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TOPIC HIGHLIGHT

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DNA-guided hepatitis B treatment, viral load is essential, but not sufficient

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Abstract

Hepatitis B virus (HBV) infection is a global public health problem that concerns 350 million people worldwide. Individuals with chronic hepatitis B (CHB) are at increased risk of developing liver cirrhosis, hepatic de-compensation and hepatocellular carcinoma. To maintain undetectable viral load reduces chronic infection complications. There is no treatment that eradicates HBV infection. Current drugs are expensive, are associated with adverse events, and are of limited efficacy. Current guidelines try to standardize the clinical practice. Nevertheless, controversy remains about management of asymptomatic patients with CHB who are hepatitis B e antigen (HBeAg)-positive with normal alanine aminotransferase, and what is the cut-off value of viral load to distinguish HBeAg-negative CHB patients and inactive carriers. We discuss in detail why DNA level alone is not sufficient to begin treatment of CHB.

Key words: Hepatitis B virus; Viral DNA; Alanine transaminase; Antiviral drug; Hepatitis B e antigen; Antiviral drug resistance

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INTRODUCTION

Hepatitis B virus (HBV) infection is a global public health problem. An estimated 350 million people worldwide are chronically infected with HBV. Approximately 500 000 die annually from HBV-related liver disease[1]. The prevalence and concerns to public health institutions about HBV infection vary according to geographical origin.

Individuals with chronic hepatitis B (CHB) are at increased risk of developing serious problems including liver cirrhosis, hepatic de-compensation and hepatocellular carcinoma (HCC). Fifteen to forty percent of these individuals will develop serious sequelae during their lifetime and have greater evolution to cirrhosis or HCC[2,3]. The 5-year rate of progression from CHB to cirrhosis is estimated to be 12%-20%[4-7]. In patients with cirrhosis, the 5-year cumulative risk of developing HCC is 17% in East Asia and 10% in Western Europe and the United States, and the 5-year liver-related death rate is 15% in Europe and 14% in East Asia[8,9]. Seropositivity for the hepatitis B surface antigen (HBsAg) is one of the most important risk factors for HCC[10]. Seropositivity for hepatitis B e antigen (HBeAg) is associated with an increased risk for HCC, and it is significant regardless of serum level of alanine aminotransferase (ALT) and status of liver cirrhosis[8,10,11]. The risk of progression appears to be greatest in patients who progress from an immunotolerant to an immune-clearance phase[12], in patients who have delayed HBeAg seroconversion[13], and in patients who have reactivation of HBV replication after HBeAg seroconversion[14-16].

Disease progression is variable and multifactorial. It is influenced by several factors including replicating activity of the virus, and host and environmental factors[17]. Four phases of CHB have been defined: immunotolerant phase, immune active phase, HBeAg seroconversion to anti-HBeAg, and inactive carrier.

HBV eradication should be useful for patients and society at large. General actions have been developed to prevent HBV infection: universal vaccination at birth, pregnancy screening measures, sexual education, and preventive and prophylactic management of clinical devices. Immigration, cheap air travel and globalization, are changing epidemiological patterns and pre-core mutation prevalence[18]. HBV suppression and reduction of necro-inflammatory activity in CHB may prevent cirrhosis, liver failure and HCC[19,20]. Unfortunately, because of extra-hepatic reservoirs, integration of HBV DNA into the host genome and protected intracellular, covalently closed circular DNA, HBV cannot be eradicated with current therapies. The next best alternative is sustained suppression of HBV replication until HBV DNA is undetectable. A viral load of > 10000 copies/mL (2000 IU/mL) is a strong risk predictor of HCC, independent of HBeAg status, ALT level and liver cirrhosis[10,21,22]. Secondary targets are ALT normalization (biochemical response), hepatic necro-inflammatory improvement (histological response) and HBeAg seroconversion. Complete response includes fulfilling biochemical criteria, virological response and loss of HBsAg.

CONSENSUS GUIDELINES

There are consensus guidelines that help the clinician to make decisions about whether or not to treat a patient[23-27]. Treatment decision items are: HBeAg-positive or HBeAg-negative, serum viral load measured by polymerase chain reaction, elevated transaminases, histological lesions, duration of CHB (age > 40 years is likely to be a surrogate marker of disease duration) and family history of HCC. However, there are still areas of controversy in actual treatment of CHB. The long-term efficacy and safety are unknown. The question is who should be treated, how and especially when. The main guidelines are from the American Association for the Study of Liver Disease (AASLD Practice Guidelines)[24]. Their recommendations are summarized.

AASLD practice guidelines (Ⅰ)

Treatment of patients with HBeAg-positive CHB: (1) Treatment should be considered if ALT is > 2 ULN or moderate/severe hepatitis is found upon biopsy, and HBV DNA is > 20000 IU/mL; liver biopsy may be considered prior to treatment if illness is compensated. Treatment should be delayed for 3-6 mo in persons with compensated liver disease, to determine if spontaneous HBeAg seroconversion occurs. Patients with icteric flares or clinical de-compensation should be promptly treated. (2) If ALT is persistently normal or minimally elevated (< 2 ULN) and viral DNA is > 20000 IU/mL, current treatment has low efficacy. Generally, treatment should not be initiated in these patients. Liver biopsy may be considered in patients with fluctuating or minimally elevated ALT, especially in those aged > 40 years old, or those with a family history of HCC. Treatment may be initiated if there is a moderate or severe necro-inflammation or significant fibrosis upon liver biopsy.

