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EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

Introduction

Our understanding of the natural history of hepatitis B virus (HBV) infection and the potential for therapy of the resultant disease is continuously improving. New data have become available since the previous EASL Clinical Practice Guidelines (CPGs) prepared in 2008 and published in early 2009 [1]. The objective of this manuscript is to update the recommendations for the optimal management of chronic HBV infection. The CPGs do not fully address prevention including vaccination. In addition, despite the increasing knowledge, areas of uncertainty still exist and therefore clinicians, patients, and public health authorities must continue to make choices on the basis of the evolving evidence.

Context

Epidemiology and public health burden

Approximately one third of the world's population has serological evidence of past or present infection with HBV and 350–400 million people are chronic HBV surface antigen (HBsAg) carriers. The spectrum of disease and natural history of chronic HBV infection are diverse and variable, ranging from an inactive carrier state to progressive chronic hepatitis B (CHB), which may evolve to cirrhosis and hepatocellular carcinoma (HCC) [2–4]. HBV-related end stage liver disease or HCC are responsible for over 0.5–1 million deaths per year and currently represent 5–10% of cases of liver transplantation [5–8]. Host and viral factors, as well as coinfection with other viruses, in particular hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV) together with other co-morbidities including alcohol abuse and obesity, can affect the natural course of HBV infection as well as efficacy of antiviral strategies [2–8]. CHB may present either as hepatitis B e antigen (HBeAg)-positive or HBeAg-negative CHB. The prevalence of the HBeAg-negative form of the disease has been increasing over the last decade as a result of aging of the HBV-infected population and predominance of specific HBV genotypes and represents the majority of cases in many areas, including Europe [4,9,10]. Morbidity and mortality in CHB are linked to persistence of viral replication and evolution to cirrhosis and/or hepatocellular carcinoma (HCC). Longitudinal studies of untreated patients with CHB indicate that, after diagnosis, the 5-year cumulative incidence of developing cirrhosis ranges from 8% to 20%. The 5-year cumulative incidence of hepatic decompensation is approximately 20% for untreated patients with compensated cirrhosis [2–4,11–13]. Untreated patients with decompensated cirrhosis have a poor prognosis with a 14–35% probability of survival at 5 years [2–4,12]. The worldwide incidence of HCC has increased, mostly due to persistent HBV and/or HCV infections; presently it constitutes the fifth most common cancer, representing around 5% of all cancers. The annual incidence of HBV-related HCC in patients with CHB is high, ranging from 2% to 5% when cirrhosis is established [13]. However, the incidence of HBV related HCC appears to vary geographically and correlates with the underlying stage of liver disease and possibly exposure to environmental carcinogens such as aflatoxin. Population movements and migration are currently changing the prevalence and incidence of the disease in several low endemic countries in Europe and elsewhere. Substantial healthcare resources will be required for control of the worldwide burden of disease.

Natural history

Chronic HBV infection is a dynamic process. The natural history of chronic HBV infection can be schematically divided into five phases, which are not necessarily sequential.

(1) The "immune tolerant" phase is characterised by HBeAg positivity, high levels of HBV replication (reflected by high levels of serum HBV DNA), normal or low levels of aminotransferases, mild or no liver necroinflammation and no or slow progression of fibrosis [2,3,6,8]. During this phase, the rate of spontaneous HBeAg loss is very low. This first phase is more frequent and more prolonged in subjects infected perinatally or in the first years of life. Because of high levels of viremia, these patients are highly contagious.
(2) The "immune reactive HBeAg-positive phase" is characterised by HBeAg positivity, relatively lower level of replication compared to the immune tolerant phase (as reflected by lower serum HBV DNA levels), increased or

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Contributors: *George Papatheodoridis (Coordinator & EASL Governing Board), Maria Buti, Markus Cornberg, Harry Janssen, David Mutimer, Stanislas Pol, Giovanni Raimondo;* ***Reviewers:*** *EASL Governing Board, Geoffrey Dusheiko, Anna Lok, Patrick Marcellin.*
* Correspondence: EASL Office, 7 rue des Battoirs, CH-1205 Geneva, Switzerland. Tel.: +41 22 807 0360; fax: +41 22 328 0724.
E-mail address: easloffice@easloffice.eu (European Association for the Study of the Liver).

Table 1. Grading of evidence and recommendations (adapted from the GRADE system) [32–37].

