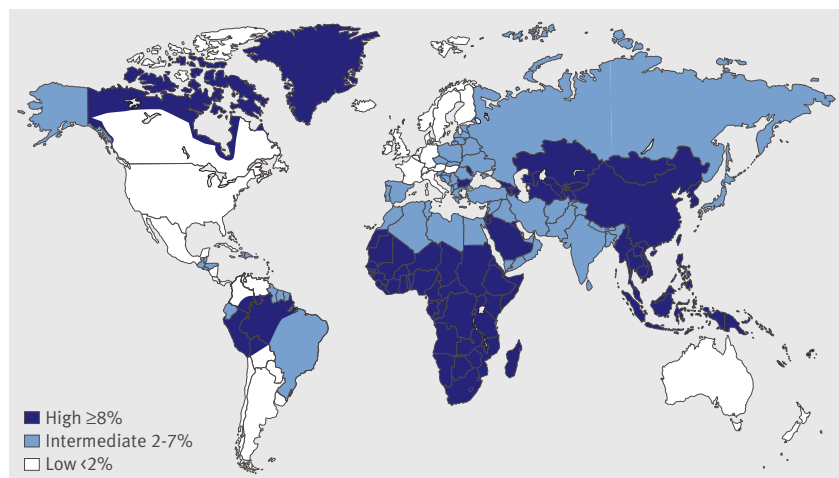


Fig 1 | Prevalence of hepatitis B surface antigen worldwide, 2006. Adapted from Centers for Disease Control and Prevention. *Health information for international travel*. 2010. <http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/hepatitis-b.aspx>

SOURCES AND SELECTION CRITERIA

We searched PubMed and online resources for recent articles and reports relevant to treatment for hepatitis B published from 1980 to 2009. This included work on prevalence, prognosis, and treatment, including treatment strategies and specific drugs

SUMMARY POINTS

Hepatitis B is common in UK practice, particularly among those born in countries with high prevalence
Hepatitis B surface antigen is the screening test of choice in most circumstances
Individuals positive for hepatitis B surface antigen should be referred for specialist evaluation
Liver biopsy remains an important part of assessment
New treatments to reduce long term complications with favourable side effect profiles are available
Most individuals at risk of death from hepatitis B cannot access treatment

Box 2 | Investigations under specialist care

Investigations related to hepatitis B

- Surface antigen (HBsAg), hepatitis B e antigen (HBeAg), anti-HBe, anti-HBs, anti-HBcore
- Quantitative hepatitis B virus DNA
- Hepatitis B virus genotype (for those considered for interferon)
- Delta virus serology

General liver investigations

- Full blood count
- Bilirubin
- Liver enzymes
- Clotting
- Ferritin
- Lipid profile
- Autoantibody screen
- Caeruloplasmin
- Tests for hepatitis C virus and HIV

Screening for liver cancer

- Ultrasonography
- α fetoprotein

Staging of disease

- Fibroelastography
- Liver biopsy

How do you diagnose the presence of hepatitis B virus infection?

The screening test for hepatitis B is the presence in blood of hepatitis B surface antigen. Chronic hepatitis B infection is defined as persistence of hepatitis B surface antigen for more than six months. In patients without evidence of hepatitis B surface antigen where it is important to know whether there has been previous infection—for example, in those about to receive chemotherapy—previous exposure can be assessed by presence of hepatitis B core antibody.

Who should be tested for hepatitis B?

