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EASL INTERNATIONAL CONSENSUS CONFERENCE ON HEPATITIS B

13–14 September, 2002

Geneva, Switzerland

Consensus statement (Long version)

The EASL Jury

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1. Introduction

Recent advances in the field of hepatitis B encouraged EASL to organize a consensus conference in order to define the state of knowledge and to elaborate recommendations for the management of patients with hepatitis B. An organizing 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 two 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 present long version of the consensus statement, provides an overview of the evidence from the published data supporting conclusions and recommendations. The short version, which is published elsewhere in a regular issue of *Journal of Hepatology*, focuses on conclusions and recommendations. The documents prepared by the experts for the Conference, which formed the basis of the Jury's work, appear elsewhere in this supplement to *Journal of Hepatology*. Conclusions 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/>).

2. What are the public health implications?

Hepatitis B virus (HBV) infection is a global health problem. Current estimates are that 2 billion people have been infected worldwide, of these, 360 million suffer from chronic HBV infection resulting in over 520 000 deaths each year (52 000 from acute hepatitis B and 470 000 from cirrhosis or liver cancer) [1]. In 2000, according to WHO estimates there were over 5.2 million cases of acute hepatitis B infection [2]. Primary liver cancer is ranked the 6th most common cancer globally; over 50% are caused by chronic HBV infection [3]. HBV is considered, after tobacco, the number two carcinogen. In 1996, it was estimated that more than 1 million people acquired acute hepatitis B infection in the 51 countries of the WHO European Region; of these, 90 000 cases progressed to chronic infection [4].

The prevalence of HBV infection and patterns of transmission vary greatly throughout the world [5]. As a general rule, in countries with high HBV endemicity (prevalence of chronic infection above 8%) the source of infection is mainly through perinatal transmission from the chronically infected mother or through infection during early childhood (grade B). The high proportion of infectious carriers associated with infection acquired early in life explains the high rate of perinatal and childhood transmission, thus perpetuating the high prevalence of HBV infection in these countries (grade B). Overall, approximately 45% of the global population live in areas of high HBV endemicity (grade B). These areas include many African and Asian countries. In these countries, HBV infection is responsible for most cases of hepatocellular

carcinoma (grade B). Universal immunization of neonates has resulted in a dramatic reduction in the prevalence of chronic HBV infection in children and adolescents (Africa and Asia) as well as the incidence of hepatocellular carcinoma in children (Taiwan) (grade C).

Areas with low HBV endemicity (prevalence of chronic infection < 1%) include Northwestern Europe, North America, and Australia. The source of infection is mainly through sexual contacts and needle sharing among injecting drug users, with a peak incidence in the 15–25-year-old age group. Nosocomial infections occasionally occur in discrete epidemics related to failures in the implementation of universal precautions and safe injection practices. In these areas, most cases of chronic hepatitis B are related to wild-type HBV (grade B). At present, co-infection or superinfection with hepatitis D virus (HDV) is usually limited to injecting drug users (grade C). In selected groups, such as immigrants from highly endemic areas, the prevalence of HBV infection can be much higher (grade C). In areas with low endemicity, a decrease in incidence of acute hepatitis B has been observed, as a result of immunization campaigns (routine infant and/or adolescent immunization) and implementation of measures for controlling human immune deficiency virus (HIV) infection through public education on safe sex practice and needle exchange programs (grade C).

Areas with intermediate HBV endemicity (prevalence of chronic infection 1–8%) include the Mediterranean countries, the Middle East and the Indian subcontinent. Perinatal, household and sexual transmission probably represented the major sources of infection in the past (grade D). Needle sharing among injecting drug users, nosocomial transmission, tattooing, and body piercing are presently important modes of transmission (grade B). In these countries, over 95% of new infections are acquired during adulthood in immune competent subjects and are therefore followed by resolution in ~95% of cases (grade A). In the Mediterranean area, over half the cases of chronic hepatitis B are related to HBeAg-negative variants (grade A). Recently, the implementation of universal vaccination programs and measures to control HIV infection have been accompanied by a dramatic decrease in the incidence of acute hepatitis B (grade B). Nevertheless, HBV infection is still an important public health problem as new infections continue to occur. In addition, the consequences of chronic infections represent a burden to health systems as a large proportion of cirrhosis and hepatocellular carcinoma are attributable to HBV infection (grade B). The prevalence of infection with HDV (the delta agent) had been high in Mediterranean countries. However, its incidence has decreased significantly [6] as a result of HBV vaccination programs and measures to control HIV infection (grade C).

In Eastern Europe and the newly independent states, the risk factors for viral hepatitis are changing, but few studies have been conducted to depict the current epidemiology of HBV infection in these countries. In some of these

countries, HBV endemicity is related to the use of non-sterile injection practices and injection drug use (grade C).

For South America, more information on prevalence, source of infection, implementation of immunization programs and their impact on the incidence of HBV infection are needed.

The economic burden of HBV infection is substantial because of the high morbidity and mortality associated with the above-mentioned complications (grade A). In Italy, the estimated yearly cost of hospitalization for chronic liver disease related to HBV infection is 60 million euros (communication from the Italian ministry of health). One United States-based study estimated the average cost per hospitalization at \$8464 (in 1999 US dollars) for a patient with hepatitis, increasing to \$14 063 for a patient with cirrhosis [7]. The cost of a liver transplant is higher still (estimated at \$89 076). In Germany, total HBV-related costs have been estimated at DM 1200 million (95% CI 924.2–1536.7) in 1997 [8]. In a South Korean study conducted in 1997 [9], the annual societal cost (direct and indirect costs) was estimated to be \$957.7 million (in 1997 US dollars). Of the total societal cost, \$126.7 million was attributable to prevention (vaccine) and the rest to HBV-related disease (including \$434.7 million for cirrhosis). For HBV-related disease, direct costs amounted to \$632.3 million (or \$1219 per year per patient), and indirect costs to \$200.3 million. The direct cost (prevention- and disease-related), was equivalent to 3.2% of the South Korean healthcare expenditure for 1997. Thus, medical costs of hepatitis B in the few countries where they have been evaluated add up to a very substantial cost to society

(grade B). The full economic impact of hepatitis B mass vaccination programmes cannot be evaluated yet because the complications generally start to appear after 15 years. Nevertheless, the results of numerous cost-effectiveness studies showed cost savings for universal immunization programmes in most countries regardless of the level of endemicity (grade A) [10].

3. What is the natural history and what are the factors influencing outcome?

The outcomes of HBV infection are depicted in Fig. 1. Perinatal infection from the infected mother is almost always asymptomatic, and evolves to chronicity in 90% of cases (grade A) [11]. The risk of perinatal infection is about 90% in babies born to HBeAg-positive mothers and 10% in babies born to HBeAg-negative mothers [12]. This risk is related to the maternal serum HBV DNA level (grade A). In about 5% of babies born to HBeAg-negative mothers, acute symptomatic or fulminant hepatitis develops within the first 3–4 months of life. Infection acquired in early childhood (1–5 years) is in general asymptomatic and evolves to chronicity in about 30% of cases. By contrast, approximately 30% of infection among adults present as icteric hepatitis and 0.1–0.5% develop fulminant hepatitis (grade B). Infection resolves with development of anti-HBs in > 95% of adults (grade A) [13]. Evolution to chronic infection occurs in 1–5% of adults who develop icteric hepatitis. Chronic infection is characterized by the persistence of serum HBsAg and anti-HBc (grade A). HBV DNA

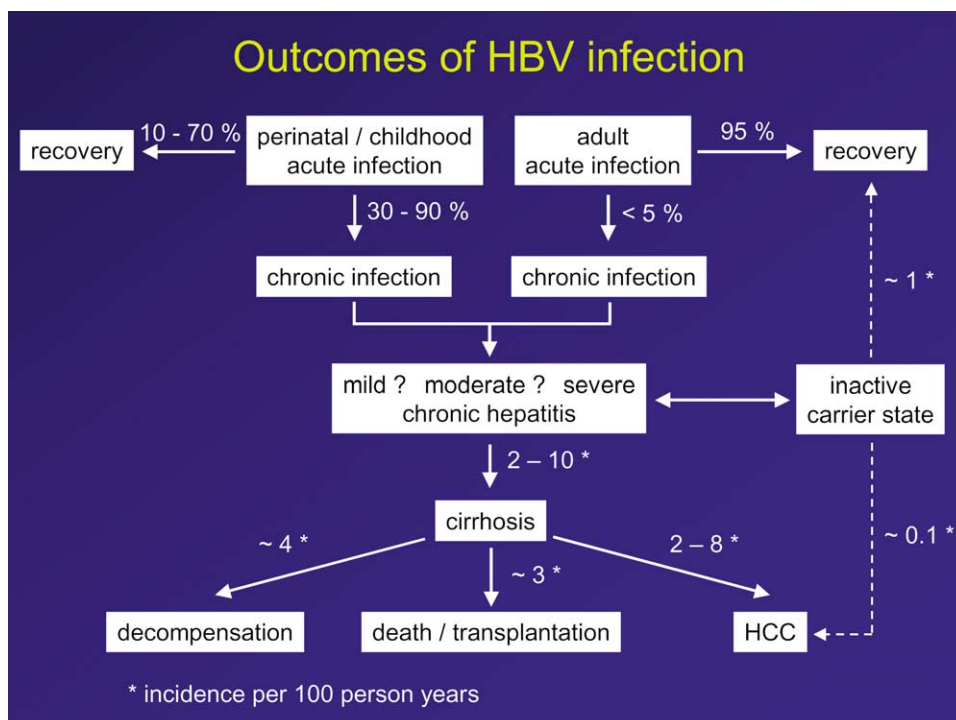


Fig. 1. Summary of the natural history of HBV infection.

may remain detectable in serum or liver using polymerase chain reaction (PCR)-based tests following disappearance of HBsAg in serum (grade B). The clinical significance of the persistence of very low levels of HBV is still unclear (grade D) [14].

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; serum aminotransferases are 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 seroconversion. The **low- or non-replicative phase** follows HBeAg seroconversion (i.e. serum HBeAg becomes undetectable and anti-HBe become detectable). It is characterized by very low serum HBV DNA levels and normal serum aminotransferases. 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.

