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Journal of Hepatology 38 (2003) 533–540

Journal of Hepatology

www.elsevier.com/locate/jhep

Special article

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/).

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

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doi:10.1016/S0168-8278(03)00083-7

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-HBc, 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 HBeAg positive patients and 8–10% in HBeAg 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 HBeAg) 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-

tion may be associated with active or inactive liver disease (see below). 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 ($<$ 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 $2 \times$ ULN and there is moderate to severe necro-inflammation 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 coinfecting 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/m^2 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 HBeAg-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 end-points 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/m^2) 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 $>2 \times$ 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 consideration.

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 investigation. Identification of the events that trigger the immunoactive phase would allow more efficient monitoring and, hopefully, 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 treatments. Further characterisation of host, viral and environmental 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 clinical 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 affordable, 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 currently 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 anticipated 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 monotherapy, combination therapy must be evaluated. A reduction in the cost of the current strategies used to prevent recurrence of HBV infection after liver transplantation is urgently needed. The strategy for management of reactivation in patients requiring immunesuppressive therapy must be clarified.

8.5. Monitoring

The major issue is the value of serum HBV DNA quantification 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.