Investigations in at-risk patients with abnormal liver transaminases (alanine aminotransferase and/or aspartate aminotransferase) routinely include testing for hepatitis B. However, reported laboratory ranges (usually 5-40 IU/l for alanine aminotransferase and aspartate aminotransferase) may be too liberal, and some specialists recommend that the upper limits should be reduced to 30 IU/l for men and 19 IU/L for women.⁹ This means that liver function tests alone could miss cases of hepatitis B.¹⁰

Individuals seeking health care will be tested as part of routine protocols (for example, in renal dialysis units) if they are considered to be at risk, but in many areas with

migrant communities healthcare providers recognise that case finding or screening strategies might be required to identify asymptomatic individuals who would benefit from treatment. The evidence base for recommendations on screening is limited by a scarcity of studies. However, recent US guidelines have been expanded to recommend testing for all those who were born in a region with a prevalence of hepatitis B surface antigen of >2% or (if unvaccinated) for children whose parents were born in such regions.¹¹

How should individuals positive for hepatitis B surface antigen be managed?

We believe that detection of hepatitis B surface antigen should prompt referral for assessment by a specialist with an interest in viral hepatitis (usually a hepatologist or infectious diseases specialist). Urgent referral might be necessary for an unwell or pregnant individual.

Detailed guidelines on the management of hepatitis B have been published by professional organisations.^{12 13} Evaluation of hepatitis B involves an assessment of the activity of the viral infection and a clinical assessment of (a) the degree of liver disease and (b) the extent to which liver disease can be attributed to the hepatitis B virus infection or to the presence of common liver comorbidities (for example, steatohepatitis). Box 2 outlines routine investigations in specialist care.

The distinction between hepatitis B viral activity and liver disease related to hepatitis B virus is important and sometimes the source of confusion. Table 1 shows definitions of different phases of chronic hepatitis B virus infection and disease. Individuals infected in childhood (which is most of those infected worldwide) often experience a period of immunotolerance during which the virus is highly replicative but minimal liver damage occurs. The infection will eventually progress to a hepatic phase associated with inflammation and liver fibrosis. Spontaneous resolution of the hepatic phase may occur with loss of hepatitis B e antigen (HBeAg) and appearance of anti-HBe. This results in an “asymptomatic” phase with normal liver functions tests and low viral load (<2×10³ IU/ml). Many adult patients with chronic hepatitis B virus infection in European settings will present in this phase of disease. In the past they may have been falsely reassured and discharged. It is now clear that viral reactivation will occur in 15-20% of this group of patients, causing HBeAg negative hepatitis.¹⁴

The role of liver biopsy

Liver biopsy continues to play an important role in determining who should start treatment. The information it can provide on the aetiology and severity of liver disease cannot easily be substituted by non-invasive tests. Different histological grading systems are used in different centres. The most commonly used are the Ishak and Metavir scores, but all systems provide some measure of inflammation (current activity) and fibrosis (more chronic scarring).

Although in the past physicians and patients have expressed concerns about the safety of liver biopsy, developments in technology, particularly ultrasonography, mean that complications from the procedure are now rare when the procedure is carried out regularly.¹⁵ Newer, non-invasive

Table 1 | Phases of chronic hepatitis B infection

Investigation	Immune tolerant (phase 1)	Immune reactive (phase 2)	Carrier of inactive hepatitis B virus (phase 3)	Chronic hepatitis negative for hepatitis B e antigen (phase 4)
Hepatitis surface antigen	Positive	Positive	Positive	Positive
Hepatitis B e antigen	Positive	Positive	Negative	Negative
Anti-HBe	Negative	Negative	Positive	Positive
Alanine aminotransferase	Normal	High	Normal	High or fluctuating
Hepatitis B virus DNA (IU/ml)	>2×10 ⁵	>2×10 ⁴	<2×10 ²	>2×10 ³
Inflammation on histology	None or minimal	Active	None or minimal	Active

imaging methods, particularly the FibroScan technique,¹⁶ are gaining favour in routine practice, though validation data are still needed in different settings. The hope has been that non-invasive biomarkers of liver fibrosis, including proprietary tests such as ELF (enhanced liver fibrosis), FibroTest, and others,¹⁷ can substitute for biopsy, which at best is unpleasant. However, the imperfect performance of non-invasive markers in clinical practice means they have yet to be widely adopted and further improvements are a priority for research.

