Chronic Hepatitis B: Update of Recommendations

Anna S.F. Lok and Brian J. McMahon

A n estimated 350 million persons worldwide and 1.25 million in the United States are infected with hepatitis B virus (HBV). Hepatitis B carriers are at risk for development of cirrhosis and hepatocellular carcinoma (HCC). The natural history of chronic HBV infection is variable. Persons with chronic HBV infection need lifelong monitoring to determine if and when intervention with antiviral therapy is needed and to observe for serious sequelae. These guidelines were developed under the auspices of, and approved by, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases. The original guidelines were published in HEPATOLOGY 2001;34:1225–1241. In light of recent progress, particularly in the treatment of chronic hepatitis B, these guidelines were updated in September of 2003. A complete version of the updated guidelines, including a review of recently published literature, can be found at the AASLD web site, www.aasld.org. Following is a summary of the updated recommendations for treatment of chronic hepatitis B. The recommendations were graded as I (randomized controlled trials), II-1 (controlled trials without randomization), II-2 (cohort or case-control analytic studies), II-3 (multiple time series, dramatic uncontrolled experiments), and III (opinions of respected authorities, descriptive epidemiology).

Summary of Recent Literature on the Treatment of Chronic Hepatitis B

Lamivudine

Approved for Use in Children. In a controlled trial that involved 286 children aged 2 to 17 years, randomized to lamivudine (3 mg/kg/d up to 100 mg/d) or placebo, hepatitis B e antigen (HBeAg) seroconversion was observed in 22% lamivudine-treated children versus 13% placebo controls (P = .06), while HBeAg loss was observed in 26% and 15%, respectively (P = 0.03). HBeAg seroconversion rate was higher among children with elevated alanine aminotransferase (ALT) levels. Lamivudine-resistant mutation was detected in 19% of treated children during the 1-year period.

Durability of HBeAg Seroconversion. Among patients who experienced HBeAg seroconversion during lamivudine treatment, the durability of response after cessation of therapy has ranged from 38% to 77%. The 3-year cumulative relapse rate varied from 36% to 54%, with most of the relapses occurring during the first year posttreatment.

Lamivudine Resistance. The risk of developing lamivudine resistance increases with the duration of therapy. In a study from Asia, genotypic resistance increased from 14% in year 1 to 38%, 49%, 66%, and 69% after 2, 3, 4, and 5 years, respectively, of treatment. Long-term follow-up studies showed that over time, the initial benefit is negated in patients with lamivudine-resistant mutants. In one study that compared liver histology in 63 patients prior to and after 3 years of lamivudine treatment, necro-inflammatory scores were improved in 77% and worsened in 5% of patients without lamivudine-resistant mutants, but improved in only 45% and worsened in 14% of those with lamivudine-resistant mutants.

For patients with confirmed lamivudine-resistance, the options include continuing lamivudine treatment as long as benefit to the patient (based on clinical assessment, ALT, and HBV DNA levels) is maintained; discontinuing treatment and monitoring for hepatitis flares; or switching to other antiviral agents such as adefovir, which are effective in suppressing lamivudine-resistant HBV. Two recent reports from Asia suggest that discontinuation of lamivudine in patients with resistant mutants is not associated with increased frequency of hepatitis flares or death, compared with those who continued to receive lamivudine. Thus, stopping lamivudine is a reasonable option for immunocompetent patients without cirrhosis, as long as they are closely monitored; but patients with underlying cirrhosis or immunosuppression should be switched to adefovir before stopping lamivudine.
**Adefovir Dipivoxil**

Adefovir dipivoxil is an orally bioavailable prodrug of adefovir, a nucleotide analog of adenosine monophosphate that inhibits both HBV reverse transcriptase and DNA polymerase activity. Adefovir has been shown to be effective in suppressing not only wild-type HBV but also lamivudine-resistant HBV mutants.

**HBeAg-Positive Patients.** In a randomized trial of 515 patients with HBeAg-positive chronic hepatitis B treated with 30-mg or 10-mg doses of adefovir or placebo for 48 weeks, histologic response, HBBeAg loss, normalization of ALT levels, and reduction of HBV DNA, compared with those who received placebo (all P < .001). \(^{10}\) HBeAg seroconversion was observed in 12% of the adefovir and 6% of the placebo groups (P = .049).

**HBeAg-Negative Patients.** In a trial of 184 patients with HBBeAg-negative chronic hepatitis B who were randomized to receive adefovir 10 mg or placebo for 48 weeks, histologic response, normalization of ALT, and undetectable serum HBV DNA by polymerase chain reaction assay were observed significantly more frequently in the treatment group (all P < .001). \(^{11}\) During year 2, the proportion of patients with undetectable serum HBV DNA and normal ALT levels increased from 46% at week 48 to 51% at week 96 among those who continued treatment, and decreased from 59% to 3% among those in whom therapy was stopped. \(^{12}\)

**Patients With Lamivudine Resistance.** In a compassionate-use study involving 128 patients with decompensated cirrhosis and 196 patients with recurrent hepatitis B after liver transplant, with lamivudine resistance, addition of adefovir was associated with a 3–4 log \(_{10}\) reduction in serum HBV DNA levels, which was sustained throughout the course of treatment. \(^{13}\) Virologic response was accompanied by stable or decreased ALT and Child-Pugh score. A pilot study in 58 patients with compensated chronic hepatitis B and lamivudine resistance found that adefovir alone had similar efficacy as combination treatment of lamivudine and adefovir in suppressing replication of lamivudine-resistant HBV. \(^{14}\)

**Safety.** Adefovir has not been evaluated in children. Nephrotoxicity (increase in serum creatinine by ≥0.5 mg/dL above baseline values on two consecutive occasions) was observed in 8% of patients who received adefovir 30 mg for 1 year and in none of the patients with compensated liver disease who received adefovir 10 mg for 1 year. However, nephrotoxicity has been reported in 2.5% of patients with compensated liver disease who received 2 years of adefovir 10 mg, and in 12% of transplant recipients and 28% of patients with decompensated cirrhosis who received 1 year of adefovir 10 mg. \(^{13,15}\)

**Dose Regimen.** The recommended dose of adefovir for adults with normal renal function is 10 mg daily orally. Dosing interval should be increased in patients with renal insufficiency. The optimal duration of adefovir treatment is unclear. Data on the durability of HBeAg seroconversion after adefovir is discontinued have not been presented. Preliminary data indicate that patients with HBeAg negative chronic hepatitis will require long-term treatment as most patients will relapse when adefovir is withdrawn after 1 year. \(^{14}\) Based on experience with lamivudine, consideration should be given to treating patients in whom HBeAg seroconversion has occurred for an additional 3 to 6 months after HBeAg seroconversion is confirmed (two occasions at least 2 months apart) to reduce post-treatment relapse. Long-term treatment will also be required for patients with lamivudine-resistant mutants, particularly those with decompensated cirrhosis or recurrent hepatitis B posttransplant.