Chronic hepatitis is always associated with active HBV replication. There are two types of chronic hepatitis B, which differ by the HBeAg or anti-HBe status (grade A). The course of **HBeAg-positive chronic hepatitis** varies depending on the age at infection (grade A). Most children who were infected at birth or in early childhood, present with mild HBeAg-positive chronic hepatitis with normal or mildly elevated serum aminotransferase levels. These patients enter the immunoactive phase of infection, with moderate to severe HBeAg-positive chronic hepatitis and elevated ALT levels, only 10–30 years after infection [15]. In contrast, patients infected in late childhood, adolescence or adulthood present with moderate or severe hepatitis after a shorter duration of infection. HBeAg-positive chronic hepatitis is more frequent in males. Liver damage may result in cirrhosis, particularly in patients with recurrent hepatitis flares (grade B) [16]. Seroconversion from HBeAg to anti-HBe is the key event in the evolution of chronic hepatitis B. Seroconversion is followed by resolution of biochemical and histologic signs of inflammatory activity (grade B) [17]. Spontaneous HBeAg seroconversion occurs in 50–70% of patients with elevated aminotransferases within 5–10 years of diagnosis (grade A). The mean annual rate of HBeAg seroconversion is 8–15% in Western countries. By contrast, in Asian children with normal aminotransferases, HBeAg seroconversion occurs in less than 2% within the first 3 years of life, and in 4–5% of children older than 3 years

[12,18–20]. Older age, female sex and high serum aminotransferase levels are predictive of HBeAg seroconversion (grade A). Preliminary evidence suggests that the rate of HBeAg seroconversion might differ among the different HBV genotypes, but this requires confirmation (grade C). In most patients, HBeAg seroconversion marks the transition from chronic hepatitis B to the inactive HBsAg carrier state (grade A). However, 1–5% of patients may show persistence or recurrence of biochemical and histological activity and high serum HBV DNA levels while HBeAg remains undetectable and anti-HBe remains detectable. These patients constitute the group of patients with **HBeAg-negative chronic hepatitis** (grade A).

HBeAg-negative chronic hepatitis is thus characterized by detection of HBsAg and anti-HBe without HBeAg in serum; detectable serum HBV DNA using non-PCR-based methods; elevated serum aminotransferase levels, and hepatic necro-inflammation (grade A) [21]. The HBeAg-negative status is related to the selection of HBV variants that are unable to express HBeAg (grade A). HBeAg-negative chronic hepatitis is present and increasing worldwide but is more prevalent in the Mediterranean area (grade B). The average age of these patients at diagnosis is 36–45 years, i.e. they are older than patients with HBeAg-positive chronic hepatitis. Other characteristics are the predominance of males, and the high proportion of patients with severe necro-inflammation and/or cirrhosis at the time of presentation (grade A). The course of HBeAg-negative chronic hepatitis is variable (grade B). Three different patterns have been described: (1) recurrent flares with normalization in between, (2) recurrent flares with persistently abnormal serum aminotransferase levels in between, and (3) persistently abnormal ALT without flares [22].

The inactive HBsAg carrier state is characterized by detectable HBsAg and anti-HBe in serum, undetectable HBeAg, low or undetectable levels of HBV DNA, normal ALT, and minimal or no necroinflammation (although inactive cirrhosis may be present if transition to an inactive carrier state occurred after many years of chronic hepatitis) (grade A) [17,23]. This condition was previously described as ‘healthy’ or ‘asymptomatic’ carrier state. These terms should be abandoned. The prognosis of the inactive carrier state (without cirrhosis) is usually benign; but up to 20–30% of these patients may undergo reactivation of hepatitis B and may develop progressive liver disease (grade A) [17]. Acute flares of hepatitis occurring during the inactive HBsAg carrier state can also be related to superinfection with other hepatotropic viruses (HDV, HCV, HAV), to HIV superinfection, or to other causes of acute liver disease (e.g. drug toxicity, alcohol abuse) (grade A). Some patients, even non-cirrhotics (albeit less commonly), may develop HCC (grade B). In Western countries, about 1–2% of carriers per year become HBsAg-negative; in endemic areas the rate of HBsAg clearance is lower (0.05–0.08% per year) (grade C) [24–26].

HDV hepatitis can result from HDV-HBV co-infection or from superinfection with HDV of a patient with chronic HBV infection [27]. Acute hepatitis D caused by co-infection with HDV and HBV (acute hepatitis D) is usually more severe than acute hepatitis B (grade C). In previously healthy individuals complete recovery is usual (grade B). In HBV carriers, super-infection with HDV usually results in chronic hepatitis D, with suppression of HBV replication but persistence of HDV replication (grade B) [28]. Chronic hepatitis D varies from mild to severe [6]. The factors determining the severity of hepatitis are unknown. One potential factor may be HDV genotype (grade D). High HBV DNA levels appear to enhance the severity of chronic hepatitis D. Spontaneous clearance of HDV and HBV is rare.

In HBeAg-positive patients, **progression to cirrhosis** occurs at an annual rate of 2–5.5%, with a cumulative 5-year rate of progression of 8–20% (grade A) [29,30]. Progression to cirrhosis appears to be faster in HBeAg-negative patients, with reported annual rates of 8–10% (grade B). The usual age of patients at the time of diagnosis of cirrhosis is 41–52 years. Predictors for progression to cirrhosis include the following: older age, detectable serum HBV DNA levels using non-PCR-based methods, concurrent HCV infection (with a rate of cirrhosis of approximately 4% per year during 1–11 years of follow-up), concurrent HDV infection (with an incidence of approximately 50% at 5 years); concurrent HIV infection (with a 4-fold increase in risk compared with HIV negative individuals); alcohol abuse (with a 6-fold increase in risk compared with non alcoholics); recurrent episodes of severe acute exacerbation with bridging hepatic necrosis; high fibrosis stage at presentation and severity of necro-inflammation at diagnosis (grade A) [31–33]. The suggested impact of HBV genotype on the risk of progression to cirrhosis requires more research (grade D) [34].

The reported yearly incidence of **hepatic decompensation** is about 3%, with a 5-year cumulative incidence of 16% (grade A) [29,31,35,36]. Ascites is the leading manifestation of decompensation (about 50%), followed by jaundice (10%) and variceal bleeding (10%), while more than one complication is present in 30% of patients (grade A).

In longitudinal studies of untreated patients, the annual incidence of **hepatocellular carcinoma** differs according to the initial characteristics of the study population. In carriers without cirrhosis the risk varies with geographical areas from 0.4–0.6% per year in Asia, to 0.2% per year in Eskimos, and < 0.2% per year in Caucasians (grade A) [23,25,37]. Among cirrhotic patients the risk is over 2% per year, with a cumulative 5-year incidence of 15–20% (grade A) [29,36]. Predictors of the occurrence of hepatocellular carcinoma in cirrhotic patients include: older age, male sex, alcohol abuse, aflatoxin exposure, HCV or HDV co-infection, liver failure, persistent hepatic inflammation, detectable serum HBeAg (in Asian patients) (grade A), and possibly HBV genotypes although this needs more research (grade D).

The 5-year **mortality rate** is 0–2% for patients with chronic hepatitis B without cirrhosis, 14–20% for patients with compensated cirrhosis, and 70–86% after the occurrence of decompensation (grade B) [29–31,33,36,38]. Reported predictors of survival are age, serum albumin, serum bilirubin, platelets and splenomegaly (grade B). Abrogated or sustained suppression of HBV replication and persistent normalization of serum aminotransferase levels correlate with increased survival (grade C) [31,39]. The development of hepatocellular carcinoma and the complications of cirrhosis are the main causes of death (grade B).

4. 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).

Biochemical assays for serum aminotransferases are widely available (grade A). Inter-laboratory variations have necessitated expression of results as multiples of the upper limit of normal values in multi-centre clinical trials. The upper limit of normal aminotransferase value varies according to anthropometric and demographic characteristics, as well as time of the day (grade A) [40,41].

Qualitative **serological assays** for the detection of HBV antigens (HBsAg and HBeAg) and antibodies (anti-HBs, total and IgM anti-HBc, and anti-HBe) are also widely available and standardized (grade A) [42]. Standardized quantitative assays for anti-HBs titres have been developed and used to monitor response to hepatitis B vaccine and to guide dosing of hepatitis B immune globulin (HBIG) in patients who received liver transplants for hepatitis B (grade A). Qualitative IgM anti-HBc assays have been developed and used to differentiate between acute and chronic hepatitis B. However, these assays may not differentiate exacerbation of chronic hepatitis B from acute hepatitis B because similarly high serum levels of IgM anti-HBc may be present in the former condition (grade A). Some investigators use quantitative assays for serum IgM-HBc, which have lower cut-off values, and found correlations between IgM anti-HBc titer and inflammatory activity. However, the latter assays have not been standardized and are not widely available (grade D). Serological tests are available for the detection of hepatitis D antibodies (total and IgM) (grade A). Elevated IgM anti-HDV levels are found in hepatitis D, whether acute or chronic (grade A).

HBV DNA may be detected in serum using methods that employ DNA hybridization with or without signal amplification (grade A) [43]. The results of these tests may be expressed qualitatively or quantitatively. Quantitative tests for HBV DNA are limited by a lack of standardization of the assays and of HBV DNA units (grade A). Different assays have different sensitivities and ranges of linearity. The assays that are commercially available include: liquid

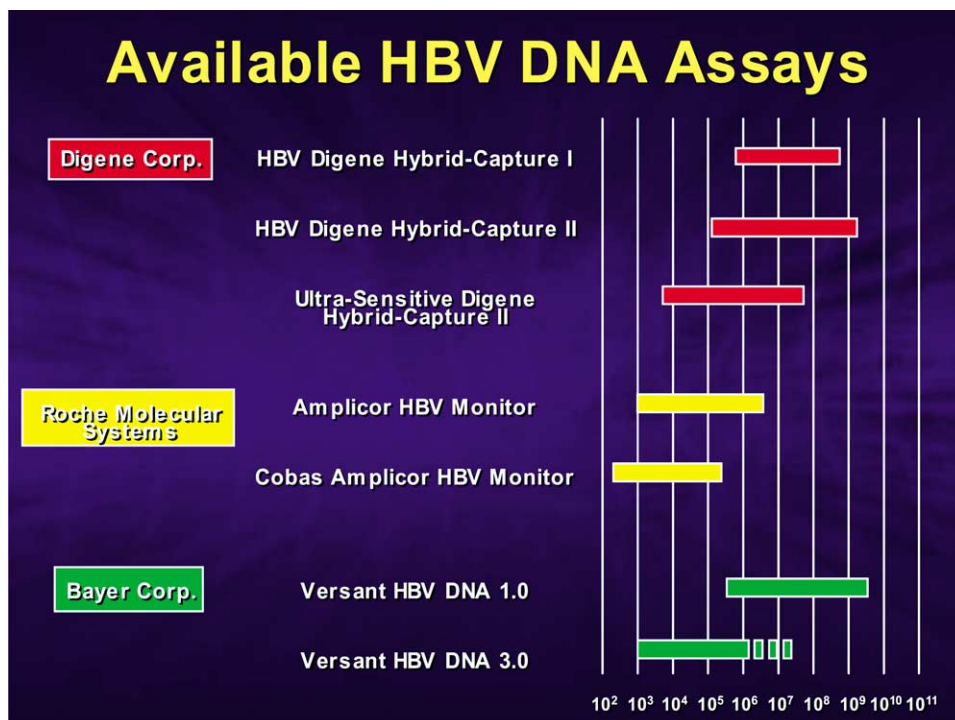


Fig. 2. Detection range for available serum HBV DNA assays.