Recommendation for monitoring HBeAg-positive patients: (1) Patients with persistently normal ALT should be tested for ALT at 3-6-mo intervals, and for ALT/HBV DNA more often if ALT becomes elevated. (2) HBeAg status should be checked every 6-12 mo. (3) Patients who remain HBeAg-positive with HBV DNA > 20000 IU/mL after 3-6 mo with elevated ALT levels of 1-2 ULN, or DNA levels > 20000 IU/mL and aged < 40 years old, should be considered for liver biopsy. Treatment should be considered if liver biopsy shows moderate/severe inflammation.

AASLD practice guidelines (Ⅱ)

Treatment of patients with HBeAg–negative CHB: (1) If ALT is > 2 × ULN, and HBV DNA is > 2000 IU/mL, treatment should be considered. (2) If ALT is 1-2 × ULN and DNA is 2000-20000 IU/mL, liver biopsy may be considered. Treatment may be initiated if liver biopsy shows moderate/severe necro-inflammation or significant fibrosis. (3) If ALT level is normal and DNA is < 2000 IU/mL, patients should not be treated. Patients should be tested for ALT every 3 mo during the first year to verify that they are truly in the inactive carrier state, and then every 6-12 mo. Test DNA and more frequent monitoring should be performed if ALT or AST increases above the normal limit. Patients should be observed and treated if HBV DNA or ALT increase.

HbeAg-negative and anti-HBeAg-positive patients with cirrhosis: Patients with compensated cirrhosis and HBV DNA > 2000 IU/mL and those with de-compensated cirrhosis and detectable HBV DNA by PCR assay should be considered for antiviral therapy, regardless of serum ALT level. The aim of the treatment in CHB patients is to achieve a maximum decrease in viral load. If serum DNA levels decrease to undetectable levels, by PCR, there is a reduction, not absence, of complications associated with HBV.

AASLD PRACTICE GUIDELINES

The new AASLD practice guidelines follow the traditional criteria of treatment, but, as with other guidelines[26,27], incorporate current tendencies to increase the viral load value. This adds the recommendation of treatment for HBeAg-negative patients with serum DNA level > 2000 IU/mL (10^4 copies/mL) and ALT < 2 × ULN, if biopsy shows moderate/severe necro-inflammation and significant fibrosis.

There is no doubt in the management of cases according to the guidelines. There are two areas of controversy. Management of asymptomatic HBeAg-positive patients with normal ALT levels and without the following criteria: advanced histological findings, recurrent hepatitis flares, age > 40 years with persistently high HBV DNA levels, and family history of HCC. The other area of ongoing debate is the differentiation between the inactive carrier state and asymptomatic

HbeAg-negative CHB with normal ALT. We do not know what is the cut-off value of DNA used to define these two phases of CHB infection. The main question in CHB treatment is if the new antiviral therapies permit treatment only guided by DNA levels and ignore other factors such as ALT level or histology.

Lok and McMahon consider that treatment is indicated if the risk of liver–related mortality and morbidity in the near future (5-10 years), and the likelihood of achieving maintained viral suppression after a defined course of treatment are high[24]. However, present therapies have a high cost and limited efficacy. Response to treatment is limited by adverse events [interferon (IFN)α and pegylated (PEG)-IFNα], drug interactions, drug resistance [nucleotide and nucleoside analogs (NAs)], relapses after suspension of treatment, and limited adherence to long-term treatments.

It may be that the approach to treatment of CHB patients with normal ALT must be done on an individual basis, and must consider serum viral levels measured by PCR, elevated transaminases, histological lesions, age, CHB phases, and family history of HCC. The response to treatment changes with the different phases of illness.

VIRAL LOAD AND TREATMENT: FAVORABLE ARGUMENTS

It is known that maintained high levels of HBV DNA are associated with progressive liver disease. Serum DNA levels are a prognostic factor, and contribute to define the phase of CHB infection, the treatment indication, and allow an assessment of the efficacy of antiviral therapy. High levels of HBV DNA are an independent risk factor for cirrhosis[28] and HCC in Asia[22,29].

The REVEAL (Risk Evaluation of Viraemia Elevation and Associated Liver Disease)-HBV study group followed a cohort of 3653 HBsAg-positive patients in Taiwan. Their average age was 45 years and they acquired HBV infection perinatally. A baseline high HBV-DNA level > 10000 copies/mL was associated with a significant increased risk of HCC[30] and with progression towards cirrhosis[22]. Those patients that have persistently high levels of viral replication, for up to four decades, are at highest risk for HCC/cirrhosis after adjusting for HbeAg status, age, sex, ALT level, cigarette smoking and alcohol consumption. Many Asian patients may be in an immunotolerant phase, and the applicability of these data to western countries is not clear.

However, Fattovich *et al*[28] have re-evaluated a cohort of 70 Caucasian patients with HBeAg-positive chronic hepatitis at presentation, and they have shown that the risk of liver-related mortality in Caucasian adults with chronic hepatitis is strongly related to sustained disease activity and ongoing high levels of HBV replication, irrespective of HBeAg status. Other risk factors for liver-related death are older age, male sex, cirrhosis at entry, and absence of sustained remission.