**Adefovir Resistance.** A major advantage of adefovir is the lack of resistance after the first year of therapy, but drug-resistant mutation, asparagine to threonine (rtN236T), downstream of the YMDD motif, has been reported in 2 of 79 (2.5%) patients with HBeAg-negative chronic hepatitis B during the second year of therapy. \(^{16}\) In vitro studies confirmed that this mutation confers resistance to adefovir, but the resistant mutant appears to be susceptible to lamivudine and entecavir.

**Antiviral Prophylaxis of Hepatitis B Carriers Who Receive Immunosuppressive Therapy or Cytotoxic Chemotherapy**

Activation of HBV replication with hepatitis flares and rarely hepatic decompensation have been reported to occur in 20% to 50% of hepatitis B carriers undergoing immunosuppressive or cancer chemotherapies, especially when corticosteroids are included. \(^{17,18}\) Administration of lamivudine has been reported to reduce the frequency and severity of the hepatitis flares, and to improve survival compared to historical controls. \(^{17,19}\)

**Recommendations for Monitoring Patients With Chronic HBV Infection**

1. HBeAg-positive patients with elevated ALT levels and compensated liver disease should be observed for 3 to 6 months for spontaneous seroconversion from HBeAg to HBs antibody prior to initiation of treatment (III).

2. Patients who meet the criteria for chronic hepatitis B (serum HBV DNA >10^5 copies/mL and persistent or intermittent elevation in aminotransferase levels) should be evaluated further with a liver biopsy (III).

3. Patients in the inactive hepatitis B surface antigen (HBsAg) carrier state should be monitored with periodic
liver chemistries every 6 to 12 months, as liver disease may become active even after many years of quiescence (III).

Recommendations for the Treatment of Chronic Hepatitis B

Who to treat and what treatment to use (Tables 1 and 2).

Current therapy of chronic hepatitis B has limited long-term efficacy. Thus, careful balance of patient age, severity of liver disease, likelihood of response, and potential adverse events and complications is needed before treatment is initiated. Except for patients with contraindications or previous nonresponse to specific therapy, either IFN-α, lamivudine, or adefovir may be used as initial therapy for patients with compensated liver disease. The advantages of IFN-α include a finite duration of treatment, more durable response, and the lack of resistant mutants. The disadvantages of IFN-α are the costs and side effects. Lamivudine is more economical (if given for 1 year only) and well tolerated, but the durability of response appears to be lower, and long-term therapy is associated with an increasing risk of drug-resistant mutants that may negate the initial benefits and in some patients result in worsening of liver disease. The main advantages of adefovir include its activity against lamivudine-resistant mutants and a very low rate of adefovir resistance during initial therapy. Adefovir is significantly more costly than lamivudine, and the durability of response and its long-term safety and risk of drug resistance remain to be determined. All three medications are FDA approved as first-line therapy. In choosing which antiviral agent to use as the first-line therapy, consideration should be given not only to long-term safety and efficacy but also the costs of the medication, monitoring tests, and clinic visits, as well as patient and provider preferences.

Table 1. Comparison of Three Approved Treatments of Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Indications</th>
<th>IFN-α</th>
<th>Lamivudine</th>
<th>Adefovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg+, normal ALT</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
</tr>
<tr>
<td>HBeAg+ chronic hepatitis</td>
<td>Indicated</td>
<td>Indicated</td>
<td>Indicated</td>
</tr>
<tr>
<td>HBeAg− chronic hepatitis</td>
<td>Indicated</td>
<td>Indicated</td>
<td>Indicated</td>
</tr>
<tr>
<td>Duration of Treatment</td>
<td>4–6 months</td>
<td>≥1 year</td>
<td>≥1 year</td>
</tr>
<tr>
<td>Route</td>
<td>Subcutaneous</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Many</td>
<td>Negligible</td>
<td>Potential</td>
</tr>
<tr>
<td>Drug Resistance</td>
<td>–</td>
<td>1 year</td>
<td>None, year 1</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>~20% year</td>
<td>~3%, year 2</td>
</tr>
<tr>
<td>Cost*</td>
<td>High</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

*Based on treatment duration of 1 year.

Abbreviations: IFN-α, interferon alfa; HBeAg, hepatitis B e antigen.

Table 2. Recommendations for Treatment of Chronic Hepatitis B

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA*</th>
<th>ALT</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>≤2 x ULN</td>
<td>Low efficacy with current treatment. Observe; consider treatment when ALT becomes elevated</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>&gt;2 x ULN</td>
<td>IFN-α, LAM, or ADV may be used as initial therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration of therapy—seroconversion from HBeAg to anti-HBe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN-α: 16 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lamivudine: minimum 1 year, continue for 3–6 months after HBeAg seroconversion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adefovir: minimum 1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN α nonresponders/contraindications to IFN-α → LAM or ADV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LAM resistance → ADV</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>&gt;2 x ULN</td>
<td>IFNα, LAM or ADV may be used as initial therapy, IFN-α or ADV is preferred because of the need for long-term therapy</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>≤2 x ULN</td>
<td>No treatment required</td>
</tr>
<tr>
<td>±</td>
<td>+</td>
<td>Cirrhosis</td>
<td>Compensated: LAM or ADV</td>
</tr>
<tr>
<td>±</td>
<td>−</td>
<td>Cirrhosis</td>
<td>Decompensated: LAM (or ADV); coordinate treatment with transplant center. Refer for liver transplant. IFN-α contraindicated</td>
</tr>
</tbody>
</table>

Abbreviations: HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; ULN, upper limit of normal; IFN-α, interferon alfa; LAM, lamivudine; ADV, adefovir; PCR, polymerase chain reaction.

*HBV DNA > 10⁵ copies/mL; this value is arbitrarily chosen.
4. Patients with HBeAg-positive chronic hepatitis B:  
   A. \( ALT \) greater than 2 times normal, or moderate/severe hepatitis on biopsy. These patients should be considered for treatment. Treatment should be delayed for 3 to 6 months in persons with compensated liver disease to determine whether spontaneous HBeAg seroconversion occurs. Treatment may result in virologic, biochemical, and histologic response (I) and also appear to improve clinical outcome (II-3). Treatment may be initiated with IFN-\( \alpha \), lamivudine or adefovir as the 3 treatments have similar efficacy.  
   B. \( ALT \) persistently normal or minimally elevated (<2 times normal). These patients should not be initiated on treatment (I). Liver biopsy may be considered in patients with fluctuating or minimally elevated ALT levels and treatment initiated if there is moderate or severe necroinflammation.  
   C. Children with elevated \( ALT \) greater than 2 times normal. These patients should be considered for treatment if ALT levels remain elevated at this level for longer than 6 months (I). Both IFN-\( \alpha \) and lamivudine are approved treatments for children with chronic hepatitis B.  