hybridization, solid-phase hybridization capture, branched DNA signal amplification, and polymerase chain reaction amplification (PCR). The lower limit of detection of these assays ranges from 10^2 to 10^6 copies/ml, as depicted in Fig. 2 (grade A). It is envisioned that other methods in development that are more sensitive including real time PCR amplification assays will be marketed in the future (grade D). Thus, positive results using new assays may be found among individuals previously considered, on the grounds of negative results in non-PCR-based assays, to be in the inactive HBsAg carrier-state (grade A). HBV DNA can also be detected by sensitive PCR after acute, resolved hepatitis B in HBsAg-negative individuals who have no evidence of ongoing hepatitis (grade B). There are currently insufficient data to assess the full clinical significance of different levels of HBV DNA. However there appears to be a level of serum HBV DNA below which hepatitis B is inactive and non-progressive. HBV DNA level of $> 10^5$ copies/ml is the typical limit of detection in the non-PCR-based assays used in many past clinical studies (grade A) [44]. Furthermore at the lowest levels of serum HBV DNA, transmission of infection may be highly unlikely (grade D). **The genotypes (A–G) and subtypes of HBV** may be differentiated on the basis of HBV genetic sequence or S epitope variation (grade A). Although HBV genotypes have been reported to correlate with spontaneous and interferon induced HBeAg seroconversion, activity of liver disease, and progression to cirrhosis and HCC, the role of HBV genotyping in the clinical management of hepatitis B patients remains to be determined (grade C) [45]. At the moment, HBV genotype should be considered a research tool. PCR-based assays for **HDV-RNA**

in serum are highly sensitive tools for the diagnosis of HDV infection (grade A). Because of genetic heterogeneity, false negative results may occur when the primers are not from the most conserved regions.

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 inter-current disease affecting the liver, and in grading the severity of necro-inflammation and the stage of fibrosis (grade B) [46]. Although many systems exist for scoring the histological abnormalities due to viral hepatitis, they are mainly of use in the context of clinical trials (grade D). The limitations of liver biopsy are sampling variation, pain or discomfort, and the risk of major complications [47]. The latter are uncommon but may still occur in patients without recognizable risk factors. Practice guidelines have been elaborated in order to keep the risk minimal [48,49]. Patients should be advised of the benefits, limitations, and the risks and discomfort of liver biopsy (grade A). Serum aminotransferase levels often reflect hepatic necro-inflammation while derangement of serum bilirubin, albumin, prothrombin time and platelet count may provide evidence of cirrhosis (grade A). However, normal results for all of these tests can be encountered in patients with compensated cirrhosis (grade A). Ultrasonography or other techniques for liver imaging can provide direct or indirect evidence for the diagnosis of cirrhosis but significant fibrosis and even early cirrhosis can escape detection by radiological imaging (grade A).

Hepatitis B virus infection produces a variety of disease states depending on the host, the stage of the infection, and the response to therapy. Standard definitions of these various states are needed for optimal design of clinical and pathophysiological studies as well as for describing the individual patient. The following definitions and classification of hepatitis B are proposed. The status of infection is separately described from that of liver disease.

Hepatitis B virus 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 defined above, HBV infection may be associated with active or with 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). **Undetectable or low serum HBV DNA levels** are associated with inactive disease (grade A) but the upper limit of serum HBV DNA level that is 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 (grade A). A provisional threshold of 10^5 copies/ml has been proposed to define high serum HBV DNA levels (grade C) [44]. This arbitrary threshold corresponds to the cut-off level of the most sensitive non-PCR-based assays available. However, because of the fluctuating course of chronic HBV infection, serial determinations are necessary to ascertain HBV replication status in individual patients. **Occult HBV infection** is characterized by undetectable serum HBsAg but detectable HBV DNA in serum or liver.

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. **Inactive liver disease** is defined by normal serum aminotransferase levels and/or no histological evidence of inflammation. Although the stage of fibrosis is likely related to cumulated activity over time, it is not considered in evaluating the grade of ongoing activity (grade A).

Acute hepatitis B is defined by the abrupt manifestations of hepatic injury (clinical, biochemical and/or histological) that occur within 6 months after exposure to HBV and that resolve within 6 months after onset. (Both clinical and biochemical evidence should be present but histology should be optional.) Diagnosis is based on raised serum aminotransferase levels and the appearance of serum HBsAg and IgM anti-HBc (grade A). In most patients, prior HBsAg and anti-HBc status is unknown and reactivation of chronic HBV infection in previously unrecognized carriers is difficult to rule out (grade A). **Fulminant hepatitis B** is defined as a severe form of acute hepatitis B that is complicated by encephalopathy in an individual with no pre-existing HBV infection. Subgroups of fulminant hepatitis B are defined by different intervals between the onset of jaundice and encephalopathy (grade B) [50]. In patients with fulminant hepatitis B, HBsAg may be

undetectable at the time of diagnosis; diagnosis then relies only on the presence of IgM anti-HBc (grade A).

In **chronic hepatitis B**, there is persistent hepatic inflammatory injury. HBsAg is present in serum and there is histological evidence of necro-inflammation or elevated serum aminotransferase levels that cannot be explained by another cause of liver injury. In *mild chronic hepatitis B* aminotransferase levels are normal or minimally elevated ($< 2\times$ upper limit of normal (ULN) on three determinations over 1 year). Biopsy is not necessary in this situation. If performed, the biopsy is likely to show minimal or mild necro-inflammation, and absent or mild (periportal) fibrosis (Grade A). A minority of patients with minimally elevated aminotransferase levels have moderate to marked necro-inflammatory lesions and fibrosis on liver biopsy. The latter patients should be managed as patients with moderate to severe hepatitis (grade C). In *moderate to severe chronic hepatitis B* aminotransferase levels are usually above $2\times$ ULN; there is moderate to severe necro-inflammation and varying amount of fibrosis (grade A).

In *HBeAg-positive chronic hepatitis B* HBeAg and HBV DNA are present in serum, and anti-HBe is undetectable (grade A). *HBeAg-negative chronic hepatitis B* (sometimes referred to as 'pre-core mutant hepatitis B') is related to infection by an HBV variant that prevents or down regulates secretion of HBeAg in serum where it becomes undetectable; anti-HBe is detectable; and HBV DNA is present in serum although large fluctuations between low and high levels can occur (grade A) [45].

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 (grade A). Such patients have either low or undetectable levels of HBV DNA in serum (grade C). The differentiation of the inactive HBsAg 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.

A **HBV variant** is characterized by any naturally occurring variation from published wild-type sequences. A **HBV mutant** is defined as a variant that develops under specific selection pressure and that has been shown to confer a specific phenotype.

The following definitions for treatment endpoints should be used. A **biochemical response** is a fall in serum aminotransferase levels to the normal range (grade A). A **virological response** implies that HBV DNA falls below 10^5 copies/ml (grade C). This HBV DNA level has been chosen to correspond to the cut-off level of all available non-PCR-based assays. In addition HBeAg becomes undetectable when present initially (grade A). For descriptive purposes, histological changes should be reported using a system that scores necro-inflammatory activity separately from fibrosis, such as the histology activity index (HAI) or the Metavir

score (grade A) [46]. In clinical studies, **histological response** is best defined as a pre-determined decrease in histological activity score with no worsening in fibrosis, as assessed by dual observers. A 2-point decrease in HAI score has been the most commonly used end-point. However, definitions of histological response used in clinical studies may not be clinically relevant to an individual patient because of sampling and inter-observer variability. Furthermore, the magnitude of the change or the threshold histological grading/staging that are associated with improved clinical outcome are still unknown. **Combined response** is the best way to assess a beneficial outcome of therapy. It occurs when criteria for biochemical, virological and if available, histological response are met (grade C). **Complete response** is defined as the loss of HBsAg with the development of anti-HBs (grade A).

Initial responses are defined as responses occurring within 3 or 6 months of starting therapy. **End-of-treatment responses** are defined as responses at the end of treatment and before withdrawal of therapy (grade A). **Maintained responses** are responses that are maintained while treatment is continued (grade A). **Sustained responses** refer to maintained response after treatment has been withdrawn (grade A). Because of the possibility of late reactivation, the most appropriate time to assess sustained response to hepatitis B treatment is unclear. A minimum of 12 months post-treatment follow-up should be conducted (grade C).

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

Vertical (mother to infant) transmission occurs worldwide and is mainly related to perinatal infection through contact with infectious blood or body fluids from the infected mother at the time of delivery (grade A) [51–53]. **Sexual transmission** of hepatitis B occurs worldwide [51,54,55]. The risk increases with the number of partners, years of sexual activity, history of other sexually transmitted infections, and with receptive anal intercourse (grade A). ‘Safe sex’ practices can prevent sexual transmission of HBV (grade C). **Injections and a variety of percutaneous procedures in health care settings** have been associated in many countries with transmission of HBV, HCV and HIV infection (grade A) [56]. Transmission occurs because of non-compliance with universal precautions and with safe injection techniques (e.g. through overuse of injections to administer medications, re-use of equipment in the absence of sterilization, inadequate cleaning and sterilization practices, and contamination of sterile equipment/medication vials) (grade B). It has been estimated that globally 8–16 million new HBV infections occur annually due to the use of unsafe injections [57]. **Infected health care workers** can infect others (grade A) [58]. Uninfected workers are themselves at risk, particularly from percutaneous injuries like needle stick (grade A) [59]. The risk of transmission from infected medical personnel to

patients is much higher for HBV than for HCV or HIV (grade A). **Intravenous injection of illicit drugs** is a major source of infection worldwide, and proportionally more so in countries of low endemicity (grade A) [54]. In this high-risk group, harm reduction counselling, drug substitution (such as methadone) and needle exchange programs have resulted in a reduction in the incidence of blood borne viral infections. Even when **blood products** are tested for HBsAg there is still a minor risk of transmission (grade B) [60]. In well-developed countries it appears to be 2–16 cases per million units of blood, depending on the prevalence of HBsAg carriers in the population (grade A). Some countries also screen for anti-HBc to further decrease HBV transmission by transfusion. The risk of transfusion related HBV infection is unknown in poor countries, where screening of donors is not always performed. WHO estimates that globally about 6 million units of blood are not properly tested [57]. Transmission by **bone marrow and non-liver solid organ transplantation** has been largely eliminated by screening donors for serum HBsAg (grade A). Transmission from donors with isolated serum anti-HBc can occur, but the risk is low for non-liver solid organs (grade A). **Liver graft** from donors with HBV serum markers can transmit HBV infection [61]. The risk is almost 100% for liver grafts from HBsAg-positive donors, over 70% for donors with isolated anti-HBc, and very low for grafts from anti-HBs and anti-HBc positive donors (grade A). For this reason liver grafts from donors who are HBsAg-positive are not used and grafts from donors with isolated anti-HBc are only used in HBsAg-positive recipients or in very urgent cases (grade B).