What is the goal of treatment?

The goal of treatment for individuals with chronic hepatitis B virus infection is to prevent morbidity and mortality related to the disease. This can be achieved with a finite course of interferon therapy or long term viral suppression with nucleoside/nucleotide analogues.⁷ There are recommended surrogate end points for treatment.¹³ Loss of hepatitis B surface antigen may be achieved, and this can be regarded as remission of the infection. In patients positive for HBeAg, seroconversion to become negative for HBeAg or positive for anti-HBe is associated with sustained suppression of hepatitis B virus DNA after treatment withdrawal and can be considered an end point of the therapy. However, cohort studies have identified the importance of high viral load in determining disease progression.^{18 19} The availability of newer treatments means that increasing emphasis is placed on the need to suppress viral load to below the limit of detectable DNA (usually below 10-15 IU/ml, depending on the assay),²⁰ with long term therapy.

Who should be treated and with what?

A systematic review of numerous clinical trials of interferon therapy in chronic hepatitis B infection found that for a subgroup of patients a finite course of treatment with pegylated interferon could be given without virological resistance and with a lasting response.²¹ Several factors have been associated with a good response to interferon (box 3). However, even with stringent patient selection, response rates are in the region of 30% at one year for patients positive for HBeAg and 15% for patients negative for HBeAg.²² Associated side effects mean that pegylated interferon is not often used in clinical practice.

The development of newer, potent, oral antivirals (table 2) with a favourable toxicity profile has made long

Box 3 | Characteristics associated with a good response to interferon among patients with chronic hepatitis B virus infection

- Alanine aminotransferase more than twice the upper limit of normal
- Hepatitis B virus DNA <10⁶ IU/ml
- Age <50 years
- Hepatitis B virus genotype A or B
- Female
- Non-vertical transmission

term suppression of hepatitis B virus replication feasible, with sustained viral suppression response rates that are cumulatively better than interferon treatment. Long term lamivudine monotherapy has been shown to improve clinical outcomes, particularly in those with late stage disease, and to prevent progression to cirrhosis or liver cancer.^{7 23} Adefovir, sometimes used in combination with lamivudine, has also shown some benefit, but its use is limited by its slow action, lack of potency, and potential for renal toxicity.²⁴

The best choice of antiviral is contentious. Although lamivudine is cheap and well tolerated, the rate at which viral resistance emerges is unacceptably high. Newer agents that can provide improved viral suppression with lower rates of emerging resistance and less toxicity have recently been licensed and reviewed by the National Institute for Health and Clinical Excellence (NICE): entecavir²⁵ and tenofovir²⁶ were both recommended as options for the treatment of individuals with chronic hepatitis B (both HBeAg positive and HBeAg negative), but telbivudine was not.²⁷ Although most specialists would now use tenofovir or entecavir as first line treatment, some still prefer combination treatments in those at high risk of resistance.

Side effects of treatment

Of drugs active against hepatitis B virus, the greatest clinical experience is with lamivudine, used widely in the treatment of patients with hepatitis B virus or HIV, or with both. The side effect profile of lamivudine is good, with very few patients experiencing problems; its use is decreasing, however, primarily because of concerns about the emergence of resistant virus.²⁸ Tenofovir is being used increasingly in HIV patients, and in these patients renal toxicity and the

Table 2 | Characteristics of drugs used to treat hepatitis B virus infection. Adapted from Dienstag et al² and Lai et al²⁰

	Lamivudine	Telbivudine	Adefovir	Tenofovir	Entecavir
Class	L-nucleosides	L-nucleosides	Acyclic nucleoside phosphonates	Acyclic nucleoside phosphonates	Deoxyguanosine analogue
Dose	100 mg/day orally	600 mg/day orally	10 mg/day orally	300 mg/day orally	0.5 mg/day*
Side effects	Rare	Rare	Renal impairment, phosphate loss	Renal impairment, phosphate loss	Rare
Drug responses in HBeAg positive patients					
HBeAg seroconversion at 1 year (% of patients)	16-21	22	12	21	21
HBV undetectable at 1 year (% of patients)	36-44	60	13-21	80	67
Resistance at 1 year (% of patients)	24	4	0	0	<1
Drug responses in HBeAg negative patients					
HBV undetectable at 1 year (% of patients)	72	88	63	93	90
Resistance at 1 year (% of patients)	21	3	0	0	<1

HBeAg=hepatitis B e antigen; HBV=hepatitis B virus.