5. Patients with HBeAg-negative chronic hepatitis B (serum HBV DNA >10^5 copies/mL, elevated \( ALT \) >2 times normal or moderate/severe hepatitis on biopsy) should be considered for treatment (I). Treatment may be initiated with IFN-\( \alpha \), lamivudine, or adefovir (I for adefovir and II-1 for IFN\( \alpha \) and lamivudine). In view of the need for long-term treatment, IFN\( \alpha \) or adefovir is preferred.  

6. Patients who failed to respond to prior IFN-\( \alpha \) therapy may be retreated with lamivudine or adefovir if they fulfill the criteria listed above (I).  

7. Persons who develop breakthrough infection while on lamivudine should be treated with adefovir if there is worsening of liver disease, if they had decompensated cirrhosis or recurrent hepatitis B after liver transplant, or if they require concomitant immunosuppressive therapy (II-2).  

8. Patients with compensated cirrhosis are best treated with lamivudine or adefovir because of the risk of hepatic decompensation associated with IFN-\( \alpha \) related flares of hepatitis.  

9. Patients with decompensated cirrhosis should be considered for lamivudine treatment (III-3). Adefovir may be used as an alternative to lamivudine, although it has not been evaluated as a primary treatment in these patients. If adefovir is used, close monitoring of renal function with testing of blood urea nitrogen and creatinine every 1 to 3 months should be performed. Treatment should be coordinated with transplant centers. IFN-\( \alpha \) should not be used in patients with decompensated cirrhosis (II-3).  

10. For patients with an inactive HBsAg carrier state, antiviral treatment is not indicated.  

**Dose Regimens**  

11. IFN-\( \alpha \) is administered as subcutaneous injections.  
   A. The recommended IFN-\( \alpha \) dose for adults is 5 million units (MU) daily or 10 MU thrice weekly (I).  
   B. The recommended IFN-\( \alpha \) dose for children is 6 MU/m^2 thrice weekly with a maximum of 10 MU (I).  
   C. The recommended treatment duration for HBeAg-positive chronic hepatitis B is 16 weeks (I).  
   D. The recommended treatment duration for HBeAg-negative chronic hepatitis B is 12 months (II-3).  

12. Lamivudine is administered orally.  
   A. The recommended lamivudine dose for adults with normal renal function and no HIV coinfection is 100 mg daily (I).  
   B. The recommended lamivudine dose for children is 3 mg/kg/d with a maximum of 100 mg/d (I).  
   C. The recommended treatment duration for HBeAg-positive chronic hepatitis B is a minimum of 1 year (I). Patients in whom HBeAg seroconversion has occurred should be maintained on treatment for 3 to 6 months after HBeAg seroconversion is confirmed (two occasions at least 2 months apart) to reduce posttreatment relapse. Treatment may be continued in patients who have not developed HBeAg seroconversion. Treatment may be continued in patients who have breakthrough infection due to lamivudine-resistant mutants as long as benefit to the patient (based on clinical assessment, ALT level, and HBV DNA level) is maintained.  
   D. The recommended treatment duration for HBeAg-negative chronic hepatitis B is longer than 1 year, but the optimal duration has not been established (II-3).  
   E. The recommended dose of lamivudine for persons coinfected with HIV is 150 mg twice daily, along with other antiretroviral medications (I).  

13. Adefovir is administered orally.  
   A. The recommended adefovir dose for adults with normal renal function is 10 mg daily (I).  
   B. The recommended treatment duration for HBeAg-positive chronic hepatitis B is a minimum of 1 year. The benefits versus risks of
longer duration of treatment are unknown (I).

C. The recommended treatment duration for HBeAg-negative chronic hepatitis B is longer than 1 year. Longer duration of treatment is likely necessary for sustained response, but the optimal duration of treatment and the benefits versus risks of longer duration of treatment remain to be determined (I).

D. The recommended treatment duration for patients with lamivudine-resistant mutants has not been determined. Long-term treatment is required particularly for patients with decompensated cirrhosis or allograft infection. For patients with compensated liver disease, there appears to be no advantage to continuing lamivudine therapy in patients switched to adeflovir but an overlap period of 2–3 months is advisable to minimize the risk of hepatitis flares during the transition (III).

**Recommendations for Antiviral Prophylaxis of Hepatitis B Carriers Who Receive Immunosuppressive or Cytotoxic Therapy**

14. HBsAg testing should be performed in persons who have high risk of HBV infection, prior to initiation of chemotherapy or immunosuppressive therapy (III).

15. Prophylactic antiviral therapy with lamivudine is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy (III).

Acknowledgment: This guideline was approved by the American Association for the Study of Liver Diseases (AASLD) and represents the position of the Association. It was produced in collaboration with the AASLD Practice Guidelines Committee. Members of the AASLD Practice Guidelines Committee included: K. Rajender Reddy, M.D. (Chair), Bruce R. Bacon, M.D., David E. Bernstein, M.D., Thomas D. Boyer, M.D., Henry C. Bodenheimer, M.D., Robert L. Carithers, M.D., Gary L. Davis, M.D., James E. Everhart, M.D., Thomas W. Faust, M.D., Stuart C. Gordon, M.D., Elizabeth H posinghende, R.N., B.S.N., F. Blaine Hollinger, M.D., Donald M. Jensen, M.D., Maureen Jonas, M.D., Jacob Korula, M.D., Michael R. Lucey, M.D., Timothy M. McCashland, M.D., Jan M. Novak, M.D., Melissa Palmer, M.D., F. Fred Poodrad, M.D., Robert Reindollar, M.D., Eve A. Roberts, M.D., Thomas Shaw-Stiffel, M.D., Margaret C. Shuhart, M.D., James R. Spivey, M.D., Brent A. Tetri, M.D., and Zobair M. Younossi, M.D.

**References**


8. Liaw YF, Chien RN, Yeh CT, Tsai SL, Chu CM. To continue or not to continue lamivudine therapy after emergence of YMDD mutations [abstract]. *Gastroenterology* 2002;122:A28.


**EASL INTERNATIONAL CONSENSUS CONFERENCE ON HEPATITIS B**

13–14 September, 2002
Geneva, Switzerland

Consensus statement (Short version)

The EASL Jury*

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**Introduction**

Recent advances in the field of hepatitis B encouraged EASL to organise a consensus conference in order to define the state of knowledge and to elaborate recommendations for the management of patients with hepatitis B. An organising committee drafted questions to be addressed at the conference, developed an agenda and selected the speakers. International experts in the field of virology, epidemiology, natural history, prevention, and the treatment of hepatitis B provided 2 days of presentation and discussions. The Jury was asked to weigh the scientific evidence and to prepare a consensus statement addressing the following eight questions.

(1) What are the public health implications of hepatitis B?
(2) What is the natural history of hepatitis B, what are the factors influencing the disease?
(3) What is the best way to diagnose and classify hepatitis B?
(4) How can transmission of hepatitis B be prevented?
(5) Which patients should be treated?
(6) What is the optimal treatment?
(7) How should untreated and treated patients be monitored?
(8) What are the main unresolved issues?