Hepatitis B infection and its complications can be prevented by vaccination (grade A) [59]. An inactivated plasma-derived vaccine has been available since 1982 and a recombinant DNA vaccine since 1986. All have been proven to be safe and immunogenic (grade A). New pre-S/S and naked-DNA hepatitis B vaccines are being evaluated. More than a billion people have been vaccinated worldwide. The efficacy of HBV vaccination in the prevention of HBV infection in newborns and children has been shown to be over 90% in most countries [59,62] and more than 80% in Taiwan [63] (grade A). The lower efficacy in China is related to the large number of HBeAg-positive mothers (grade C), highlighting the need for immediate prophylaxis using HBIG in countries with a high prevalence of HBeAg among HBV carriers (grade C). Hepatitis B vaccination has been demonstrated to reduce the incidence of liver cancer in Taiwanese children [64].

Currently available vaccines are safe and their benefit outweighs their untoward effects (grade A). Minimal reactions are frequent, including local pain, mild and transient fever, mostly lasting only 24 h [65]. In placebo-controlled studies only local pain was more frequent in vaccine recipients. The estimated incidence of anaphylaxis is one per 600 000 vaccine doses distributed. No severe or fatal anaphylactic reaction has been reported (grade A).

Further dosing with hepatitis B vaccine is contraindicated in people with a history of anaphylaxis to a previous dose. Although vaccination against hepatitis B has been suggested as a cause of several other adverse events these reports have not been confirmed (including demyelinating diseases [66]) (grade A). Careful scrutiny of the reported cases by various committees did not support a causal relationship. In most instances, the likely explanation was a coincidental association (grade A). Concerns about the accumulation of mercury in the infant immunization schedule have been resolved with vaccines that do not contain thiomersal (grade A).

Breakthrough infections due to HBV escape mutants have been reported in successfully vaccinated children born to carrier mothers (grade B) [67]. The most common mutant, G145R, has a single amino acid substitution at codon 145 of the S region, and has been reported in Italy, China, the Gambia, Thailand, Singapore, Japan, Brazil and the United States. The occurrence of these escape mutants is rare (grade B). To date, there is no evidence that these mutants threaten the efficacy of immunization programs using current vaccines (grade C). Nevertheless, surveillance is needed to monitor the rate of emergence of these escape mutants and their impact on the efficacy of vaccination programs (grade D). If these S escape mutants become more prevalent in the future, hepatitis B vaccines with the addition of pre-S antigens may be effective (grade C).

Immunization offered only to high-risk groups has proved to be an inefficient strategy for controlling HBV infection at the population level (grade B) [68]. The greatest fall in incidence and prevalence of hepatitis B is in countries with high vaccine coverage at birth or in infancy (grade B). However, vaccination of adolescents is also valuable as it protects against transmission through sexual contact or injection drug use. Several studies demonstrated long-term efficacy of hepatitis B vaccine (grade A). As immunological memory generally lasts more than 15 years in immunocompetent individuals, booster doses are not recommended for those who responded to a standard course of vaccination (grade A). More information is necessary to decide if booster injection for adults beyond 15 years after vaccination, and for children immunized at birth should be recommended.

The vaccine should be given intramuscularly (into the quadriceps for new-borns and infants, and the deltoid for adults) (grade A). In healthy infants and children, the immunogenic response to three doses of HBV vaccine is more than 95% (grade A). Infant immunization may be given in a variety of schedules, e.g. 6 weeks, 10 weeks and 14 weeks; 2 months, 4 months and 6 months; at birth, 1 month and 6 months. In countries with a high rate of perinatal transmission, the first dose of vaccine should be given at birth (grade B). In other countries HBV vaccine should be integrated into routine infant immunization programs (if maternal screening and vaccination is offered for new-borns of maternal carriers) (grade B). In adolescents

and adults, the first two doses of the vaccine should be given I.M. 4 weeks apart, followed by a third dose within 6–12 months (grade B).

Some population groups have a poor response to vaccination. Male gender, over weight, smoking, renal failure, chronic liver disease and immunodeficiency are predictive factors for a poor response (grade A). In these individuals, additional vaccine doses can increase the response rate (grade B). However, a response is unlikely beyond three additional doses. Unresponsive individuals are susceptible to HBV infection (grade B).

In children born to HBsAg-positive mothers, administration of vaccine and hepatitis B immune globulin (HBIG) has 95% protective efficacy when HBIG is given and vaccination is initiated at birth (grade B). Vaccine and HBIG should be injected into distant sites (grade C). High maternal serum HBV DNA levels are associated with an increased risk of vaccine failure (grade B). **In health care workers with accidental percutaneous exposure to HBV**, either non-vaccinated or unresponsive to vaccination, early post-exposure administration of HBIG with or without prompt vaccination prevents 95% of HBV infection (grade B). Where the HBV immune status cannot be determined within a few hours, vaccination should be initiated without delay (grade C). Outside the health care setting, recent percutaneous or sexual exposure to HBV can be managed in the same way (grade D). **Household contacts and sexual partners of a HBV-infected individual** should be screened for serum HBsAg and anti-HBs (grade A). Individuals negative for both markers should be vaccinated (grade A).

HBIG is expensive and not available in all countries. Administration of HBIG alone at birth is less efficient than vaccination to prevent perinatal transmission (grade A). Simultaneous administration of HBIG and HBV vaccine at birth increases the efficacy of protection against perinatal transmission by 5–20% compared to vaccination alone at birth (grade B) [69–72].

In conclusion, there is a need to improve compliance with universal precautions in the health care setting (grade B); and to adherence to safe sex practices and, for illicit drug users, harm reduction programs (grade B). Programs of universal HBV vaccination at birth must be implemented in all countries (grade B). In areas of low endemicity, immunization in late childhood or early adolescence is an acceptable alternative (grade B). Universal immunization programs do not obviate the need to immunize high-risk individuals, including health care workers, subjects with multiple sex partners, intravenous drug users, patients with chronic diseases who are likely to undergo multiple percutaneous procedures, 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, before the possible occurrence of factors rendering them unresponsive (e.g. terminal renal failure, immune suppressive therapy) (grade C). Individuals at risk of acquiring HBV infection because of their 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); in babies born to HBsAg carrier women vaccination should be initiated at birth (grade C). HBIG, where available, is an adjunct to early vaccination in neonates of HBV-infected women and in subjects with recent percutaneous or sexual exposure to HBV (grade B).

6. Which patients should be treated?

The outcome of acute hepatitis B is good in the vast majority of immunocompetent adult patients with symptomatic disease (grade A) [13]. Therefore antiviral treatment is not recommended. Some patients with acute hepatitis B run a protracted course, HBV DNA remains detectable in serum (using non-PCR-based assays) more than 3 months after the onset of illness with persistent jaundice and/or signs of liver failure. As stated above, this condition may be difficult to differentiate from a severe exacerbation of chronic hepatitis B in a previously unrecognized carrier. Antiviral therapy should be considered but there are very little data to support its benefit because of the difficulty of conducting clinical trials in this setting (grade C). In patients with fulminant hepatitis B, viral replication is usually suppressed at the time of presentation; therefore, antiviral therapy is of doubtful benefit when serum HBV DNA is not detectable using non PCR-based assays (grade D). Transplantation has to be considered for patients with fulminant hepatitis. For this reason, patients with acute hepatitis and decreased coagulation factor levels should be referred to specialized liver units, preferably before signs of overt encephalopathy develop.

6.1. HBeAg-positive chronic hepatitis B

In patients with *mild chronic hepatitis B*, treatment is not recommended because of the low efficacy of existing therapies [20,73–76]. These patients should be monitored as they may develop progressive liver disease later that would warrant antiviral therapy. In patients with *moderate to severe chronic hepatitis*, spontaneous suppression of viral replication may be observed. In about 15% of those with serum aminotransferases above 5× ULN, HBeAg becomes undetectable within a year [19,20,73]. Treatment is recommended if there is active HBV replication (HBV DNA above 10⁵ copies/ml) and persistent elevation of aminotransferases after 3–6 months of observation (grade A).

6.2. HBeAg-negative chronic hepatitis B

In this group, liver disease tends to progress more rapidly than its HBeAg-positive counterpart. Spontaneous sustained suppression of viral replication or a durable response to therapy is less likely. Marked fluctuations in hepatitis

activity and viral replication are common. Because of the need for long-term treatment, therapy is indicated only for patients with *moderate to severe chronic hepatitis* (grade A). Differentiation between HBeAg-negative chronic hepatitis B and the inactive HBsAg carrier-state may be difficult and require serial testing over at least 6–12 months.

6.3. Inactive HBsAg carrier state

Long-term outcome is good. Reactivation of viral replication and hepatitis occurs in a small percent in the absence of immune suppression. Treatment is not recommended as there is no evidence that available antiviral therapy affects HBsAg status (grade A).

6.4. Decompensated cirrhosis

Suppression of viral replication may cause marked improvement of the liver disease (grade A) [77,78]. Liver transplantation may then become less urgent or unnecessary, and the rate of HBV recurrence post-transplant may be reduced (grade A). However, ‘flares’ related to emergence of antiviral drug resistant mutants can be severe or fatal, and worsening liver failure and HCC may develop even in patients with no evidence of drug resistance [78]. The benefit of antiviral treatment in patients with low or undetectable HBV DNA level (below 10⁵ copies/ml) is unclear.

