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KASL Clinical Practice Guidelines: Management of chronic hepatitis B

The Korean Association for the Study of the Liver (KASL)*

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PREAMBLE

Introduction

The guideline on the management of chronic hepatitis B (CHB) was first developed in 2004 and revised in 2007 by the Korean Association for the Study of the Liver (KASL). Since then there have been many developments, including the introduction of new antiviral agents and the publications of many novel research results from both Korea and other countries. In particular, a large amount of knowledge on antiviral resistance–which is a serious issue in Korea–has accumulated, which has led to new strategies being suggested. This prompted the new guideline discussed herein to be developed based on recent evidence and expert opinion.

Target population

The main targets of this guideline comprise patients who are newly diagnosed with CHB and those who are followed or treated for known CHB. This guideline is also intended to provide guidance for the management of patients under the following special circumstances: malignancy, transplantation, dialysis, coinfection with other viruses, pregnancy, and children.

Intended users

This revised CHB guideline is designed as resource for all Korean clinicians caring for patients with CHB. It also provides physicians in training courses with practical information on the management of CHB.

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Abbreviations:

AASLD, American Association for the Study of Liver Diseases; AGREE II, Appraisal of Guidelines for Research and Evaluation II; ALP, alkaline phosphatase; ALT, alanine aminotransferase; anti-HAV, hepatitis A virus antibody; anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B envelop antibody; anti-HBs, hepatitis B surface antigen; APR, Antiretroviral Pregnancy Registry; AST, aspartate aminotransferase; BCP, basal core promoter; cccDNA, covalently closed circular DNA; CDC, Center for Disease Control; CHB, chronic hepatitis B; CPGRC, Clinical Practice Guideline Revision Committee; cpm, copies/mL; EASL, European Association for the Study of the Liver; GGT, gamma-glutamyl transpeptidase; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HAART, highly active antiretroviral therapy; HBcAg, HBV core antigen; HBeAg, Hepatitis B envelop Antigen; HBIG, Hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; IFN, interferon; IgG,immunoglobulin G; IgM, immunoglobulin M; IU, international unit; KASL, The Korean Association for the Study of the Liver; NUC, nucleos(t)ide analogue; PC, precore; PCR, polymerase chain reaction; peginterferon, pegylated interferon; REVEAL-HBV, Risk Evaluation of Viral Load Elevation and Association Liver Disease/Cancer-Hepatitis B Virus; ULN, upper limit of normal

Developer and funding source

The CHB Clinical Practice Guideline Revision Committee (CPGRC) comprising 15 hepatologists and 1 pediatrician was formed with support from KASL (Appendix 2). All of the required funding was provided by KASL. Each member of CHB-CPGRC collected and evaluated evidence, and contributed to writing the manuscript. Conflicts of interests of the CHB-CPGRC members are summarized in Appendix 1.

Evidence collection

Relevant evidence obtained in a comprehensive literature search using MEDLINE (up to 2011) was systematically reviewed and selected. The literature languages were limited to English and Korean. In addition to published articles, abstracts of important meetings published before 2011 were also evaluated. The following search terms were used: "hepatitis B", "hepatitis B virus", "HBV", "chronic hepatitis", and other key words related to clinical questions (see below). These clinical questions covered a variety of pertinent topics ranging from epidemiology, natural course, and prevention to diagnosis, treatment, antiviral resistance, and special situations.

Levels of evidence and grades of recommendation

The evidences and recommendations were graded according to the GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) with minor modifications.[1-4] (Table 1) The levels of evidences were determined by the possibility of change in the estimate of clinical effect by further research, and were described as high (A), moderate (B) or low (C). The grades of recommendation were either strong (1) or weak (2), as determinted by the quality of evidence as well as patient-important outcomes and socioeconomic aspects.

List of the clinical questions

The committee considered the following questions as key components to be covered in this guideline.

1. How does this guideline differ from previous guidelines?
2. What is the updated knowledge on the epidemiology and natural course?
3. How should the infection be prevented?
4. How are the patients evaluated prior to treatment?
5. When should treatment be considered?
6. What are the goals and endpoints of treatment?
7. What are the optimal first-line treatments for different disease status?
8. How should the treatment be monitored?
9. When can we consider stopping treatment?
10. What are the predictors of the treatment response?
11. What are the definitions of treatment failure, antiviral resistance, and recurrence after treatment completion, and how should these aspects be managed?
12. How should the following special groups be managed: acute hepatitis B, liver transplantation, chemotherapy/immunosuppression, renal failure, coinfection [with hepatitis C virus (HCV), hepatitis D virus (HDV), and/or human immunodeficiency virus (HIV)], pregnancy, and children?

Review of the manuscript

Drafts of the revised guideline were thoroughly reviewed at six separate meetings of the committee. In addition to the con-

Table 1. Grading of recommendations, assessment, development and evaluation (GRADE)

Quality of evidence	Criteria
High (A)	Further research is unlikely to change confidence in the estimate of the clinical effect
Moderate (B)	Further research may change confidence in the estimate of the clinical effect
Low (C)	Further research is very likely to impact confidence on the estimate of clinical effect
Strength of recommendation	**Criteria**
Strong (1)	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
Weak (2)	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption

Of the quality levels of evidence, we excluded "very low quality (D)" in our guideline for convenience, which was originally included in the GRADE system and indicates that any estimate of effect being very uncertain.