The current version of the consensus statement focuses on the conclusions and recommendations. A longer version, which will be published in a supplement to *Journal of Hepatology* later this year, provides an additional overview of the evidence from the published data supporting conclusions and recommendations. The documents prepared by the experts formed the basis of the Jury’s work. These documents will also appear in the same supplement to *Journal of Hepatology*. Statements and recommendations are graded in decreasing order of strength from A to D, according to the topic (therapy/prevention, prognosis, diagnosis, symptom prevalence) as recommended by the Oxford Centre for Evidence-Based Medicine (http://minerva.minervation.com/cebm/).

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1. **What are the public health implications?**

Hepatitis B virus (HBV) infection is a global health problem. Two billion people have been infected worldwide; 360 million suffer from chronic HBV infection; over 520,000 die each year (50,000 from acute hepatitis B and 470,000 from cirrhosis or liver cancer) (grade C). The prevalence of HBV infection and patterns of transmission vary throughout the world (grade B). In Africa and Asian countries the prevalence of chronic infection is more than 8%; infection is mainly through perinatal transmission from an infected mother or infection during early childhood (grade B). Infection in infancy or early childhood usually becomes chronic thus perpetuating the high prevalence of HBV infection in these regions (grade A).

In Northwestern Europe, North America, and Australia the prevalence of chronic infection is less than 1% (grade A). Infection is mainly through sexual contact or needle sharing among injecting drug users, with a peak incidence in the 15–25 age group (grade B). Nosocomial infections occasionally occur in discrete epidemics related to poor implementation of universal precautions and unsafe injection practices. In these developed areas, most chronic hepatitis B is due to wild-type HBV (grade B). Co-infection or super-infection with hepatitis D virus now occurs usually in injecting drug users. In selected groups (e.g. immigrants...
from high endemicity areas) the prevalence of HBV infection can be much higher (grade B).

Areas with intermediate HBV endemicity (prevalence of chronic infection 1–8%) include the Mediterranean countries and Eastern Europe (grade A). Household, sexual and perinatal transmission, as well as nosocomial infection were probably the major sources of infection in the past (grade C). In these countries, over 95% of new infections occur in immune competent adults and resolution occurs in about 95% of cases (grade A). In the Mediterranean area, most cases of chronic hepatitis B are due to hepatitis B ‘e’ antigen (HBeAg) negative variants (grade C). The prevalence of hepatitis D (HDV) infection used to be high in Mediterranean countries but is decreasing thanks to HBV immunisation and measures to control human immunodeficiency virus (HIV) infection (grade C).

Countries with high, low, or intermediate endemicity that implement early universal vaccination have shown a fall in acute hepatitis B in adults and in hepatocellular carcinoma (HCC) in children, and a lower prevalence of hepatitis B surface antigen (HBsAg) carriers in children and adolescents (grade A).

The economic burden of HBV infection is substantial because of the high morbidity and mortality associated with cirrhosis and HCC (grade A). Because complications of chronic HBV infection may not appear for many years the full economic impact of hepatitis B mass vaccination programmes cannot yet be evaluated. However, numerous cost-effectiveness studies show savings even in countries with intermediate or low endemicity (e.g. Belgium, Italy, Spain, USA) (grade B).

2. What is the natural history and what are the factors influencing the disease?

Infection acquired perinatally and in early childhood is usually asymptomatic, becoming chronic in 90 and 30% of cases, respectively (grade A). Approximately 30% of infection among adults present as icteric hepatitis and 0.1–0.5% develop fulminant hepatitis. Infection resolves in >95% of adults with loss of serum HBsAg and the appearance of anti-HBs (grade A). Chronic infection is characterised by the persistence of HBsAg and anti-HBe, and by serum HBV-DNA levels detectable for more than 6 months using non-polymerase chain reaction (PCR) based assays (grade A).

Chronic HBV infection presents as one of three potentially successive phases – immunotolerant, immunoactive, and low- or non-replicative (grade A). In the immunotolerant phase, serum HBsAg and HBeAg are detectable; serum HBV-DNA levels are high; and serum aminotransferases normal or minimally elevated. In the immunoactive phase, serum HBV-DNA levels decrease and serum aminotransferase levels increase. During this phase, symptoms may appear and flares of aminotransferases may be observed. In some patients, these flares are followed by HBeAg-anti HBe seroconversion. The non-replicative phase follows HBeAg-anti HBe seroconversion. HBV replication persists but at very low levels being suppressed by the host immune response. This phase is also termed the ‘inactive carrier state’. It may lead to resolution of HBV infection where serum HBsAg becomes undetectable and anti-HBs is detected. In some patients HBeAg seroconversion is accompanied by the selection of HBV variants that are unable to produce HBeAg. A proportion of these HBeAg negative patients may later develop higher levels of HBV replication and progress to HBeAg negative chronic hepatitis.

There are two types of chronic hepatitis B, differing in their HBeAg or anti-HBe status (grade A). The course of HBeAg positive chronic hepatitis depends on the age at infection. Patients with perinatal infection develop moderate to severe HBeAg positive chronic hepatitis with elevated alanine-aminotransferase (ALT) levels only after 10–30 years of infection. In contrast, patients infected later in life usually present with moderate or severe liver disease after a shorter duration of infection (grade A). HBeAg positive chronic hepatitis is more frequent in males. Liver damage may result in cirrhosis, particularly in patients with recurrent flares of hepatitis (grade B). HBeAg seroconversion is followed by resolution of biochemical and histological signs of inflammatory activity (grade B). Spontaneous HBeAg seroconversion occurs in 50–70% of patients with elevated aminotransferases within 5–10 years of diagnosis (grade A). Older age, female gender and high serum aminotransferase levels are predictive of HBeAg seroconversion (grade A). HBeAg seroconversion rate may differ with different HBV genotypes, but this requires confirmation (grade C). In the majority of cases HBeAg seroconversion marks the transition from chronic hepatitis B to the inactive HBsAg carrier state. However, in 1–5% of patients biochemical and histological activity persists with high serum HBV-DNA levels. These patients constitute the group of HBeAg negative chronic hepatitis in which HBsAg and anti-HBe are present in serum; serum HBV-DNA is detectable using non-PCR based methods; serum aminotransferase levels are elevated, and liver biopsy shows necro-inflammation (grade A). HBeAg is undetectable because of the predominance of mutant HBV strains that cannot express HBeAg (grade A). Patients with HBeAg negative chronic hepatitis tend to be older, male, and to present with severe necro-inflammation and cirrhosis (grade A). HBeAg negative chronic hepatitis has a variable course, often with fluctuating serum aminotransferase and serum HBV-DNA levels (grade B).