6.5. Liver transplant recipients

Recurrence is the rule without specific prophylaxis against HBV (grade A) [79]. Post-transplant recurrence is much lower if HBV replication is suppressed at the time of transplantation (grade A) [79]. Recurrent HBV infection results in a high rate of chronic infection, rapid evolution to cirrhosis and decompensation (grade A). If HBV recurrence can be prevented, survival rates are similar to those observed after transplantation for other types of chronic liver disease (grade B) [80]. If prophylaxis is interrupted, even late in the post-transplant period, recurrence may still occur (grade B).

6.6. Recurrent hepatitis B post-transplant

In patients with a severe recurrence of HBV infection after a liver transplant, suppression of HBV replication causes a marked improvement in the liver disease (grade C) [81]. Patients with recurrent hepatitis B after liver transplant generally develop rapidly progressive liver disease if the hepatitis B is not treated (grade B). 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.

6.7. Special patient groups

Health care workers with mild chronic hepatitis, either HBeAg-positive or HBeAg-negative – In this group, persistent suppression of HBV replication with antiviral therapy may allow them to perform invasive procedures. However, the advantage of being able to return to work must be balanced against potential problems with therapy: adverse events, a low probability of durable response, and breakthrough infection (grade D). Furthermore, there are currently no data to define the serum HBV DNA level below which the risk of transmission is nil.

Subjects with mild chronic hepatitis B in institutions – In this group, permanent suppression of HBV replication is also desirable to prevent transmission to contacts. The limitations are the same as those for health care workers. Vaccination of contacts is more effective in preventing transmission in this setting (grade B).

Extra-hepatic manifestations of HBV – These are uncommon problems and there are few data on the response to treatment. Some patients have been reported to benefit from interferon therapy, but there are few data on the use of nucleoside analogues in this condition. Antiviral treatment should be considered for patients with severe extra-hepatic manifestations (e.g. renal or neurological manifestations) that are caused by HBV infection (grade C).

Co-infection with other virus(es) – Patients with HIV co-infection and marked immune deficiency tend to have mild chronic hepatitis B but to have high levels of HBV DNA (grade B) [82]. Severe fibrosing cholestatic hepatitis may develop. Overall morbidity and mortality may be higher than in patients with only HIV infection because of the added risk of HBV-related liver disease (grade C) [83]. Restoration of immune function in patients on highly active anti-retroviral therapy (HART) may be associated with suppression of HBV replication and loss of HBeAg but immune reconstitution may also be associated with hepatitis flares (grade C). It is unclear whether co-infection with HBV increases the risk of HART-related hepatotoxicity in HIV-infected patients.

Co-infection with HCV – In most patients, HBV replication is suppressed while HCV replication remains active. However, the opposite has also been observed. Patients with HCV and HBV co-infection tend to have more severe chronic hepatitis, and cirrhosis and HCC are more common (grade B) [84]. There is little information on the efficacy of antiviral treatment in such patients.

Co-infection with HDV and HBV causing acute hepatitis D is usually followed by complete recovery. Treatment is therefore not recommended (grade A). Chronic hepatitis D (usually resulting from HDV super infection of previous HBV carrier) varies from mild to severe. Spontaneous clearance of HDV and HBV is rare. Treatment is recommended in patients with moderate to severe chronic hepatitis (grade A). When a biochemical response is maintained there is improvement in liver histology [85].

Patients on haemodialysis – It is not clear to what extent liver morbidity and mortality are increased in HBV-infected haemodialysis patients as compared to their non-HBV-infected counterparts. Studies taking into account HCV co-infection are lacking. The response to antiviral agents has not been well evaluated. There is no study on the effect of pre-operative suppression of HBV replication on the outcome of renal transplantation.

Patients requiring immunosuppressive therapy – Chronic hepatitis B is associated with reduced survival in the second decade after renal or cardiac transplantation (grade A) [86,87]. Short-term improvements in liver histology have been demonstrated in HBV-infected recipients of a kidney or heart given treatment with anti-viral agents (grade C). Severe fibrosing cholestatic hepatitis B has followed renal transplantation. Interferon is contra-indicated in solid organ transplant recipients due to the risk of inducing rejection (grade A). During or after a course of immunosuppressive therapy severe reactivation of HBV replication may occur, and may cause hepatic decompensation and death (grade C) [88]. There have been occasional reports of reactivation of HBV replication in anti-HBc and anti-HBs positive individuals, but most cases occur in HBsAg-positive subjects. Interferon is contra-indicated because of its suppressive effect on the bone marrow, and because of the risk of further exacerbation of hepatitis (grade B). Pre-emptive antiviral therapy using nucleoside analogues appears logical in patients receiving short courses of immunosuppression, e.g. cancer chemotherapy (grade C) [89]; however, in patients on long-term immunosuppression the development of drug resistance might limit the benefit of prolonged antiviral therapy. The optimal timing and duration of antiviral therapy in this setting remains to be determined.

Children – Treatment should be reserved for children with moderate to severe hepatitis (grade A). Children with mild disease (normal or minimally elevated aminotransferases), like adults, have a low rate of durable response to current treatment [19,90]. Interferon and lamivudine are safe in children and their efficacy is similar to that in adults [19,73,91]. Adefovir has not yet been evaluated in children.

Pregnant women – Infection in newborns might be further reduced by suppression of HBV replication in pregnant women with high serum HBV DNA levels (grade C). However, there are no data to substantiate the benefit of antiviral therapy in this setting.

In conclusion, current treatment of chronic hepatitis B has limited long-term efficacy. Thus, careful balance of patient's age, severity of liver disease, likelihood of response, and potential adverse effects and complications is needed before treatment is initiated (grade A). Antiviral therapy is not necessary in patients with acute hepatitis (grade B). Patients with fulminant hepatitis should be considered for transplantation (grade B) Decision to treat patients with chronic hepatitis should be based on hepatitis severity. Patients with mild chronic hepatitis should be

monitored and therapy considered if there is evidence of progression to moderate to severe hepatitis (grade A). Patients with *moderate to severe chronic hepatitis*, should be managed according to HBeAg status, and co-infecting virus(es) (HDV, HCV, HIV) (grade A). HBeAg-positive patients should be followed for 3–6 months and antiviral therapy administered if active HBV replication (HBV DNA above a provisional cut-off of 10^5 copies/ml) and elevated aminotransferase persist (grade A). HBeAg-negative patients should be treated with antiviral agents when there is evidence of active viral replication (HBV DNA above 10^5 copies/ml); if there is no evidence of active HBV replication other causes of liver injury should be excluded (grade A). HDV-infected patients should be treated with antiviral therapy (grade A). Patients with HCV co-infection and active HBV replication should be considered for interferon therapy, which is active against both HBV and HCV (grade B). HIV and HBV co-infected patients whose immune status is preserved or restored on HART should be considered for anti-HBV therapy following the above recommendations (grade B). Liver biopsy is recommended even in patients with normal or minimally increased serum aminotransferase levels (grade B). Anti-HBV treatment should not interfere with anti-retroviral therapy (grade C). Patients with *well-compensated cirrhosis* should be treated as above (grade A). HBsAg-positive patients with *extra-hepatic manifestations* should be considered for antiviral treatment if HBV replication is active and thought to be the cause of the clinical manifestations (grade C).

Patients with *decompensated cirrhosis* should be treated in specialized 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). It may include antiviral therapy during the pre-transplant waiting period in patients with high HBV DNA levels. Otherwise, HBV prophylaxis is started at the time of transplant. Because of the risk of late recurrence, prophylactic therapy is generally recommended for life (grade C). In patients with recurrent hepatitis B post-liver transplant, treatment with

a nucleosid(t)e analogue is recommended (grade B). The treatment chosen will depend on the patient's prior treatment history and the likelihood of drug resistance (grade C).

Health care workers with mild chronic hepatitis B should be counselled about the risk and benefit of antiviral therapy to diminish the risk of HBV transmission to patients. Patients with mild disease should be considered for treatment only if they perform procedures that may place patients at risk of infection, and if HBV DNA is detectable in serum (grade D). At present, no recommendation can be made about the lower level of HBV DNA that should trigger consideration of treatment. *Institutionalized persons* should be treated according to the above recommendations (grade B); immunization of contacts is the best way of preventing transmission (grade B).

7. What is the optimal treatment?

Available treatments for HBV infection have limited long term efficacy and potential drawbacks. Recombinant interferon- α and lamivudine have been approved for use in many countries. Adefovir has been recently approved for use in the United States and Europe, and is under review in several other regions. The advantages and limitations of interferon- α , lamivudine and adefovir are summarized in [Table 1](#). Their efficacy will be discussed below according to the forms of hepatitis B.

Other treatment that are being evaluated, have either antiviral or immunomodulatory properties, or both. New antiviral agents include entecavir, emtricitabine, clevudine, and β -L-nucleosides (β -L-thymidine and β -L-deoxycytidine). Results of phase III trials are not yet available. Immunomodulatory strategies include the use of cytokines and vaccination (using recombinant HBsAg + /- pre-S antigens with or without more potent adjuvants, an HBcAg-derived CTL epitope, or naked HBV DNA). Thymosin α -1 is the best studied of these immunomodulatory approaches. A recent meta-analysis showed a significant, although delayed, effect on virological response [92]. Thymosin α -1 has not yet been approved for use in HBV infection in many countries. In one

Table 1
Advantages and drawbacks of treatment of chronic hepatitis B with interferon, lamivudine or adefovir

	Interferon	Lamivudine	Adefovir
Route	Subcutaneous	Oral	Oral
Side effects	Many	Negligible	Nephrotoxicity (only observed at a dose higher than recommended)
Contraindications	Numerous	Uncommon	Uncommon
Drug resistance	None	– 20% year 1 – 60% year 4	None, yr 1
Costs at 1 year ^a	High	Low	Intermediate

^a Based on a 4–6-month course of interferon and 1 year of treatment duration for nucleos(t)ide analogues. The costs per sustained virological response for the three agents have not been compared. Prolongation of treatment with nucleos(t)ide analogues increases their cost compared with that of a limited course of interferon.