It seems that a high level of HBV DNA is an independent risk factor for development of cirrhosis and HCC. The correlation between HBV DNA level and degree of liver injury upon biopsy is not well characterized. Serum HBV DNA level of > 100000 copies/mL is not correlated with histological grade or stage of liver disease in CHB patients, whatever the status of HBeAg[9]. Kumar *et al*[31], in a recent, large prospective study, have shown clearly that baseline ALT and DNA level are good predictors of histologically significant fibrosis. However, in an analysis of clinical trial data using NAs, Mommeja-Marin *et al*[32] have shown that there is a strong linear correlation between log-reduction of HBV-DNA levels and improvement in inflammation and fibrosis in liver biopsy.

The interpretation of serum DNA level is not easy, because we do not know the cut-off value for defining indication for and response to treatment. The 2000 National Institutes of Health conference chose an arbitrary value of 20000 UI/mL (> 10^5 copies/mL)[33]. As DNA levels have a fluctuating nature, monitoring changes in serum DNA levels is an essential tool.

VIRAL LOAD AND TREATMENT: UNFAVORABLE ARGUMENTS

Presently, the viral load cannot be considered as the only treatment criterion. HBV DNA persists even in persons who have serological recovery from acute HBV infection[34]. Patients with low HBV-DNA levels, between 300 and 10^4 copies/mL, have, although a very low one, a risk of progression to cirrhosis and HCC[9]. The progression in CHB infection is a multi-factorial process including interaction between host and environmental factors.

ALT value

Host immune response against HBV is essential to control infection. Immune response produces necrosis and inflammation of the liver. Liver biopsy assesses necro-inflammatory activity and cirrhosis, and it is measured indirectly by aminotransferase level. There is no significant interaction between ALT and HBV-DNA levels[35].

Many studies have shown a low prevalence of significant liver injury in CHB patients with normal ALT levels[36-39]. There is a possible bias for including blood donors, and a high proportion of patients in the immunotolerant phase. However, ALT values may vary with body mass, sex, abnormal lipid and carbohydrate metabolism. In addition, recent studies have suggested that ALT is an imperfect marker for liver disease activity. Some studies have detected significant liver injury in CHB patients with normal ALT[40,41]. In a retrospective study, Lai et al have investigated 192 CHB patients, with viral DNA at 10000 copies/mL and hepatic biopsy or clinical cirrhosis. There were significant fibrosis and inflammation in 37% of patients with persistently normal ALT, and a trend for the normal ALT group to include younger patients[42].

Kumar *et al*[31] have found a correlation between

histologically significant fibrosis (F score > 2) and persistently or intermittently elevated baseline ALT and baseline DNA > 10000 copies/mL. However, a normal ALT level in an individual patient does not always indicate absence of significant liver disease. Among HBeAg-positive patients with persistently normal ALT, 60.3% have baseline DNA levels > 5-log copies/mL, 63% have histological activity of hepatitis (HAI) > 3, and 39.7% have fibrosis stage > 2. Concerning HbeAg-negative CHB patients with persistently normal ALT (PNALT), they observed that 35.3% of patients have baseline DNA levels > 5-log copies/mL, 39.7% have HAI > 3, and 13.8% have fibrosis stage > 2. Following ASSLD practical guidelines, the inactive carrier state is differentiated from HBeAg-negative CHB by serial testing of ALT and serum HBV levels, because of the fluctuating pattern of AST/ALT. The inactive carrier state is defined by normal ALT and HBV DNA < 2000 IU/mL (10000 copies/mL). Some studies have observed that a cut-off of 10000 copies/mL may lead to misclassification of 13%-20% of HBeAg-negative CHB patients[43,44]. Kumar *et al*[31] have obtained similar results: 21 of HBeAg-negative patients with baseline DNA levels < 5-log copies/mL and PNALT, have HAI > 3 and fibrosis stage > 2.

Revision of normal limits for ALT level is advisable. The current standards for normal ALT level have been defined by using populations that include persons with subclinical liver disease, chronic HCV infection or non-alcoholic fatty liver disease. We considered normal ALT to be 40 IU/mL and normal aspartate aminotransferase (AST) to be 30 IU/mL. Recently, new upper limits of normal for ALT for men (30 IU/mL) and women (19 IU/mL) have been proposed. Revision of normal limits for ALT level is advisable to obtain a new cut-off, i.e. ALT = 39 IU/mL (men) and 19 IU/mL (women)[45]. Patients with a persistently normal ALT, HBV-DNA level >10000 copies/mL, and significant fibrosis and inflammation upon liver biopsy usually have an ALT in the high range of normal (26-40 IU/mL), and are older than 40 years old. This is consistent with new AASLD guidelines and recent data from Lin *et al*[46], which correlate parameters of progressive disease with high normal ALT. AASLD guidelines suggest decreasing the upper limits of normal for ALT.