The inactive HBsAg carrier state is characterised by HBsAg and anti-HBe in serum, undetectable HBeAg low or undetectable levels of HBV DNA, and normal serum aminotransferases. Histology shows little or no necroinflammation and mild or no fibrosis (although inactive cirrhosis may be present if transition to an inactive carrier
state occurred after many years of chronic hepatitis) (grade A). The prognosis of the carrier state without cirrhosis is usually benign; but 20–30% of patients may undergo reactivation of hepatitis B (grade A). Acute flares of hepatitis are usually due to reactivation of HBV replication but can occur with superinfection with other hepatotropic viruses (HDV, HCV, HAV) or other causes of acute liver disease (e.g. drug toxicity, alcohol abuse). Some patients, even non-cirrhotics (albeit less commonly), may develop HCC. In Western countries, about 1–2% of carriers become HBsAg negative each year; in endemic areas the rate of HBsAg clearance is lower (0.05–0.08% per year) (grade C).

HDV hepatitis can result from simultaneous infection with HDV and HBV (‘coinfection’), or HDV superinfection of a patient with chronic HBV infection. In HBV carriers superinfection with HDV usually results in chronic hepatitis D, with suppression of HBV replication but persistence of HDV replication (grade B). Chronic hepatitis D varies from mild to severe. The factors determining severity are not known. Spontaneous clearance of HDV and HBV is rare (grade B).

Progression to cirrhosis occurs at an annual rate of 2.0–5.5% in HBsAg positive patients and 8–10% in HBsAg negative patients with chronic hepatitis (grade A). The usual age of patients at the time of diagnosis of cirrhosis is 41–52 years. There are several predictors for progression to cirrhosis: older age; serum HBV DNA detectable by non-PCR-based methods; infection with HCV, HDV or HIV, alcohol abuse, recurrent episodes of severe acute exacerbation with bridging hepatic necrosis, fibrosis stage at presentation and severity of necroinflammation at diagnosis (grade A). The role of HBV genotype on the risk of progression to cirrhosis requires more research (grade D). The reported yearly incidence of hepatic decompensation is about 3.3%, ascites being the leading manifestation (49%), followed by jaundice (12%) and variceal bleeding (9%); more than one complication is present in 30% of patients (grade A).

The annual incidence of HCC differs according to the study population. In chronic carriers without cirrhosis the cumulative risk varies with geographical areas from <0.2% per year in western countries to 0.6% per year in Asia (grade A). In cirrhotic patients the overall risk is over 2% per year. Predictors of the occurrence of HCC in cirrhotic patients are: older age, male gender, alcohol abuse, aflatoxin exposure, HCV or HDV co-infection, liver failure, persistent inflammation, HbeAg positivity (in Asian patients) (grade A); and possibly HBV genotype (grade D).

The 5-year mortality rate is 0–2% for patients without cirrhosis; 14–20% for patients with compensated cirrhosis and 70–86% following decompensation (grade B). Reported predictors of survival are age, serum albumin, serum bilirubin, platelet count and splenomegaly (grade B). Low HBV replication and persistently normal of serum aminotransferases correlate with increased survival (grade C). HCC and complications of cirrhosis are the main causes of death (grade B).

3. What is the best way to diagnose and classify hepatitis B?

A combination of biochemical, serological and virological tests, and histological features have been used to diagnose and classify HBV infection (grade B). Assays for serum aminotransferases, HBV antigens (HBsAg and HBsAg) and antibodies (anti-HBs, anti-HBc [total and IgM] and anti-HBe), are widely available and standardised (grade A). Serum HBV DNA may be detected by DNA hybridisation, with or without signal amplification; test results may be expressed qualitatively or more usually, quantitatively (grade A). Quantitative tests for HBV DNA are limited by a lack of standardisation of the assays and of HBV DNA units (grade A). Different assays have different sensitivities and ranges of linearity. Positive HBV-DNA results using more sensitive PCR based assays may be found in HBsAg positive individuals who were previously considered in the inactive HBsAg carrier state (grade A). HBV DNA can also be detected by sensitive PCR assays after acute, resolved hepatitis B in HBsAg negative individuals who have no evidence of ongoing hepatitis (grade B). There are too few data to assess the full clinical significance of different levels of HBV DNA. However, there appears to be a level below which hepatitis B is inactive and non-progressive, $10^5$ copies/ml, which corresponds to the typical limit of detection in the non-PCR based assays used in many past clinical studies (grade C). HBV genotyping remains a research tool (grade D). PCR-based assays for HDV RNA in serum are highly sensitive tools for the diagnosis of HDV infection (grade A).

The assessment of a liver biopsy by an expert pathologist, in association with a clinician is accepted to be an integral part of the diagnosis and management of patients with HBV infection. Liver biopsy has been used for confirming the diagnosis of chronic hepatitis B, for identifying other causes of liver diseases, and in grading the severity of necroinflammation and the stage of fibrosis (grade B). Patients should be advised of the benefits, limitations and the risks and discomfort of liver biopsy (grade A). Although many systems exist for scoring the histological abnormalities associated with viral hepatitis, they are mainly of use for clinical trials (grade D).

Because HBV infection produces a variety of disease states, standard definitions are needed. The following definitions and classification of hepatitis B are proposed where infection and disease status are separately described. HBV infection is defined by the presence of the virus in the infected host. Diagnosis relies on the demonstration of HBsAg or HBV DNA in serum or, for research purposes, in liver tissue (grade A). As mentioned above, HBV infec-
HBV infection can be associated with various levels of HBV replication, which are inferred from serum HBV-DNA levels (grade B). Persistently undetectable or low serum HBV-DNA levels are associated with inactive disease (grade A). The upper limit of serum HBV-DNA levels that are consistently associated with inactive disease has not yet been clearly established. High serum HBV-DNA levels may or may not be associated with active disease. A provisional threshold of $10^5$ copies/ml is proposed to define high serum HBV-DNA levels (grade C). This arbitrary threshold corresponds to the cut-off level of the most sensitive non-PCR based assays available (grade A). However, because of the fluctuating course of chronic HBV infection, serial determinations are necessary to ascertain HBV replication status of individual patients. Occult HBV infection is characterised by undetectable serum HBsAg but detectable HBV-DNA in serum or liver (grade A).

HBV-related active liver disease is defined by raised serum aminotransferases and/or histological evidence of liver inflammation that cannot be explained by another cause (grade A). Inactive liver disease is defined by normal serum aminotransferase levels and/or absent or minimal histological evidence of inflammation (grade A). Although the stage of fibrosis is likely related to cumulative activity over time, it should not be considered in evaluating the grade of ongoing activity (grade A).

Diagnosis of acute hepatitis B is based on the history, raised serum aminotransferase levels and the presence of serum HBsAg and anti-HBc IgM. In patients whose prior HBsAg and anti-HBc status is unknown, reactivation of chronic HBV infection in a previously unrecognised carrier require consideration. Fulminant hepatitis B is a severe form of acute hepatitis B complicated by liver failure. In chronic hepatitis B there is persistent hepatic inflammatory injury. In mild chronic hepatitis B aminotransferase levels are normal or minimally elevated ($<\text{twice the upper limit of normal values (ULN) on three determinations over 1 year}$); biopsy reveals minimal or mild necro-inflammation and absent or mild (periportal) fibrosis. In moderate to severe chronic hepatitis B aminotransferase levels are usually above $2 \times \text{ULN}$ and there is moderate to severe necro-inflammatory and fibrosis.