Table 2
Response rates (%) to antiviral therapy in patients with HBeAg-positive chronic hepatitis B

	Interferon- α		Lamivudine		Adefovir	
	12–24 weeks	Control	52 weeks	Control	48 weeks	Control
Loss of serum HBV DNA ^a	37	17	44	16	21	0
Loss of HbeAg	33	12	17–32	6–11	24	11
HBeAg seroconversion		18 ^b	16–18	4–6	12	6
Loss of HbsAg	7.8	1.8	<1	0	0	0
Normalization of ALT		23 ^b	41–72	7–24	48	16
Histologic improvement	NA ^c	NA ^c	49–56	23–25	53	25

^a Hybridization assays for interferon- α and lamivudine. PCR-based assays for adefovir.

^b Mean difference in response rate between treated and controls.

^c Not available.

recent phase II trial, pegylated interferon was compared to standard interferon, and found to be at least as effective as the latter [93]. Further phase III trials are under way, comparing pegylated interferon to lamivudine and to a combination of pegylated interferon plus lamivudine. Combination of standard interferon and lamivudine has been evaluated in randomized and non-randomized trials [94–96]. The results are inconclusive. Combinations of nucleos(t)ide analogues are under evaluation but the results are not yet available.

7.1. HBeAg-positive chronic hepatitis B

Randomized studies comparing all three agents are not available. Tables 2 and 3 summarize the available data. In patients with *mild chronic hepatitis*, sustained responses are unlikely with all three agents (grade A) [20,73–76]. Data regarding *moderate to severe chronic hepatitis* are discussed below.

7.1.1. Initial response

Based on limited data, decrease in serum HBV DNA appears more rapid with lamivudine or adefovir than with interferon (grade C). On-treatment flares in aminotransferases are more common with interferon than with lamivudine or adefovir (grade C).

7.1.2. End-of-treatment response

Data are limited for all three therapeutic agents because of the timing at which response is assessed. The response to interferon is usually assessed 6–12 months after completion of a 3–6 month course of treatment. The response to

lamivudine or adefovir has been reported after 1 year of treatment, but in many studies treatment continued beyond the first year and end-of-treatment response has not yet been reported. The results of the major clinical trials suggest that the rate of virological response is similar after a 4–6 month course of interferon or a 1-year course of lamivudine or adefovir (grade C) [20,73,91,94,97–99].

7.1.3. Predictive factors for end-of-treatment response

Pre-treatment factors predictive of response are similar for all 3 treatments and include high serum aminotransferase (> 5 \times ULN), the degree of necro-inflammatory activity, and low serum HBV DNA level (grade A) [20,73–76]. Pre-treatment aminotransferase appears to be the most important; response rates in patients with normal or minimally elevated (< 2 \times ULN) serum aminotransferase levels are low and similar to untreated patients (grade A). Recently, HBV genotype has also been shown to affect the response to interferon- α therapy, with genotype B having a higher rate of response than genotype C (grade C) [100]. However, the effect of other HBV genotypes and the influence of genotype on treatment with lamivudine and adefovir have not been examined. It should be noted that factors associated with better response are also associated with higher rates of spontaneous viral suppression and HBeAg clearance (grade A). *Dose and duration of treatment* appear to have some effect on the response to interferon [20]. Virological response is higher with doses of 9–10 MU thrice weekly (or 5 MU daily, or 6 MU/m² thrice weekly) than with lower doses. Treatment for 4–6 months or longer is superior to 3 months of therapy (grade A).

7.1.4. Sustained response

In patients who have a virological response within 1 year of the start of a 3–6 month course of *interferon- α* , the sustained virological response rate is 80–90% at 5 years (i.e. about 20% of the initial treated group). A complete response rate of 20–30% was found at 5 years in studies from Europe [20,73,101]; and 70% at 10 years in one United States study [102]. The complete response rate is less than

Table 3
Durability of response to antiviral therapy in patients with chronic hepatitis B (% sustained among end-of-treatment virological response)

	Interferon	Lamivudine	Adefovir
HBeAg + chronic hepatitis	80–90%	60–80%	?
HBeAg – chronic hepatitis	20%	< 10%	?

10% in studies from Asia [103,104]. A sustained virological response to interferon is associated with resolution of necro-inflammatory activity, no change or improvement in fibrosis, a reduced risk of hepatic decompensation, and an improvement in long-term survival (grade A). At the end of a 1-year course of *lamivudine*, the probability that the virological response achieved during treatment will be sustained for 12–16 weeks is 73–81%, with a complete response seen in only 2% [91,94,97,98]. There are few data on the sustained response rate after longer periods of follow-up. Studies from Asia have reported 1–2 year sustained response rates of 40–80% [105]. The variability of sustained response rates appears to be related to the length of treatment and more importantly the length of treatment after achieving virological response (grade C). There are as yet no data on the sustained response rate in patients given a 1-year course of *adefovir*.

7.1.5. Maintenance therapy

Data on maintenance therapy with *interferon* is limited due to adverse effects, poor tolerance and cost. *Lamivudine* therapy is well tolerated for up to 5 years (grade C) [106, 107]. Serum HBV DNA and aminotransferase levels remain lower than before treatment, the number of patients in whom HBeAg becomes undetectable continues to increase and liver histology shows no change or improvement (grade C) [108]. Continued improvement is most likely if drug resistance does not develop (grade C). However, reversal of initial benefit and hepatitis flares have been reported in patients who develop drug resistance. Data on the use of *adefovir* for longer than 1 year are limited.

7.1.6. Drug resistant mutants

The selection of drug resistant mutants has not been described with *interferon* therapy. With continuous administration of *lamivudine*, 15–30% of patients have resistant mutants at the end of 1 year of treatment and 60% after 4 years (grade B) [91,97,98,106,107,109]. The most important mutation is a substitution of valine or isoleucine for methionine in the YMDD motif of the HBV polymerase gene (rtM204V/I) (grade B). In many patients this is accompanied by a second mutation substituting methionine for leucine in an upstream region (rtL180M) [110]. *Lamivudine* resistance is more likely to occur in patients with high serum aminotransferase or high serum HBV DNA levels before treatment (grade B). Previous treatment with famciclovir may promote development of *lamivudine* resistance if there is prior selection of the L180M mutation (grade C). Previous treatment with *interferon* does not appear to promote selection of *lamivudine* resistant mutants (grade C). The emergence of *lamivudine* resistant mutants is associated with increase in serum HBV DNA levels and elevated aminotransferase levels (virological and biochemical breakthrough) (grade B). In most patients with resistant mutants, the HBV DNA and aminotransferase levels remain lower than

the pre-treatment values but some patients have significant flares in hepatitis and occasional patients develop hepatic decompensation (grade B) [98,107–109]. One study found that patients who developed hepatitis flares after development of *lamivudine* resistance were more likely to undergo HBeAg seroconversion [109]. Resistant mutants have not yet been found in patients given *adefovir* for 1 year (grade C). There are as yet no data on the rate of *adefovir* resistance after more than a year of treatment.

7.1.7. Management of treatment failure

The virological response to *lamivudine* is not affected by previous failure to respond to *interferon* (grade C). Addition of *interferon* to *lamivudine* in patients who failed therapy with *interferon* alone does not seem to confer any additional benefit compared to retreatment with *lamivudine* alone (grade C) [111]. The only phase III clinical trial of *adefovir* included a small number of patients who had not had a virological response to previous *interferon* therapy [99]. Their data were not analysed separately so the impact of non-response to prior *interferon* therapy on response to *adefovir* is unknown. Data regarding on-treatment failure during *lamivudine* therapy are scanty. Breakthrough infection (increase in serum HBV DNA after initial undetectability, and an elevated aminotransferase when the level had been normal) may be due to non-compliance or the emergence of drug resistant mutations (grade B). History taking and laboratory detection of the signature resistant mutation (M204V/I) can differentiate the two situations. With non-compliance there may be a response to restarting *lamivudine* (grade C). Drug resistant mutations have been managed with continuation of *lamivudine* (with or without addition of *adefovir*); or cessation of *lamivudine* (with or without the introduction of *adefovir*) (grade C). Recent data suggest that withdrawal of *lamivudine* was not associated with increased risk of hepatitis flares in patients who have developed *lamivudine* resistance but whose aminotransferases remain normal [112]. *Adefovir* has been shown in clinical trials to be effective in suppressing *lamivudine* resistant mutants, with a 3–4 log₁₀ reduction in serum HBV DNA level maintained for more than 48 weeks (grade B) [113]. A pilot study in patients with compensated liver disease suggested that *adefovir* alone is as effective as *adefovir* plus *lamivudine* in patients in whom *lamivudine* resistance has developed [114]. Patients who relapse after discontinuation of *lamivudine* and who do not have evidence of *lamivudine* resistance have responded to re-initiation of treatment (grade C).

7.2. HBeAg-negative chronic hepatitis B

It is difficult to compare the efficacy of the three agents as no uniform criteria were used for defining response, and wide variations in the duration of treatment were employed. Because spontaneous improvement is rare, many studies did

Table 4
Response to antiviral therapy in patients with HBeAg-negative chronic hepatitis B

Treatment	On-therapy response	Sustained response
IFN (3–6 MU t.i.w.)		
> 12 months	50–75%	20–25%
Lamivudine (100–150 mg)		
12 months	65–80%	~10%
24 months	50–60%	?
> 36 months	30–40%	?
Adefovir		
12 months	70%	?

not include placebo controls. Tables 3 and 4 summarize the available data [21].

7.2.1. Initial response

Changes in serum aminotransferase or HBV DNA levels with interferon, lamivudine and adefovir have not been assessed using comparable methods.

7.2.2. End-of-treatment response

Serum HBV DNA becomes undetectable (using non-PCR-based assays) in about 60% of patients treated with *interferon* for 4–12 months, and about 15% of untreated controls [21]. Complete response has not been achieved. With regard to *lamivudine* [21], serum HBV DNA becomes undetectable after 12 months of therapy in about 70–90% of patients using non-PCR-based assays and in about 70% if a PCR-based assay is used. Aminotransferase levels normalized in approximately 75% of patients who have a virological response with a non-PCR-based assay. A combined biochemical and virological response is achieved in about 60% of treated patients. A fall in HBV DNA and normalization of aminotransferase occur in only about 5% of untreated patients. Histological response is observed in 60% of treated patients. Complete response has not been reported. In the only phase III trial of *adefovir*, assessment at week 48 showed a much higher response rate in patients who received adefovir than in those given placebo - aminotransferase normalized in 72 vs. 29%; undetectable serum HBV DNA (PCR-based assay) in 51 vs. 0%; and histological response (decrease in HAI > 2 points with no worsening of fibrosis) in 64 vs. 33% [115].

7.2.3. Predictive factors for response

Pre-treatment factors that are predictive for response are poorly defined for all three agents. Treatment-related factors for interferon appear to include longer duration of therapy and earlier biochemical response [115]. Treatment-related factors for lamivudine and adefovir have not been established.