Current costs for one year's prescription are £1015 (lamivudine), £3769 (telbivudine), £3664 (adefovir), £3094 (tenofovir), £4404 (entecavir).

*A higher dose is required in the setting of HBV resistance.

QUESTIONS FOR FUTURE RESEARCH

- Who should be screened for hepatitis B virus?
- Which patients will not get complications and could avoid treatment?
- How do we best monitor patients before and after starting treatment?
- What is the most efficient way to eradicate hepatitis B virus infection?
- How do we best use the new antivirals available for treatment?
- How do we get treatments for hepatitis B virus to resource-poor settings?

metabolic consequences of urinary phosphate loss have been observed (table 2).²⁹ Experience is more limited in those infected with hepatitis B virus, and renal toxicity has not been described.

What are the risks of poor adherence to treatment?

Two major risks come from poor adherence to treatment. Firstly, stopping suppressive therapy for hepatitis B virus can lead to a flare-up of liver disease related to the virus. This can be fatal, although more commonly in patients with advanced cirrhosis.³⁰ Secondly, there is a risk of developing resistance. This can lead to a flare-up of disease and to the development of accumulation of resistance mutations, some of which may compromise alternative treatment options.

Special situations**Acute hepatitis**

The differentiation between acute hepatitis B, a flare-up of chronic hepatitis B, and hepatitis resulting from other viruses can sometimes be difficult as IgM against the core antigen can be positive in all settings. Of patients with acute hepatitis B virus, 95-99% will develop antibody to hepatitis B surface antigen and recover spontaneously. Some evidence exists that antivirals can be beneficial in the acute setting when there is derangement of coagulation (international normalised ratio >1.5),³¹ but no randomised trials have been conducted to help understand this better.

Coinfection of hepatitis B virus and HIV

Hepatitis B virus and HIV have an important relation, not only because of their overlapping transmission risks but also because of the clinically important interactions of the two diseases.³² All the agents in table 2 have shown some evidence of *in vivo* activity against HIV. For HIV patients, who are often also infected with hepatitis B virus, both viruses can be treated with a simplified combination of drugs (usually tenofovir and emtricitabine). However, patients with hepatitis B virus who are starting antiviral therapy must be offered HIV testing as monotherapy or even dual therapy can rapidly lead to the emergence of HIV resistance mutation, thereby limiting the treatment options.

Pregnancy

The universal prevention of transmission of hepatitis B virus from mother to child during the perinatal period remains an achievable goal. Testing of mothers for hepa-

titis B surface antigen allows those with a positive result to get hepatitis B immune globulin and early vaccination for their children, a strategy that has been proved to reduce transmission by 95-99%. The advent of low toxicity antiviral treatment might help in this regard too, with emerging evidence that addition of antivirals in the third trimester, particularly for those with high viral loads, might further reduce infant infection.³

Risk of reactivation of hepatitis with immunosuppression

Individuals positive for hepatitis B surface antigen are at risk of a flare-up in disease if given immunosuppressants or cytotoxic chemotherapy.³³ In addition to routine screening for hepatitis B surface antigen, it is now recommended that exposure to hepatitis B virus should also be assessed using anti-HB core antibody as even patients who are negative for the surface antigen are at risk of reactivation and should be given prophylactic treatment. Guidelines recommend that patients positive for hepatitis B surface antigen should receive antiviral therapy for the duration of the immunosuppressive period and for 12 months thereafter.¹³