In HBeAg positive chronic hepatitis B, HBeAg and HBV DNA are present in serum, and anti-HBe is undetectable. In HBeAg negative chronic hepatitis B anti-HBe is present and HBeAg is absent in serum; HBV DNA is present in serum although large fluctuations in levels can occur.

In the inactive HBsAg carrier state, HBsAg and anti-HBe are present in serum, but serum aminotransferase levels are persistently normal and there is little or no necro-inflammatory activity on liver biopsy. Such patients have either low or undetectable levels of HBV-DNA in serum. The differentiation of inactive HBV carrier state from HBeAg negative chronic hepatitis B requires serial testing. Therefore, diagnosis of the inactive HBsAg carrier state can only be made after monitoring serum aminotransferase and HBV-DNA levels for 1 year.

The following definitions should be used for treatment endpoints. A biochemical response is a normalisation of serum aminotransferases (grade A). A virological response implies that HBV-DNA falls below $10^5$ copies/ml (grade C) and that HBeAg becomes undetectable when present initially (grade A). In clinical trials it is necessary to use a histological activity scoring system to quantify the histological response, preferably using two observers (grade A). The criteria used to assess histological response used in clinical trials may not be clinically relevant in an individual patient because of sampling error and inter-observer variability. A combined response occurs when criteria for biochemical, virological and, if available, histological responses are met (grade C). A complete response is the loss of HBsAg with the development of anti-HBs (grade A).

4. How can the transmission of hepatitis B be prevented?

Compliance with universal precautions in the health care setting need to be ensured (grade B); and ‘safe sex’ practices promoted. For illicit drug users, harm reduction programs must be encouraged (grade B). An effective and safe vaccine exists, and several studies show a long-term effectiveness of vaccination. At the moment, booster doses are generally not recommended and the occasional emergence of HBV escape mutants does not threaten effectiveness of immunisation programs with current vaccine. Programs of universal HBV vaccination at birth should be implemented in all countries. In areas of low endemicity, immunisation in late childhood or early adolescence is an acceptable alternative (grade B). Universal immunisation programs do not obviate the need to immunise high-risk individuals, including health care workers, subjects with multiple sexual partners, intravenous drug users, and contacts of HBV infected individuals (grade B). Individuals at high risk of acquiring HBV infection for any medical reason (e.g. haemodialysis) should be offered vaccination early, if there is a possibility that they may become unresponsive later (e.g. terminal renal failure, immunesuppressive therapy) (grade C). Individuals at risk of acquiring HBV infection because of life style should also be offered vaccination (grade C). Where universal vaccination at birth is not available, pregnant women should be screened for HBsAg in the third trimester (grade A); the babies of HBsAg positive mothers should be vaccinated at birth (grade C). The key to post-exposure prophylaxis is early vaccination (grade C). Hepatitis B immune globulin (HBIG), where available, should also be administered to neonates of HBV infected mothers and to subjects with recent percutaneous or sexual exposure to HBV (grade B).
5. Which patients should be treated?

Current treatment of chronic hepatitis B has limited long-term efficacy. The patient’s age, severity of liver disease, likelihood of response, and the possibility of adverse effects and complications should be considered before deciding on treatment (grade A).

Antiviral therapy is unnecessary in patients with acute hepatitis B (grade B).

Patients with fulminant hepatitis B should be considered for liver transplantation (grade B).

Patients with mild chronic hepatitis should be monitored; therapy should be considered only if there is evidence of moderate to severe activity during follow-up (grade A).

Patients with moderate to severe chronic hepatitis should be managed according to HBeAg status and the presence of co-infecting virus(es) (HDV, HCV, HIV) (grade A). HBeAg-positive patients should be followed for 3–6 months. Antiviral therapy should be considered if there is active HBV replication (HBV-DNA above $10^5$ copies/ml) and persistent elevation of aminotransferases after 3–6 months of observation (grade A). HBeAg–negative patients should be considered for antiviral therapy when there is active viral replication (serum HBV-DNA above $10^5$ copies/ml). If there is no evidence of HBV replication, other causes of liver injury should be considered. HDV infected patients should be considered for antiviral therapy (grade A). Patients with HCV co-infection and active HBV replication should be considered for interferon, which is active against HBV and HCV (grade C).

HIV and HBV co-infected patients whose immune status is preserved or restored on highly active antiretroviral therapy (HAART) should be considered for anti-HBV therapy following the above recommendations (grade C). Liver biopsy is most helpful in these patients (grade B). Treatment of HBV infection should not impact negatively on antiretroviral therapy (grade B).

Patients with well compensated cirrhosis should be treated according to the above recommendations (grade A).

HBsAg positive patients with extra-hepatic manifestations of HBV infection should be considered for antiviral therapy if HBV replication is active and deemed to be responsible for the clinical manifestations.

Patients with decompensated cirrhosis should be treated in specialised liver units, where they can be considered for antiviral therapy and/or liver transplantation (grade D).

Prophylactic therapy is recommended for all patients undergoing liver transplantation for hepatitis B (grade B). In most patients it should start at the time of transplant. Antiviral therapy during the pre-transplant waiting period should be considered for patients with high HBV-DNA levels (although the threshold HBV-DNA level for initiation of treatment has not been determined) (grade B). Because of the risk of late recurrence, the treatment should be continued for life (grade C). Although the strategies giving the best results have combined HBIG and lamivudine, further studies are needed to clarify cost/effectiveness according to pre/post transplant infection and disease status.

In patients with recurrent hepatitis B post-liver transplant, treatment with a nucleos(t)ide analogue is recommended (grade B). The treatment chosen will depend on the patient’s prior treatment history and the likelihood of drug resistance.

Health care workers with mild chronic hepatitis B should be counselled about the risk and benefit of antiviral therapy (which may be given to diminish the risk of transmission of HBV to patients). Treatment is recommended for those with mild disease and HBV-DNA positivity only if they perform procedures that may place patients at risk of HBV infection, and if HBV DNA is detectable in their serum (grade D). There is no general consensus regarding the level below which transmission is unlikely.

Institutionalised persons should be treated according to the above recommendations for other persons (grade B); immunisation of contacts is the best way of preventing transmission (grade B).