ALT, likely with a new-updated cut-off value, is a factor to consider in the treatment of HBC patients. A high ALT value is a predictor of necro-inflammatory activity and a marker of response to actual treatment. In HBeAg-negative patients, its role as predictor of response to therapy is unclear. However, a high ALT level helps to distinguish between the inactive carrier state and asymptomatic HBeAg-negative CHB patients with normal ALT. A normal serum ALT level alone in patients with active viral replication does not predict mild or normal histological findings.

Value of biopsy: fibrosis and necro-inflammatory activity

Patients with moderate/severe inflammation or bridging fibrosis/cirrhosis must be treated[24]. The degree of fibrosis or inflammation upon liver biopsy cannot be predicted for HBV-DNA levels >10000 copies/mL. ALT is an imperfect marker for liver disease (see above). Traditional and current guidelines recommend liver biopsy for patients who meet the criteria for chronic hepatitis (HBsAg positive for > 6 mo, serum HBV DNA > 10^5 copies/mL or > 20000 IU/mL, persistent or intermittent elevation in ALT/AST levels). These patients must be treated if we follow the guidelines, and we believe that liver biopsy may be unnecessary.

Liver biopsy is more important for patients who do not meet the current criteria for treatment but have serum HBV-DNA levels of 10^4 to 10^5 copies/mL (2000-20000 IU/mL) and/or ALT/AST levels that are normal or mildly elevated (< 2 × ULN). The presence of significant inflammation or bridging fibrosis/cirrhosis is an indication for treatment. In a subgroup of these patients, hepatic elastography can avoid the need to carry out a liver biopsy for detection of significant fibrosis. This is a novel non-invasive method to assess hepatic fibrosis in patients with a chronic disease, by measuring liver stiffness. Its failure rate is about 5% of cases, mainly in obese patients[47,48]. Elastography has a high positive predictive value (92%) for diagnosing significant fibrosis (F3 and F4) in Asian CHB patients[49]. This method does not have a defined role in HBeAg-negative patients because histological inflammation during reactivation may affect the results[50].

GENOTYPE VALUE

The relationship between genotype and treatment indication is not well known as yet. The characteristics of the virus during evolution of the illness and the response to the treatment are acquiring an ever-increasingly important role. The prevalence of HBV genotypes varies depending on geographical location. It differs between Asia and Europe, and within European countries. Genotypes B and C are almost the only ones present in Asia. Genotypes A and D, with a lower prevalence of types F and G, are the most frequent in Europe[51]. Migration is changing this distribution[52,53]. In Europe, different genotypes may play a role in establishing the response to treatment, the manner and time of transmission, and the rate of HBeAg seroconversion with or without therapy[54]. HBV genotype may be associated with disease progression[55].

PROBBABILITY OF RESPONSE TO TREATMENT AND APPEARANCE OF RESISTANCE

Treatment is indicated if there is a high risk of liver-related mortality and morbility and a high likehood of manteined viral supression after a defined course of therapy[24]. This risk is variable during the course of HBV infection.

There are several treatment strategies for CHB: IFN and PEG-IFN, lamivudine, adefovir dipivoxil,

telbivudine and entecavir. None of theses achieves complete HBV eradication and they have limited long-term efficacy. In the majority of patients, particularly those with HBeAg-negative disease, HBV is suppressed but not eradicated by treatment, and relapses occur when drug treatment is interrupted.

For HBeAg-positive patients, the likelihood of a sustained virological response to antiviral therapy is < 20%-30% of treated patients, but long-term response depends upon HBeAg seroconversion. IFN has proven to be efficacious for ALT and DNA normalization, and for HBeAg seroconversion in 25%-40% of HBeAg-positive patients. HBeAg seroconversion is sustained in < 20% at 12 mo. After HBeAg seroconversion is achieved, viral suppression is sustained in 50%-90% of patients[56,57]. PEG-IFNα2A combined response (HBeAg and DNA suppression, and ALT normalization) is better than IFN response at 6 mo (24% *vs* 12%)[58,59]. For NAs, HBeAg/anti-HBeAg seroconversion rate is 16%-24%, and is similar among different drugs[60-63]. These patients have a sustained remission even after therapy is stopped. Entecavir seroconversion rates increase in time but there are no studies after 3 years of treatment, therefore, we do not know if these responses will be maintained[64,65].

For HBeAg-negative patients, the sustained response is low: 15% show normalization of serum ALT and suppression of serum HBV DNA[66-69]. For HBeAg-positive patients, the likelihood of response to nucleoside64/nucleotide analogs[70-74] and IFN[75,76]/PEG-IFN[77] depends greatly upon degree of serum aminotransferase elevation. In general, treatment with any of these drugs does not result in higher rates of HBeAg seroconversion compared to non- treatment in those who have a serum ALT < 2 × ULN. After a year of treatment, HBeAg seroconversion occurs in < 10% of these patients treated with IFN, lamivudine or adefovir. ASSLD guidelines do not recommend treatment in normal ALT patients, because it is unlikely to achieve HbeAg seroconversion.