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C
Grading of recommendation	**Notes**	**Symbol**
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty; higher cost or resource consumption	2

fluctuating levels of aminotransferases, moderate or severe liver necroinflammation and more rapid progression of fibrosis compared to the previous phase [2–4,6,8]. This phase may occur after several years of immune tolerance (partial breakdown of tolerance) and is more frequently and/or more rapidly reached in subjects infected during adulthood, paralleling maturation of specific anti-HBV immunity. It may last for several weeks to several years. The rate of spontaneous HBeAg loss is enhanced. This phase ends with seroconversion to anti-HBe.

(3) The "inactive HBV carrier state" may follow seroconversion from HBeAg to anti-HBe antibody. It is characterised by very low or undetectable serum HBV DNA levels and normal serum aminotransferases. A minimum follow-up of 1 year with alanine aminotransferase (ALT) levels at least every 3–4 months and serum HBV DNA levels is required before classifying a patient as inactive HBV carrier. ALT levels should remain persistently within the normal range according to traditional cut-off values (approximately 40 IU/ml) [14] and HBV DNA should be below 2000 IU/ml. Some inactive carriers, however, may have HBV DNA levels greater than 2000 IU/ml (usually below 20,000 IU/ml) accompanied by persistently normal ALT levels [14–17]. Patients with HBV DNA <2000 IU/ml and elevated ALT values should be usually advised to undergo liver biopsy for the evaluation of the cause of liver injury. As a result of immunological control of the infection, the inactive HBV carrier state confers a favourable long-term outcome with a very low risk of cirrhosis or HCC in the majority of patients [18–20]. HBsAg loss and seroconversion to anti-HBs antibody may occur spontaneously in 1–3% of cases per year, usually after several years with persistently undetectable HBV DNA [15]. On the other hand, progression to CHB, usually HBeAg-negative, may also occur [21]. Therefore, inactive HBV carriers should be followed up for life with ALT determinations at least every 6 months after the first year and periodical measurement of HBV DNA levels [14]. The follow-up should be closer in cases with baseline serum HBV DNA levels above 2000 IU/ml, in whom non-invasive evaluation of liver fibrosis may be useful and even liver biopsy might be considered [14]. Inactive carriers have been reported to have serum HBsAg levels <1000 IU/ml, but such HBsAg levels may occasionally be detected in CHB patients as well [22].

(4) "HBeAg-negative CHB" may follow seroconversion from HBeAg to anti-HBe antibodies during the immune reactive phase or may develop after years or decades of the inactive carrier state. It represents a later immune reactive phase in the natural history of chronic HBV infection. It is characterised by periodic reactivation with a pattern of fluctuating levels of HBV DNA and aminotransferases and active hepatitis [4,23–25]. These patients are HBeAg-negative and harbour a predominance of HBV virions with nucleotide substitutions in the precore and/or the basal core promoter regions that are hence unable to express or express low levels of HBeAg. HBeAg-negative CHB is associated with low rates of prolonged spontaneous disease remission [4,23]. It is important and sometimes difficult to distinguish true inactive HBV carriers from patients with active HBeAg negative CHB in whom phases of spontaneous remission may occur. The former patients have a good prognosis with a very low risk of complications, while the latter patients have active liver disease with a high risk of progression to advanced hepatic fibrosis, cirrhosis and subsequent complications such as decompensated cirrhosis and HCC. A careful assessment of the patients is needed and, as reported in the inactive carrier state, a minimal follow-up of 1 year with serum ALT levels every 3–4 months and HBV DNA levels usually allows detection of fluctuations of activity in patients with active HBeAg-negative CHB [23].

(5) In the "HBsAg-negative phase" after HBsAg loss, low-level HBV replication may persist with detectable HBV DNA in the liver [26]. Generally, HBV DNA is not detectable in the serum, while anti-HBc antibodies with or without anti-HBs are detectable. HBsAg loss before the onset of cirrhosis is associated with improvement of the outcome with reduced risk of cirrhosis, decompensation and HCC. The clinical relevance of occult HBV infection [detectable HBV DNA in the liver with low level (<200 IU/ml) or undetectable HBV DNA in blood] is unclear [26]. Immunosuppression may lead to HBV reactivation in these patients [27,28]. If cirrhosis has developed before spontaneous or treatment-induced HBsAg loss, patients remain at risk of