6. What is the optimal treatment?

Patients should be counselled on the risk of transmission to household, sexual, and professional contacts (grade B). They should be instructed about safe sex, safe injections, and (for health care providers) the value of universal precautions (grade B). Sexual and household contacts should be vaccinated (grade B). Patients should be advised on minimising the danger from other factors that might exacerbate liver damage – such as obesity, hepatotoxic drugs or excessive alcohol consumption (grade C). They should be vaccinated against hepatitis A if not already immune and at risk (grade B). Immunosuppressive therapy of any kind may adversely affect the course of hepatitis B. If immunosuppressive treatment is needed, patients should consult a hepatologist as careful monitoring and antiviral therapy may be needed (grade D).

Recombinant interferon alpha and lamivudine are approved for use in many countries. Adefovir dipivoxil is now approved for use in the USA and Europe. No randomised controlled trials have compared all three agents. The bulk of data available refers to monotherapies, and the efficacy of suitable combination therapies is currently being evaluated. Thus a consensus document that summarises the optimal treatment of hepatitis B will require regular revision in the light of new data. Decisions about antiviral therapy should take into account the limited long-term efficacy of the three main therapeutic agents available, their side effects, costs and the predictive factors for response. Full discussion with the patient regarding the pros and cons of different strategies should lead to a joint decision about management (grade D).

The following strategies are recommended for patients with HBeAg-positive moderate or severe chronic hepatitis without cirrhosis. A 4–6 month course of interferon alpha (5
MU daily or 9–10 MU thrice weekly, or 6 MU/m² thrice weekly in children) may be used as initial therapy (grade A). If interferon is contraindicated, ineffective or poorly tolerated, lamivudine or adefovir should be considered (grade B). Lamivudine should be given at a dose 100 mg daily for at least 1 year (grade A). Adefovir should be given at a dose 10 mg daily for at least 1 year (grade A). Treatment with lamivudine or adefovir should be continued for 4–6 months after a virological response is achieved (grade C). If a virological response is not achieved after 1 year, decision to continue treatment should weigh the likelihood of a sustained response against the risk of developing drug resistance (higher for lamivudine, lower for adefovir), or drug toxicity (minimal with lamivudine, some concern for renal function with adefovir) (grade B). If hepatitis relapses on stopping lamivudine therapy the drug should be reintroduced as maintenance therapy if drug resistance has not developed. More information on safety and frequency of drug resistance with long-term use of adefovir is needed.

For patients with HBsAg-negative moderate or severe chronic hepatitis without cirrhosis, the following strategies are recommended. A 12–24 month course of interferon alpha, 5–6 MU thrice weekly may be considered as initial therapy (grade B). If interferon is contraindicated, ineffective or poorly tolerated, lamivudine or adefovir therapy should be considered (grade B). Lamivudine should be given at a dose of 100 mg daily (grade A). Adefovir should be given at a dose of 10 mg daily (grade A). Because HBeAg is already undetectable the endpoints of treatment are not clearly established. Sustained suppression of HBV replication is associated with histological improvement and therefore appears a realistic goal for treatment (grade C). The optimal duration of therapy is not known. Most patients will require more than a year of treatment but a decision to continue treatment beyond 1 year should weigh the likelihood of benefit against the risk of developing drug resistance or drug toxicity, similar to the above statement for HBeAg positive chronic hepatitis B (grade C). If hepatitis relapses on stopping lamivudine therapy the drug should be reintroduced as maintenance therapy if the patient has not developed drug resistance (grade C). Again, more information is needed on safety and propensity for causing drug resistance with long-term use of adefovir.

If a breakthrough on lamivudine therapy (for HBeAg-positive or –negative chronic hepatitis B) is thought to be due to the emergence of lamivudine-resistant mutants, treatment options include (grade C): (i) continue lamivudine if serum HBV-DNA and aminotransferase levels are lower than they were pretreatment; (ii) discontinue lamivudine in patients without underlying cirrhosis and who are not immunosuppressed; and (iii) change to or add adefovir if available.

Patients with cirrhosis, but without clinical or laboratory signs of decompensation can be managed like non-cirrhotic patients (grade A). Particular care should be paid to these patients, as flares due to antiviral response, antiviral resistance or after cessation of treatment can lead to severe decompensation (grade B). Decompensated cirrhotic patients should be evaluated for liver transplantation (grade C). If they show active HBV replication they should receive antiviral therapy (grade C). The optimal timing of antiviral therapy depends on the patient’s condition and expected waiting time for a transplantation. Several options are available (grade C). (i) Start lamivudine early, in the hope that a successful virological response may delay or obviate the need for liver transplantation. Adefovir can be added to or substituted for lamivudine when lamivudine resistance develops. (ii) Start lamivudine only when transplant is imminent (e.g. within the next 6 months). (iii) Use adefovir as first-line therapy with close monitoring of renal function.

Post-transplant patients with recurrent hepatitis B who have not previously received lamivudine should be treated with lamivudine or adefovir (grade C). Breakthrough during lamivudine therapy should be treated with adefovir (grade C). Careful monitoring of renal function is required in transplant patients receiving adefovir.

No clear recommendation can be made at present for treatment of health care workers with mild hepatitis B.

Patients with moderate to severe chronic hepatitis D should be treated with interferon alpha, 9 MU (or 5 MU/m²) thrice weekly, for at least 1 year (grade A). Patients with biochemical response at the end of treatment, and those with relapsing hepatitis, may be treated with maintenance interferon therapy according to the balance between tolerance to the drug and the severity of the liver disease (grade C).

If HAART is indicated for a patient coinfected with HBV and HIV, lamivudine (150 mg bid) should be included in HAART (grade A). Exacerbation of hepatitis due to emergence of lamivudine resistant mutants in patients on HAART can be treated with addition of tenofovir to the HAART, because tenofovir acts against lamivudine resistant HBV and HIV (grade C). If HAART is not indicated do not use lamivudine because HIV drug resistance develops rapidly when it is used as a monotherapy (grade A); adefovir should then be used as the first line anti-HBV agent (grade D).

No clear recommendation can be made for treating hepatitis B in haemodialysis patients.

In HBV infected patients requiring immunosuppressive therapy, lamivudine is generally preferable to interferon as antiviral therapy (grade C). Treatment can be started 2–4 weeks before immunosuppression or at the first sign of an exacerbation of the hepatitis (grade C). For patients receiving a finite course of immunosuppression, such as cancer chemotherapy, it seems sensible to implement antiviral therapy and to continue for 3–6 months after cessation of immune suppressive therapy (grade C). In patients who are to receive life-long immunosuppression (e.g. kidney transplant recipients), the risk of resistance to lamivudine is increased (grade B). The role of adefovir in this setting has not been evaluated. Adefovir may be an alternative to
lamivudine if further data confirm its long-term safety (grade D).

7. How should patients with chronic hepatitis B be monitored?

Monitoring is used to assess progression of liver disease, the need for treatment, and the response to therapy (grade A).

In patients with severe acute hepatitis, the main aim of monitoring is to decide whether and when liver transplantation is needed. This is best achieved in specialised units (grade D).