A global perspective and future developments

The coming years will bring important changes in our approach to hepatitis B virus. With a growing range of treatments available, the rationale for active case finding and screening will become stronger and needs to be informed by better evidence. How new treatments are best deployed will need to be explored through trials of different drug combinations and treatment strategies. With the existing tools for treatment of hepatitis B virus, the time is right for a global initiative to deliver the treatment to those most in need.³⁴ This initiative will be debated at the World Health Assembly in early 2010, and it has to be hoped that advances in treatment that have been achieved in recent years can be implemented beyond wealthy countries.

Contributors: The authors jointly planned the review. GSC wrote the first

ADDITIONAL EDUCATIONAL RESOURCES**For healthcare professionals**

- American Association for the Study of Liver Diseases (www.aasld.org)—US based professional organisation publishing detailed management guidelines for viral hepatitis
- European Association for the Study of the Liver (www.easl.eu)—Europe based professional organisation publishing detailed management guidelines for viral hepatitis

For patients

- British Liver Trust (www.britishlivertrust.org.uk/)—UK charity offering support and information
- Hepatitis B Foundation, UK (www.hepb.org.uk/)—UK charity offering advice and information to individuals with hepatitis B and to their families and friends; it also facilitates networking between patients and/or families
- Hepatitis B Foundation, USA (www.hepb.org/)—US based foundation serving as a primary source of information for patients and their families, the medical and scientific community, and the general public

TIPS FOR NON-SPECIALISTS

- Consider hepatitis B in anyone born in a country with high prevalence
- A positive hepatitis B surface antigen result requires either investigation or referral
- A flare-up of hepatitis requires detailed assessment to establish the cause
- All patients with hepatitis B require HIV testing (and vice versa)

draft, and all authors worked on subsequent revisions. MRT is the guarantor.

Competing interests: JM has participated in advisory boards and clinical trials and has given lectures for GlaxoSmith Kline, Gilead, Roche, Schering Plough, and Bristol-Myers Squibb. MRT has participated in advisory boards for Gilead and Bristol-Myers Squibb.

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ANSWERS TO ENDGAMES, p 107. For long answers go to the Education channel on bmj.com

PICTURE QUIZ

The perils of a “FOOSH”

- 1 The radiograph shows completely displaced Salter-Harris II distal radial fracture with dorsal angulation.
- 2 The radiographs are inadequate because they should extend to the elbow.
- 3 The neurovascular structures are of concern, particularly the median nerve, and to a lesser degree the radial artery and superficial branch of the radial nerve.
- 4 Median nerve motor function can be assessed by testing the abductor pollicis brevis via thumb abduction; sensory function can be tested in the radial 3 1/2 fingers (classic distribution of thumb, index finger, middle finger, and radial half of ring finger). The superficial branch of the radial nerve can be tested by checking sensation in the first web space. Finally the presence of a radial pulse should also be checked.
- 5 The Salter-Harris classification should be applied to this type of injury.
- 6 Urgent reduction of the fracture by performing a manipulation under general anaesthetic should be undertaken, followed by the application of a well moulded plaster. If the fracture is unstable it should be fixed using a percutaneous wire. The patient should then be regularly examined to assess median nerve function.

CASE REPORT

Microscopic colitis in primary care

- 1 Chronic diarrhoea can be caused by pathology of the colon, small bowel, or pancreas; infection; endocrine disease; and autonomic causes. Consumption of exogenous substances that stimulate diarrhoea should also be considered.
- 2 Microscopic colitis is thought to account for 10% of cases of chronic diarrhoea. It classically causes watery diarrhoea in the absence of blood or mucus in the stool. Diagnosis is histological through multiple colonic biopsies.
- 3 To date, budesonide is the only treatment that significantly improves symptoms.

STATISTICAL QUESTION

Study design II

b