IFNs are administered for predefined durations, do not select antiviral-resistant mutants, but produce more secondary effects (5%-8% treatment withdrawal). NA oral agents are administrated until specific endpoints are achieved. NA treatment is costly and their long-term safety and efficacy have yet to be proven. The HBeAg-positive patients with normal/low pre-treatment ALT level must not be treated with IFNs because the sustained response is very low. This subgroup and HBeAg-negative patients need long-term or continuous treatment. The hardest challenge for NAs is the selection of antiviral-resistant mutants, with long-term treatment. The rate at which resistant mutants are selected is related to pre-treatment serum HBV-DNA level, speed of viral suppression, duration of treatment, and prior response to NA therapy. Therefore, resistance is greater in normal-level ALT, HBeAg-positive patients, because slower DNA suppression occurs in the first 6 mo of treatment (12 mo for adefovir)[78]. In patients without an early virological decrease (3 and 6 mo), treatment should be maintained for the long term, which does increase the risk of resistance developing.

Lamivudine has the higher rate of resistance, 70% after 4 years of treatment in both HBeAg-positive/negative patients. Adefovir and telbivudine have the same problem. Adefovir resistance in the first year is lower than lamivudine resistance, but later, the accumulated resistance is of the order of 2.5% per year. Telbivudine selects the same resistant mutants as lamivudine. Entecavir-resistant mutation is observed in < 1% of nucleoside-naive patients after 2 and 3 years of treatment; data are lacking after 3 years, although resistance is higher in lamivudine-refractory patients[79,80]. The most effective method against the development of antiviral-resistant HBV is not to treat if therapy is not indicated.

Many new treatments are undergoing testing. None of the combination therapies has been proven to be superior to monotherapy, but with some disadvantages, such as greater cost, toxicity and drug interactions. Finally, current treatments do not eradicate HBV and have limited long-term efficacy, especially if ALT is below two times the normal upper average limit. For HBeAg-negative patients, prediction of response is unclear. While IFNs are administered for predefined durations, NAs are usually administrated until specific endpoints. Treatment is long term in normal-level ALT, HBeAg-positive and -negative patients, and is associated with adverse events and drug resistance.

CONCLUSION

DNA viral load is associated with disease progression, cirrhosis and HCC. In the subgroup of HBeAg-positive patients with DNA levels > 20 000 IU/mL and normal (or minimally elevated) ALT, current therapies are of limited efficacy and treatment should be considered long-term. The risk of this attitude is the appearance of secondary effects and drug resistance. Therefore, viral load is not sufficient for treatment, and we must give some thought to other factors, such as histological factors (fibrosis/cirrhosis and liver inflammation), patient age, disease evolution time, family history of HCC, adverse drug events and development of resistance. If patients have high DNA levels and normal ALT, without other unfavorable prognostic factors, it is advisable to follow the patients and not to treat them. The fluctuations in viral DNA, ALT and liver histology in patients with CHB allow us to choose the best time to begin treatment. The time required for the best response following clinical guidelines may be with the same as that required for the best sustained response. In HBeAg-negative patients, the cut-off value of viral load needed to distinguish asymptomatic HBeAg-negative CHB patients from those with normal ALT and inactive carrier state is not known.

Therefore, it is not the time to treat CHB patients, guided only by viral load. We agree with the clinical practice guidelines of the European Association for the Study of the Liver)[81], in which there are three criteria

for beginning HBV therapy: serum HBV-DNA levels, serum aminotransferase levels, and histological grade and stage. Patients should be considered for treatment when HBV-DNA levels are > 2000 IU/mL (10 000 copies/mL) and/or serum ALT is above ULN, and liver biopsy (or non-invasive markers when validated) shows moderate to severe active necro-inflammation and/or fibrosis (greater than A2 or F2 by METAVIR histological scoring). This may change if new, short-term therapies appear, and HBV eradication should be possible during long-term treatment, without development of resistance.