Patients with mild chronic hepatitis should have serum aminotransferase levels measured at least 6-monthly to detect transition to moderate or severe chronic hepatitis. When there is a sustained increase of aminotransferases to a level >2 × ULN, antiviral treatment should be considered (grade A). A liver biopsy may be performed to confirm progression to moderate or severe hepatitis (grade A).

Patients with mild chronic hepatitis are at risk of developing HCC but the risk is lower than in patients with more active disease (grade A). Unfortunately, data on the optimal frequency and cost-effectiveness of surveillance for HCC and, more importantly, on the impact of HCC screening on survival are lacking.

Patients with newly diagnosed HBeAg-positive moderate to severe chronic hepatitis should be monitored for 6 months, with 1–3 monthly determination of serum aminotransferases, HBeAg and HBV DNA, to identify those that spontaneously clear HBeAg and therefore do not require antiviral therapy (grade A). Antiviral treatment should not be delayed in patients with hepatic decompensation due to a severe hepatitis flare (grade C).

In patients with HBeAg-negative moderate to severe chronic hepatitis a period of monitoring before starting treatment is not necessary once the diagnosis is established as spontaneous sustained improvement is rare (grade B).

Patients with moderate to severe chronic hepatitis (HBeAg-positive or -negative) whether treated or not, should be monitored for the progression of liver disease and the development of complications (grade A). The required frequency of assessment will depend on the overall severity of the liver disease.

In patients with well compensated cirrhosis monitoring is needed to identify patients for whom therapy may minimise the risk of serious complications, such as variceal bleeding, encephalopathy, fluid retention and HCC development (grade A).

The optimal strategy for HCC screening is not clear. Ultrasound is effective in detecting small tumours but is operator-dependent. Serum alpha-fetoprotein (AFP) monitoring detects some asymptomatic HCC but there are problems with false positive and false negative results. The value of combining AFP determination and ultrasound is not established. Based on the average tumour doubling time, a 6-month interval is most commonly used for HCC screening (grade C).

In patients receiving antiviral therapy, monitoring allows assessment of response, detection of treatment related hepatitis flares, identification of drug-resistant mutants and treatment related side effects, and the evaluation of the patient’s compliance with treatment (grade A). Aminotransferases should be monitored every 1–3 months during the first 6 months of therapy, and then every 6 months.

Among patients with HBeAg-positive chronic hepatitis, those treated with a course of interferon should be tested for serum HBeAg, anti-HBe and HBV-DNA levels at the end of treatment and 6 months thereafter to assess the virological response (grade A). If serum aminotransferase levels are persistently normal during lamivudine or adefovir therapy, tests for the above virological markers should be done every 3–6 months during treatment to assess virological response to guide decisions on when to stop treatment, and to detect virological and biochemical breakthroughs (grade B). Monitoring of serum HBV DNA by PCR, and testing for YMDD mutant (where available, for patients on lamivudine), may permit earlier detection of genotypic resistance and virological breakthrough. In patients receiving antiviral treatment for HBeAg-negative chronic hepatitis monitoring serum HBV DNA is the only way of assessing virological status (grade C). The therapeutic end-points are unclear as relapses are common even when serum HBV-DNA is persistently undetectable by PCR.

Durability of virological response should be established by testing 1–3 monthly for 12 months after stopping antiviral therapy, and every 6–12 months thereafter. Monitoring should include liver chemistries, HBV DNA, and HBeAg and anti-HBe (the latter two only in patients who were previously HBeAg-positive). HBsAg should be determined annually in patients with a sustained virological response (grade B).

It is not clear whether repeated liver biopsy has any benefit in patients showing a sustained biochemical and virological response. The decision to repeat liver biopsy should be made on a case by case basis, depending on the likelihood that the findings will affect management (grade C).

8. What are the main unresolved issues?

8.1. Public health implications and prevention of transmission

The most important issues are the cost of preventing HBV infection, and treating infected patients in poor countries (where most HBV infected persons live); and the decrease in acceptance of HBV vaccine. The need for booster doses 15 years after initial vaccination and the impact of universal vaccination on the selection of S escape mutants also need further evaluation. The attitude towards employment of HBV-infected health care workers and students, although
quantitatively a less important issue, needs further considera-
tion.

8.2. Natural history and factors influencing the outcome

The role of HBV genotype and viral variants in the natural history of HBV infection requires further investiga-
tion. Identification of the events that trigger the immunoac-
tive phase would allow more efficient monitoring and, hope-
fully, a better timing of antiviral therapy. Clarification of the
factors resulting in a resolution of HBV infection may help to
design new therapies or to refine available treat-
ments. Further characterisation of host, viral and environ-
mental factors associated with HCC development would
allow better targeting of screening programs. Development
of more sensitive serum markers is urgently needed to
improve early detection and, ultimately, survival of patients
with HCC.

8.3. Diagnosis and classification

The main issue is quantification of serum HBV-DNA. HBV-DNA
assays need to be standardised. Studies are needed on the clinical significance of low serum HBV-
DNA levels in relation to the natural history of hepatitis B
and the relation between serum HBV-DNA levels and clin-
ical outcome. The distinction between the inactive carrier
state and HBeAg-negative chronic hepatitis also needs
attention. Surrogate tests proposed for the assessment of
disease activity or viral replication such as quantification
of anti-HBc IgM or HBeAg must be standardised and
their clinical value assessed. We need reliable non-invasive
tests that might be an alternative to liver biopsy for grading
and staging chronic hepatitis B.

8.4. Therapy

Currently available monotherapies have limited long-
term efficacy. Treatments that induce a sustained virological
response in a broad range of patients, are safe and afford-
able, and are not associated with hepatitis flares and drug
resistance are needed. The added value of pegylated interferons over the cheaper standard alpha interferons, singly
and in combination with nucleos(t)ide analogues, and the
benefit of prolonging interferon therapy beyond the cur-
tently accepted duration need to be assessed. Factors
that predict sustained response to a limited course of lamivudine or adefovir, the development of drug-resistant
mutants, and renal toxicity of adefovir should be examined.
Studies should be conducted to determine the long-term
clinical benefit of antiviral therapy. The outcome of patients
with drug resistant-mutants or relapse following cessation of
lamivudine or adefovir requires further study. It is antici-
pated that future treatment trials will use active treatment
and not placebo controls arms. Because of the development
of drug resistance with nucleos(t)ide analogue monother-
apy, combination therapy must be evaluated. A reduction
in the cost of the current strategies used to prevent recur-
rence of HBV infection after liver transplantation is urgently
needed. The strategy for management of reactivation in
patients requiring immunesuppressive therapy must be clar-
ified.

8.5. Monitoring

The major issue is the value of serum HBV DNA quanti-
fication to assess response to antiviral therapy. The value of
viral kinetic studies needs examination. HBV-DNA levels
associated with clinically significant virological response
should be determined. Once standardised, cheap surrogate
markers for virological response (e.g. serum anti-HBc IgM
or HBeAg titer) need further evaluation, as do non-invasive
markers for the assessment of histological grading and
staging.