7.2.4. Sustained response

Sustained virological response is almost always associated with biochemical response and histological

improvement (grade A) [115]. Less than 50% of patients who have responded at the end of a 4–12 month course of *interferon* show a sustained virological response 1 year after the end of treatment (grade A). Relapse usually occurs within 1 year and in about 60% of patients is associated with a hepatitis flare (grade A). Non-randomised cohort studies with 6-year follow-up after a short (< 1 year) initial course of interferon indicated that virological and biochemical response is sustained in approximately 20–25% of treated patients [115]. It should be noted that some of the patients included in these studies had been re-treated. At a median follow-up of 6 years, HBsAg became undetectable in approximately 50% of patients with a sustained virological response but in only 10% of those who relapsed after an initial response (grade A) [115]. Long-term prognosis appears to be improved in sustained responders as compared to non-responders (grade C) [115]. In patients with a virological response at the end of a 6–12 month course of *lamivudine*, the 6-month sustained virological response rate is less than 15% (grade A) [115]. Complete response has not been reported following lamivudine therapy. The rate of sustained response to *adefovir* is still unknown.

7.2.5. Maintenance therapy

Data on maintenance *interferon* therapy beyond 2 years are lacking. With regard to *lamivudine*, virological and biochemical response rates peak at 12 months and decrease thereafter. At 30 months, rates of virological and biochemical responses are about 30% and 60%, respectively [21]. There are no data on maintenance therapy with *adefovir*.

7.2.6. Drug resistant mutants

Drug resistant mutants have not been reported with *interferon*. *Lamivudine* resistant mutants appear in 10–40% of patients treated with lamivudine for 1 year, and in 50–60% of those treated continuously for 3 years (grade B) [21]. The emergence of resistant mutants is accompanied by an increase of HBV DNA in serum and in most patients, after a few months delay, by elevation in aminotransferase levels (grade B) [116]. Emergence of lamivudine resistant mutants can be associated with reversion of the precore stop codon mutation and return of detectable serum HBeAg [117]. Flares occur in about 30% of patients with a lamivudine resistant mutant (grade C) [21,116]. These flares can be symptomatic or severe (grade B). Duration of therapy has been associated with the rate of lamivudine resistance (grade C) [117]. Drug resistant mutants have not been reported after the administration of *adefovir* for 1 year (data for longer periods of treatment are not available).

7.2.7. Management of treatment failure

Data are as described above for HBeAg-positive patients (grade C).

7.3. Decompensated cirrhosis

Interferon treatment is poorly tolerated. Infectious complications and exacerbation of hepatitis can be lethal in these patients (grade A) [118]. *Lamivudine* therapy can induce marked improvement in liver disease, impacting favourably on survival but the clinical effects are slow and benefit is observed mainly in patients who complete at least 6 months of treatment (grade B) [77,78]. Thus, patients with advanced liver failure derive little benefit from lamivudine. Emergence of lamivudine resistant mutants may be associated with flares in hepatitis, worsening of liver disease and death (grade B). In addition, patients in whom lamivudine resistance develops before transplant have a higher risk of recurrent hepatitis B post-transplant (grade C). In a recent study, adefovir reduced serum HBV DNA levels and improved or stabilized liver disease; however, an increase in serum creatinine > 0.5 mg/dl was observed in 28% of patients after 48 weeks of treatment [119]. There are no data on the use of adefovir as a first line therapy in patients with decompensated cirrhosis.

7.4. Special patients groups

7.4.1. Prevention of HBV recurrence post liver transplant

For patients with undetectable or low serum HBV DNA level, there is no evidence that pre-transplant antiviral therapy is beneficial (grade C). HBV re-infection can be significantly reduced by intravenous administration of HBIG but the rate of HBV reinfection remains high (30–60% at 3 years post-transplant) in cirrhotics who were HBeAg and/or serum HBV DNA positive (using non-PCR-based assays) pre-transplant (grade A) [79,80]. Therefore, patients with high serum HBV DNA levels should receive antiviral therapy prior to transplantation, and combination of HBIG alone or in combination with lamivudine should be used post-transplant (grade B). Various protocols aimed at decreasing the requirement for HBIG, and thus the cost, are under study. They include HBV vaccination, and low dose or limited duration of HBIG in combination with antiviral agents. The optimal prophylactic regimen in the era of nucleosid(e) analogues has not been determined.

7.4.2. Post-transplant patients with recurrent hepatitis B

Administration of *interferon* is associated with an increased risk of rejection, and its efficacy in patients with recurrent hepatitis B is uncertain. *Lamivudine* therapy for recurrent hepatitis B following transplantation achieves results similar to those in non-transplant patients with respect to inhibition of HBV replication, and normalization of serum aminotransferase (grade B) [81]. It can also be beneficial for patients with fibrosing cholestatic hepatitis. The incidence of drug resistant mutation may be higher than in non-transplant patients (grade C). Breakthrough infection secondary to lamivudine resistance may lead to severe hepatitis flares, rapidly progressive liver failure and graft

loss (grade C) [120]. *Adefovir* has been effective in decreasing serum HBV DNA levels and in improving or stabilizing liver disease in patients who have lamivudine resistant mutants post-transplant (grade B) [119–121]. *Adefovir* has not been evaluated as a first-line therapy in the transplant setting and increase in serum creatinine has been observed in a proportion of patients after 1 year of therapy [119]. It is unclear if the worsening in renal function is due to adefovir or to other nephrotoxic medications given concurrently.

7.4.3. HIV and HBV co-infection

The response to *interferon* was poor in studies performed before the introduction of HART (grade C). There have been no studies evaluating the efficacy of interferon since the introduction of HART. From the limited data available *lamivudine* appears to show similar effect in HBeAg-positive patients on HART (with preserved or restored immune function), in terms of virological and biochemical response, as in patients with chronic hepatitis B who are not infected with HIV (grade C) [122,123]. Drug resistant HIV emerges rapidly during monotherapy with lamivudine (grade A). At the dose recommended for HBV, *adefovir* has no effect on HIV replication. Tenofovir is effective in suppressing replication of wild-type and lamivudine resistant HIV and HBV (grade C) [124].

7.4.4. Chronic hepatitis D

Lamivudine is ineffective (grade B). *Adefovir* has not been evaluated. *Interferon-α* is the only treatment that has been shown to be effective in chronic hepatitis D (grade A). The response is related to the dose and duration (grade B). A dose of 9 MU thrice weekly for 1 year inhibits HDV replication (undetectable serum HDV-RNA and anti-HDV IgM) in 10–30% of treated patients whereas end-of-treatment biochemical response is achieved in 70% of patients (Grade A) [85]. Biochemical response appears to be sustained in about 50% of patients (Grade B). In long-term sustained responders there may be reversion of fibrosis and in some instances reversal of cirrhosis, and HBsAg can become undetectable (grade C). Whether therapy should be maintained in all patients, only in biochemical responders, or in those who relapse after a 1-year course of interferon treatment has not been addressed. Factors that can predict efficacy have not yet been identified.

7.4.5. HBV-infected patients requiring immunosuppressive therapy

Interferon therapy is contra-indicated because of haematological side effects (in association with cancer chemotherapy) and the risk of exacerbating immune-mediated diseases (auto-immune disorder, graft rejection or graft-versus-host disease) (grade A). Pre-emptive therapy with lamivudine has reduced hepatitis B exacerbation following haematopoietic stem cell transplantation (grade B) [89]. From limited data, it appears that lamivudine given at the time of

Table 5
Recommended management strategies for chronic hepatitis B

HBeAg	HBV DNA ^a	ALT	Cirrhosis	Management
+	+	<2 × ULN	No	Low efficacy of interferon, lamivudine, adefovir Observe
+	+	>2 × ULN	No	(1) Interferon, (2) lamivudine or adefovir Interferon non response or contraindications: → lamivudine or adefovir
–	+	>2 × ULN	No	(1) Interferon, (2) lamivudine or adefovir Long-term treatment required
–	–	Normal	Yes	No treatment required
+/-	+	Abnormal	Yes	Compensated → Interferon, lamivudine or adefovir
+/-	–		Yes	Decompensated → Lamivudine or adefovir, transplant Compensated → Observe Decompensated → Transplant

^a HBV DNA in serum >10⁵ copies/ml.

an exacerbation of hepatitis suppresses HBV replication and leads to improvement in liver disease (grade C). There are no studies comparing pre-emptive versus as-needed lamivudine therapy.

7.4.6. Hemodialysis patients

Data on all three agents are limited.

7.5. Recommendations

Based on the above evidence, the following recommendations can be made. Patients should be counselled on the risk of transmission to household, sexual, and professional contacts (grade B). They should be instructed in the need for safe sex, safe injections, and in the case of health care providers the use of universal precautions (grade B). Vaccination should be considered for contacts, especially sexual and household contacts (grade B). Patients should be advised and helped to control other conditions that might result in liver damage, such as obesity or excessive alcohol consumption (grade C). Hepatitis A vaccination should be considered if not already immune, and at risk (grade B). Patients should be informed that immunosuppressive therapy can adversely affect the course of hepatitis B. Should such treatment be required, patients should be recommended to seek advice from a hepatologist (grade D).

Antiviral strategies are summarized in Tables 5 and 6. The approach to antiviral therapy should take into account the limited long-term efficacy of the three approved therapeutic agents, their side effects, their costs and the predictive factors for response. Full discussion with the patient regarding the pros and the cons of different strategies should lead to a joint decision about management.

The following strategies are recommended for patients with *HBeAg-positive moderate or severe chronic hepatitis without cirrhosis*. If there is no contra-indication to interferon therapy: a 4–6 month course of interferon- α (5 MU daily or 9–10 MU thrice weekly, or 6 MU/m² thrice weekly in children) can be considered initially (grade A). If interferon is contra-indicated, or if a patient does not

respond to or cannot tolerate interferon, lamivudine or adefovir should be considered (grade B). Lamivudine should be given at a dose of 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 response against the risk of developing drug resistance (higher for lamivudine, lower for adefovir), or drug toxicity (lower for lamivudine, higher for adefovir) (grade B). If hepatitis relapses on stopping lamivudine therapy, the drug can be reintroduced as maintenance therapy if the patient has not developed drug resistance (grade C). More information on safety and propensity for causing 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. If there is no contra-indication to interferon therapy, an initial 12–24 month course of interferon- α , 5–6 MU thrice weekly should be considered (grade B). If interferon is contra-indicated, or if a patient does not respond to or cannot tolerate interferon, lamivudine or adefovir therapy should be considered (grade B). Lamivudine should be given at a dose of 100 mg daily (grade A).