REFERENCES

1 **Lee WM**. Hepatitis B virus infection. *N Engl J Med* 1997; **337**: 1733-1745
2 **Beasley RP**. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer* 1988; **61**: 1942-1956
3 **Bosch FX**, Ribes J, Cléries R, Díaz M. Epidemiology of hepatocellular carcinoma. *Clin Liver Dis* 2005; **9**: 191-211, v
4 **Fattovich G**, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, Christensen E, Krogsgaard K, Degos F, Carneiro de Moura M. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The EUROHEP Study Group on Hepatitis B Virus and Cirrhosis. *Hepatology* 1995; **21**: 77-82
5 **Liaw YF**, Tai DI, Chu CM, Chen TJ. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *Hepatology* 1988; **8**: 493-496
6 **Liaw YF**, Lin DY, Chen TJ, Chu CM. Natural course after the development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *Liver* 1989; **9**: 235-241
7 **Fattovich G**, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol* 2008; **48**: 335-352
8 **You SL**, Yang HI, Chen CJ. Seropositivity of hepatitis B e antigen and hepatocellular carcinoma. *Ann Med* 2004; **36**: 215-224
9 **Shao J**, Wei L, Wang H, Sun Y, Zhang LF, Li J, Dong JQ. Relationship between hepatitis B virus DNA levels and liver histology in patients with chronic hepatitis B. *World J Gastroenterol* 2007; **13**: 2104-2107
10 **Yang HI**, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, Hsiao CK, Chen PJ, Chen DS, Chen CJ. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002; **347**: 168-174
11 **Geier A**, Gartung C, Dietrich CG. Hepatitis B e Antigen and the Risk of Hepatocellular Carcinoma. *N Engl J Med* 2002; **347**: 1721-1722; author reply 1721-1722
12 **Hui CK**, Leung N, Yuen ST, Zhang HY, Leung KW, Lu L, Cheung SK, Wong WM, Lau GK. Natural history and disease progression in Chinese chronic hepatitis B patients in immune-tolerant phase. *Hepatology* 2007; **46**: 395-401
13 **Chu CM**, Liaw YF. Chronic hepatitis B virus infection acquired in childhood: special emphasis on prognostic and therapeutic implication of delayed HBeAg seroconversion. *J Viral Hepat* 2007; **14**: 147-152
14 **McMahon BJ**, Holck P, Bulkow L, Snowball M. Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. *Ann Intern Med* 2001; **135**: 759-768
15 **Hsu YS**, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, Liaw YF. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology* 2002; **35**: 1522-1527
16 **Chu CM**, Liaw YF. Predictive factors for reactivation of hepatitis B following hepatitis B e antigen seroconversion in chronic hepatitis B. *Gastroenterology* 2007; **133**: 1458-1465
17 **Chen CJ**, Chen DS. Interaction of hepatitis B virus, chemical carcinogen, and genetic susceptibility: multistage hepatocarcinogenesis with multifactorial etiology. *Hepatology* 2002; **36**: 1046-1049
18 **Williams R**. Global challenges in liver disease. *Hepatology* 2006; **44**: 521-526
19 **Everhart JE**, Hoofnagle JH. Hepatitis B-related end-stage liver disease. *Gastroenterology* 1992; **103**: 1692-1694
20 **Hoofnagle JH**. Hepatitis B--preventable and now treatable. *N Engl J Med* 2006; **354**: 1074-1076
21 **Iloeje UH**, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006; **130**: 678-686
22 **Iloeje UH**, Yang HI, Jen CL, Su J, Wang LY, You SL, Chen CJ. Risk and predictors of mortality associated with chronic hepatitis B infection. *Clin Gastroenterol Hepatol* 2007; **5**: 921-931
23 **Lok AS**, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007; **45**: 507-539
24 **de Franchis R**, Hadengue A, Lau G, Lavanchy D, Lok A, McIntyre N, Mele A, Paumgartner G, Pietrangelo A, Rodés J, Rosenberg W, Valla D. EASL International Consensus Conference on Hepatitis B. 13-14 September, 2002 Geneva, Switzerland. Consensus statement (long version). *J Hepatol* 2003; **39** Suppl 1: S3-S25
25 **Liaw YF**, Leung N, Guan R, Lau GK, Merican I, McCaughan G, Gane E, Kao JH, Omata M. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2005 update. *Liver Int* 2005; **25**: 472-489
26 **Keeffe EB**, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, Tobias H, Wright TL. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States. *Clin Gastroenterol Hepatol* 2004; **2**: 87-106
27 **Arroyo V**. [Presentation.] *Gastroenterol Hepatol* 2006; **29** Suppl 2: 1
28 **Fattovich G**, Olivari N, Pasino M, D'Onofrio M, Martone E, Donato F. Long-term outcome of chronic hepatitis B in Caucasian patients: mortality after 25 years. *Gut* 2008; **57**: 84-90
29 **Yu MW**, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, Shih WL, Kao JH, Chen DS, Chen CJ. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. *J Natl Cancer Inst* 2005; **97**: 265-272
30 **Chen CJ**, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65-73
31 **Kumar M**, Sarin SK, Hissar S, Pande C, Sakhuja P, Sharma BC, Chauhan R, Bose S. Virologic and histologic features of chronic hepatitis B virus-infected asymptomatic patients with persistently normal ALT. *Gastroenterology* 2008; **134**: 1376-1384
32 **Mommeja-Marin H**, Mondou E, Blum MR, Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. *Hepatology* 2003; **37**: 1309-1319
33 **Lok AS**, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000--summary of a workshop. *Gastroenterology* 2001; **120**: 1828-1853
34 **Rehermann B**, Ferrari C, Pasquinelli C, Chisari FV. The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. *Nat Med* 1996; **2**: 1104-1108
35 **Dragosics B**, Ferenci P, Hitchman E, Denk H. Long-term follow-up study of asymptomatic HBsAg-positive voluntary blood donors in Austria: a clinical and histologic evaluation of 242 cases. *Hepatology* 1987; **7**: 302-306
36 **Kim HC**, Nam CM, Jee SH, Han KH, Oh DK, Suh I. Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. *BMJ* 2004; **328**: 983
37 **Ricci G**, De Bac C, Caramia F. Carriers of hepatitis B antigen: an epidemiologic and histologic study. *J Infect Dis*

1973; **128**: 125-128
38 **Tapp E**, Jones DM, Hollanders D, Dymock IW. Serial liver biopsies in blood donors with persistent HBs antigenaemia. *J Clin Pathol* 1976; **29**: 884-886
39 **De Franchis R**, D'Arminio A, Vecchi M, Ronchi G, Del Ninno E, Parravicini A, Ferroni P, Zanetti AR. Chronic asymptomatic HBSAg carriers: histologic abnormalities and diagnostic and prognostic value of serologic markers of the HBV. *Gastroenterology* 1980; **79**: 521-527
40 **Wang CC**, Lim LY, Deubner H, Tapia K, Lau AW, Manansala J, Krows M, Shuhart MC, Kowdley KV. Factors predictive of significant hepatic fibrosis in adults with chronic hepatitis B and normal serum ALT. *J Clin Gastroenterol* 2008; **42**: 820-826
41 **Tsang PS**, Trinh H, Garcia RT, Phan JT, Ha NB, Nguyen H, Nguyen K, Keeffe EB, Nguyen MH. Significant prevalence of histologic disease in patients with chronic hepatitis B and mildly elevated serum alanine aminotransferase levels. *Clin Gastroenterol Hepatol* 2008; **6**: 569-574
42 **Lai M**, Hyatt BJ, Nasser I, Curry M, Afdhal NH. The clinical significance of persistently normal ALT in chronic hepatitis B infection. *J Hepatol* 2007; **47**: 760-767
43 **Manesis EK**, Papatheodoridis GV, Hadziyannis SJ. Serum HBV-DNA levels in inactive hepatitis B virus carriers. *Gastroenterology* 2002; **122**: 2092-2093; author reply 2093
44 **Seo Y**, Yoon S, Truong BX, Kato H, Hamano K, Kato M, Yano Y, Katayama M, Ninomiya T, Hayashi Y, Kasuga M. Serum hepatitis B virus DNA levels differentiating inactive carriers from patients with chronic hepatitis B. *Eur J Gastroenterol Hepatol* 2005; **17**: 753-757
45 **Prati D**, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, Vianello L, Zanuso F, Mozzi F, Milani S, Conte D, Colombo M, Sirchia G. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002; **137**: 1-10
46 **Lin CL**, Liao LY, Liu CJ, Yu MW, Chen PJ, Lai MY, Chen DS, Kao JH. Hepatitis B viral factors in HBeAg-negative carriers with persistently normal serum alanine aminotransferase levels. *Hepatology* 2007; **45**: 1193-1198
47 **Castéra L**, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Lédinghen V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; **128**: 343-350
48 **Castera L**, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol* 2008; **48**: 835-847
49 **Chang PE**, Lui HF, Chau YP, Lim KH, Yap WM, Tan CK, Chow WC. Prospective evaluation of transient elastography for the diagnosis of hepatic fibrosis in Asians: comparison with liver biopsy and aspartate transaminase platelet ratio index. *Aliment Pharmacol Ther* 2008; **28**: 51-61
50 **Coco B**, Oliveri F, Maina AM, Ciccorossi P, Sacco R, Colombatto P, Bonino F, Brunetto MR. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. *J Viral Hepat* 2007; **14**: 360-369
51 **De Mitri MS**, Cassini R, Morsica G, Bagaglio S, Andreone P, Loggi E, Muratori P, Bernardi M. Virological analysis, genotypes and mutational patterns of the HBV precore/core gene in HBV/HCV-related hepatocellular carcinoma. *J Viral Hepat* 2006; **13**: 574-581
52 **Rodriguez-Frias F**, Jardi R, Buti M, Schaper M, Hermosilla E, Valdes A, Allende H, Martell M, Esteban R, Guardia J. Hepatitis B virus genotypes and G1896A precore mutation in 486 Spanish patients with acute and chronic HBV infection. *J Viral Hepat* 2006; **13**: 343-350
53 **Echevarría JM**, Avellón A, Magnius LO. Molecular epidemiology of hepatitis B virus in Spain: identification of viral genotypes and prediction of antigenic subtypes by limited sequencing. *J Med Virol* 2005; **76**: 176-184
54 **Ramos B**, Núñez M, Martín-Carbonero L, Sheldon J, Rios P, Labarga P, Romero M, Barreiro P, García-Samaniego J, Soriano V. Hepatitis B virus genotypes and lamivudine resistance mutations in HIV/hepatitis B virus-coinfected patients. *J Acquir Immune Defic Syndr* 2007; **44**: 557-561
55 **Sánchez-Tapias JM**, Costa J, Mas A, Bruguera M, Rodés J. Influence of hepatitis B virus genotype on the long-term outcome of chronic hepatitis B in western patients. *Gastroenterology* 2002; **123**: 1848-1856
56 **Wong DK**, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. *Ann Intern Med* 1993; **119**: 312-323
57 **Tinè F**, Liberati A, Craxì A, Almasio P, Pagliaro L. Interferon treatment in patients with chronic hepatitis B: a meta-analysis of the published literature. *J Hepatol* 1993; **18**: 154-162
58 **Cooksley WG**, Piratvisuth T, Lee SD, Mahachai V, Chao YC, Tanwandee T, Chutaputti A, Chang WY, Zahm FE, Pluck N. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. *J Viral Hepat* 2003; **10**: 298-305
59 **Lau GK**, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, Gane E, Fried MW, Chow WC, Paik SW, Chang WY, Berg T, Flisiak R, McCloud P, Pluck N. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; **352**: 2682-2695
60 **Lai CL**, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, Wu PC, Dent JC, Barber J, Stephenson SL, Gray DF. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med* 1998; **339**: 61-68
61 **Dienstag JL**, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, Crowther L, Condreay LD, Woessner M, Rubin M, Brown NA. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999; **341**: 1256-1263
62 **Lai CL**, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, Chen Y, Heathcote EJ, Rasenack J, Bzowej N, Naoumov NV, Di Bisceglie AM, Zeuzem S, Moon YM, Goodman Z, Chao G, Constance BF, Brown NA. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007; **357**: 2576-2588
63 **Marcellin P**, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, Jeffers L, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosgart CL. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; **348**: 808-816
64 **Sherman M**, Yurdaydin C, Simsek H, Silva M, Liaw YF, Rustgi VK, Sette H, Tsai N, Tenney DJ, Vaughan J, Kreter B, Hindes R. Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. *Hepatology* 2008; **48**: 99-108
65 **Gish RG**, Lok AS, Chang TT, de Man RA, Gadano A, Sollano J, Han KH, Chao YC, Lee SD, Harris M, Yang J, Colonno R, Brett-Smith H. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. *Gastroenterology* 2007; **133**: 1437-1444
66 **Bonino F**, Marcellin P, Lau GK, Hadziyannis S, Jin R, Piratvisuth T, Germanidis G, Yurdaydin C, Diago M, Gurel S, Lai MY, Brunetto MR, Farci P, Popescu M, McCloud P. Predicting response to peginterferon alpha-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. *Gut* 2007; **56**: 699-705
67 **Lai CL**, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, DeHertogh D, Wilber R, Zink RC, Cross A, Colonno R, Fernandes L. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006; **354**: 1011-1020
68 **Tassopoulos NC**, Volpes R, Pastore G, Heathcote J, Buti M, Goldin RD, Hawley S, Barber J, Condreay L, Gray DF. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant)