Table 6
Main characteristics of the three antiviral therapies for chronic hepatitis B

	IFN	Lamivudine	Adefovir
Indications			
HBeAg +, normal ALT	–	–	–
HBeAg + chronic hepatitis	+	+	+
HBeAg – chronic hepatitis	+	+	+
Decompensated cirrhosis	–	+	+
Duration of treatment			
HBeAg + chronic hepatitis	4–6 months	>1 year	>1 year
HBeAg – chronic hepatitis	12 months	>>1 year	>>1 year
Decompensated cirrhosis	NA	Indefinite	Indefinite

Adefovir should be given at a dose 10 mg daily (grade A). Because HBeAg is already undetectable, the end-points for 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 1 year of treatment but a decision to continue therapy beyond 1 year should weigh the likelihood of benefit against the risk of developing resistance or drug toxicity, similar to the above statement for HBeAg-positive chronic hepatitis B (grade C). If hepatitis relapses on stopping lamivudine therapy, lamivudine 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 is thought to be due to emergence of *lamivudine resistant mutants*, the therapeutic options include (grade C): (i) continue lamivudine if serum HBV DNA and aminotransferase levels are lower than they were pretreatment; (ii) discontinue lamivudine and monitor, in patients without underlying cirrhosis and who are not immunosuppressed; (iii) change to or add adefovir.

Patients with *cirrhosis* but without clinical or laboratory signs of decompensation (normal prothrombin, serum bilirubin and serum albumin levels) 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). Cirrhotic patients with clinical or laboratory signs of decompensation should be evaluated for liver transplantation (grade C). If they show active HBV replication they should receive antiviral therapy (grade C). The optimal timing for antiviral therapy should depend on the patient's condition and expected waiting time for a new liver. 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) Delay the initiation of lamivudine until transplant is imminent (i.e. 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- α , 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 and severity of liver disease (grade C).

If highly active anti-retroviral therapy (HART) is indicated for a *patient co-infected with HIV* lamivudine should be included in HART (grade A). Exacerbation of hepatitis deemed to be due to emergence of lamivudine resistant mutants should be treated with tenofovir, which has an effect on HIV and lamivudine resistant HBV (grade C). If HART is not indicated, lamivudine should not be used because it rapidly induces HIV drug resistance when used as a monotherapy (grade A). Adefovir should then be used as a first line anti-HBV agent (grade D).

No clear recommendation can be made at present for treatment of hepatitis B in *haemodialysis patients*.

If *HBV-infected patients require immunosuppressive therapy*, lamivudine is generally preferable to interferon as antiviral therapy (grade C). There is no data to support whether treatment should be started pre-emptively (2–4 weeks before starting immune suppressive therapy) or at the first sign of an exacerbation of the hepatitis, and when treatment should be stopped (grade C). For patients receiving a *finite course of immunosuppressive treatment* such as cancer chemotherapy, it seems sensible to use pre-emptive antiviral therapy and continue for 3–6 months after cessation of immune suppressive therapy (grade C). In patients who are to receive *life-long immune suppressive treatment* (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. It may be an alternative to lamivudine if further data confirm its long-term safety (grade D).

8. How should patients with chronic hepatitis b be monitored?

Monitoring aims to assess liver disease progression, clarify the indications for treatment and to evaluate the response to therapy.

In patients with **severe acute hepatitis**, the aim of monitoring is to decide whether and when urgent liver transplantation is needed. These patients should be referred to specialized units (grade D).

Patients with **mild chronic hepatitis** should be monitored to detect the progression to moderate to severe chronic hepatitis using 6-monthly determination of serum aminotransferase levels (grade A). When a sustained increase of aminotransferases to a level $> 2 \times$ ULN is confirmed and serum HBV DNA level is $> 10^5$ copies/ml, antiviral treatment should be considered (grade A). A liver biopsy may be performed to document the progression to moderate to severe hepatitis (grade A). Patients with mild chronic hepatitis are at increased risk of developing hepatocellular carcinoma although to a lesser extent than patients with more active disease and cirrhosis (grade A). A major limitation in recommending surveillance for HCC is the lack

of data on the optimal frequency, the cost-effectiveness, and more importantly, the impact on survival.

Patients with newly diagnosed **HBeAg-positive moderate to severe chronic hepatitis** should be monitored for 3–6 months with 1–3-monthly determination of serum aminotransferases, HBeAg and HBV DNA to identify those patients that will spontaneously clear HBeAg and therefore will not require antiviral therapy (grade A). Antiviral treatment should not be delayed for patients with hepatic decompensation due to severe hepatitis flare (grade C). Markers of on-going viral replication (serum HBeAg, anti-HBe and HBV DNA) should be repeated just before initiating therapy (grade A).

Patients with **HBeAg-negative moderate to severe chronic hepatitis** can be initiated on treatment 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 (grade A). For this purpose, abdominal ultrasound, platelet count, and determination of prothrombin time, serum albumin and bilirubin levels appear appropriate. The required frequency of assessment will depend on the overall severity of the liver disease.

In patients with **well-compensated cirrhosis**, monitoring aims at identifying patients who may benefit from early therapy for complications. Endoscopy should be performed to screen for oesophageal varices and β -adrenergic blockers administered to patients with moderate to large varices (grade A). Endoscopy should be repeated every 2–3 years when varices are initially absent (grade A). The optimal strategy for HCC surveillance is not clear. Ultrasound can detect small tumors but it is operator dependent. Serum α -foetoprotein monitoring can detect some asymptomatic HCC but there are problems with false positive and false negative results. The additional value of α -foetoprotein determination is not established. Based on the average tumor doubling time, 6-month interval is most commonly used in HCC surveillance (grade C). The frequency of clinical and laboratory examination (prothrombin, serum albumin and bilirubin) should be adapted to the overall severity of disease (grade B). The aim is to detect early signs of impaired hepatic function that will prompt consideration for liver transplantation (grade A).

In patients given antiviral therapy, monitoring aims at the assessment of response, the detection of treatment related hepatitis flares, selection of drug resistant mutants, occurrence of treatment related side effects and the evaluation of treatment compliance (grade A). Aminotransferases should be monitored monthly for 3–6 months during antiviral therapy, for 6 months afterwards, and then 6-monthly. Among patients with **HBeAg-positive chronic hepatitis**, those treated with *interferon* should be tested for serum HBeAg, anti-HBe, and HBV DNA levels at the termination of the course, and every 6 months thereafter to

assess virological response (grade A). In those patients treated with *lamivudine* or *adefovir*, tests for 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 breakthrough (grade B). Monitoring serum HBV DNA level using a PCR-based assay and testing for YMDD mutant (where available) in patients receiving lamivudine therapy may permit earlier detection of genotypic resistance and virologic breakthrough (grade B). Further research is needed to determine the optimal timing for treatment modification and the impact of this approach on the outcome of the patients. In patients receiving antiviral treatment for **HBeAg-negative chronic hepatitis**, monitoring serum HBV DNA level is the only means to assess virological response (grade C). The therapeutic end-point is unclear as relapse is common even in patients with persistently undetectable serum HBV DNA using PCR assays.

Durability of virological response should be monitored every 1–3 months during the first 12 months after cessation of antiviral therapy, and every 6–12 months thereafter (grade B). Monitoring will include testing of liver chemistries and HBV DNA. Patients who were previously HBeAg-positive, should be tested for HBeAg and anti-HBe. HBsAg should be re-tested yearly in patients with sustained virological response (grade B).

Outside clinical trials the benefit of repeating **liver biopsy** in sustained biochemical and virological responders has not been established. Because of marked variability in the course of chronic HBV infection, decision on when to repeat liver biopsies should be made on a case by case basis, according to the likelihood that the results will affect management (grade C).

9. What are the main unresolved issues?

9.1. Public health implications and prevention of transmission

By far the most important issue is how to lessen or to share the economic burden of prophylaxis and care for HBV infection in poor countries where most of the HBV-infected persons live. Other major issues include: the impact of universal vaccination on the selection of vaccine escape mutants; the decrease in the acceptance of HBV vaccine; the position of HBV-infected health care workers (quantitatively less important).

9.2. 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 which trigger the immunoreactive phase would allow more efficient monitoring and hopefully better timing of the initiation of antiviral

therapy. Clarification of the factors responsible for a rapid resolution of infection may help in designing new therapies or in refining available treatment. Further characterization of the host, viral and environmental factors associated with development of HCC would allow targeting of surveillance programs. Development of more sensitive serum markers of HCC is urgently needed to improve the early detection and ultimately survival of patients with HCC.

9.3. Diagnosis and classification

The main issue pertains to quantification of serum HBV DNA levels. Standardization of the assays should be promptly achieved. The clinical significance of low serum HBV DNA levels in relation to the natural history of hepatitis B should be examined and the relation between serum HBV DNA levels and clinical outcome studied. The distinction between the inactive carrier state and HBeAg-negative chronic hepatitis needs to be defined. Surrogate tests proposed for the assessment of disease activity or viral replication such as quantification of IgM anti-HBc or HBeAg must be standardized and their clinical value assessed. Reliable non-invasive tests that may be an alternative to liver biopsy for grading and staging hepatitis B should be developed.

9.4. 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 not associated with hepatitis flares and drug resistance are needed. The added value of pegylated interferon over the less expensive standard α interferons, singly and in combination with nucleoside(t) analogues, and the benefit of prolonging the duration of interferon therapy beyond the currently accepted duration should be assessed. Factors that predict sustained response to a limited course of lamivudine or adefovir or the development of drug resistant mutants, and those that determine the renal toxicity of adefovir should be examined. It is anticipated that future treatment trials will use active and not placebo controls. Because of drug resistance with nucleoside analogue monotherapy, combination therapy must be evaluated. Reducing the cost of measures that prevent recurrence after liver transplantation is urgently needed. The strategy for management of reactivation in patients requiring immune suppressive therapy must be clarified.

9.5. Monitoring

The major issue is the value of serum HBV DNA quantification to assess the antiviral response to therapy and in monitoring disease progression. The value of viral kinetics in predicting treatment response should be examined. HBV DNA levels associated with clinically significant virological response need to be defined. When

they have been standardized, cheaper surrogate markers for virological response (e.g. serum IgM anti-HBc or HBeAg titer) need further evaluation as do non-invasive markers for the assessment of necroinflammation and fibrosis.

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