chronic hepatitis B.Lamivudine Precore Mutant Study Group. *Hepatology* 1999; **29**: 889-896

69 **Hadziyannis SJ**, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, Lim SG, Goodman Z, Ma J, Brosgart CL, Borroto-Esoda K, Arterburn S, Chuck SL. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006; **131**: 1743-1751

70 **Chien RN**, Liaw YF, Atkins M. Pretherapy alanine transaminase level as a determinant for hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. Asian Hepatitis Lamivudine Trial Group. *Hepatology* 1999; **30**: 770-774

71 **Perrillo RP**, Lai CL, Liaw YF, Dienstag JL, Schiff ER, Schalm SW, Heathcote EJ, Brown NA, Atkins M, Woessner M, Gardner SD. Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B. *Hepatology* 2002; **36**: 186-194

72 **Liaw YF**, Tsai SL, Chien RN, Yeh CT, Chu CM. Prednisolone priming enhances Th1 response and efficacy of subsequent lamivudine therapy in patients with chronic hepatitis B. *Hepatology* 2000; **32**: 604-609

73 **D'Antiga L**, Aw M, Atkins M, Moorat A, Vergani D, Mieli-Vergani G. Combined lamivudine/interferon-alpha treatment in "immunotolerant" children perinatally infected with hepatitis B: a pilot study. *J Pediatr* 2006; **148**: 228-233

74 **Sarin SK**, Sandhu BS, Sharma BC, Jain M, Singh J, Malhotra V. Beneficial effects of 'lamivudine pulse' therapy in HBeAg-positive patients with normal ALT*. *J Viral Hepat* 2004; **11**: 552-558

75 **Brook MG**, Karayiannis P, Thomas HC. Which patients with chronic hepatitis B virus infection will respond to alpha-interferon therapy? A statistical analysis of predictive factors. *Hepatology* 1989; **10**: 761-763

76 **Lok AS**, Wu PC, Lai CL, Lau JY, Leung EK, Wong LS, Ma OC, Lauder IJ, Ng CP, Chung HT. A controlled trial of interferon with or without prednisone priming for chronic hepatitis B. *Gastroenterology* 1992; **102**: 2091-2097

77 **Fried MW**, Piratvisuth T, Lau GK, Marcellin P, Chow WC, Cooksley G, Luo KX, Paik SW, Liaw YF, Button P, Popescu M. HBeAg and hepatitis B virus DNA as outcome predictors during therapy with peginterferon alfa-2a for HBeAg-positive chronic hepatitis B. *Hepatology* 2008; **47**: 428-434

78 **Lok AS**, Zoulim F, Locarnini S, Bartholomeusz A, Ghany MG, Pawlotsky JM, Liaw YF, Mizokami M, Kuiken C. Antiviral drug-resistant HBV: standardization of nomenclature and assays and recommendations for management. *Hepatology* 2007; **46**: 254-265

79 **Colonno RJ**, Rose R, Baldick CJ, Levine S, Pokornowski K, Yu CF, Walsh A, Fang J, Hsu M, Mazzucco C, Eggers B, Zhang S, Plym M, Klesczewski K, Tenney DJ. Entecavir resistance is rare in nucleoside naïve patients with hepatitis B. *Hepatology* 2006; **44**: 1656-1665

80 **Sherman M**, Yurdaydin C, Sollano J, Silva M, Liaw YF, Cianciara J, Boron-Kaczmarska A, Martin P, Goodman Z, Colonno R, Cross A, Denisky G, Kreter B, Hindes R. Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. *Gastroenterology* 2006; **130**: 2039-2049

81 **European Association For The Study Of The Liver.** EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *J Hepatol* 2008; Epub ahead of print

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