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tents, methodological validity was also assessed according to the AGREE II (Appraisal of Guidelines for Research and Evaluation II) instrument.[5,6] A revised manuscript was reviewed at a meeting of an external review board, and at a symposium open to all KASL members, and was modified further prior to publication. The external review board comprised of 12 specialists on CHB who are members of KASL. The final manuscript was endorsed by the board of executives of KASL (see Appendix 2).

Release of the guideline

The revised CHB guideline of KASL was released on December 1, 2011 (http://www.kasl.org).

Plan for updates

Updates or full revision will be planned when new major evidences are accumulated in diagnosis and/or treatment of CHB. Detailed plans for updates will be posted on the KASL webside later.

EPIDEMIOLOGY

Hepatitis B infection is a major etiology of acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). It has been recognized as an important public health problem in Korea since the 1970s,[7] and was designated as a third-class infectious disease by law in 1982. Hepatitis B infection is currently classified as one of the second group of infectious disease designated by law and is addressed by national vaccination programs.[8]

The prevalence of HBV infection in the Korean population as estimated by positivity rates for hepatitis B surface antigen (HBsAg) was 8-9% for males and 5-6% for females during the early 1980s.[9] Thereafter the prevalence of HBV infection tended to decline gradually due to the initiation of a vaccination program for newborn infants in 1991 and a national vaccination program in 1995. For example, the prevalence of HBV among children aged 4 to 6 years had decreased to 0.2% in 2006.[10] Nevertheless, according to the 2005 Korean National Health and Nutrition Examination Survey, the positivity rate for HBsAg among people aged 10 years or older was 4.8% for males and 3.0% for females, with 3.7% of the total population being infected with HBV.[11] Positivity rates for HBsAg among pregnant women–who represent a major infection route for hepatitis B–declined during the 1980s but remained stagnant during the 1990s. Perinatal infection rates of HBV have not decreased, being 3.4% in 1995 and 3.2% in 2006; moreover, the incidence of sporadic acute hepatitis B infection has been increasing since 2001.[11] Given that HBsAg is detected in approximately 70% of patients with chronic hepatitis or cirrhosis,[12] and in 65-75% of HCC patients,[13,14] it can be concluded that CHB infection still greatly affects public health in Korea.

Most Korean CHB patients are infected with HBV subgenotype C2[15]; these patients are known to have lower hepatitis B e antigen (HBeAg) seroconversion rates, more rapidly progress to HCC and cirrhosis, lower interferon treatment effects, and are subject to have higher rates of relapse after antiviral treatments, compared to those infected with other HBV genotypes.[16,17]

Natural History of CHB

The progression of CHB may be divided into five clinical phases: immune-tolerant phase, immune-reactive phase, inactive HBV-carrier phase, HBeAg-negative CHB phase, and HBsAg-clearance phase. Individual patients do not necessarily experience different clinical stages in a continuous manner.[18,19] The five phases have the following characteristics:

1) The "immune tolerant" phase: In cases of perinatal infection, the immune-tolerant phase is characterized by HBeAg positivity, high levels of serum HBV DNA (generally $\geq 10^7$ IU/mL), normal levels of aspartate aminotransferase/alanine aminotransferase (AST/ALT), and mild or no liver necroinflammation.[20-22] This phase may continue for longer than 3 decades in those infected with HBV genotype C, which is common among Korean patients, and the rate of spontaneous HBeAg loss is very low.[23] Therefore, many women infected with this genotype are in the HBeAg-positive immune-tolerant phase when they are of childbearing age. No or only mild histologic liver damage, despite high levels of HBV DNA, is attributed to immune tolerance to HBV.[24]

2) The "immune reactive" phase: Most patients in the immune-tolerant phase will experience immune responses against HBV as they grow older, and finally reach the immune-reactive phase that is characterized by HBeAg positivity, lower serum HBV DNA levels, and increased or fluctuating levels of ALT.[25,26] Histologic findings in this phase include moderate-to-severe liver inflammation and, in some patients, rapid progression of fibrosis.[27] Such changes are due to enhancement of HBV core antigen (HBcAg) or HBeAg-specific cytotoxic T-lymphocyte activity and the resulting destruction of infected hepatocytes.[28] Sustained HBV DNA suppression occasionally accompanies HBeAg seroconversion.

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Once HBeAg seroconversion occurs, the natural course of the disease may have one of three clinical features: repeated HBeAg reversion and seroconversion, inactive HBV-carrier state, or HBeAg-negative CHB.[29,30] Typically 10-40% of patients who experience seroconversion revert to HBeAg positivity and then experience the recurrence of seroconversion at least once with progression of hepatitis activity.[27,31,32] In particular, reversion frequently occurs in patients with HBV genotype C, with its rates declining with age.[23]

3) The "inactive HBV-carrier" phase: Most patients who seroconvert during the immune-reactive phase progress to the inactive HBV-carrier phase, which is characterized by HBeAg negativity, persistent normal ALT levels, and HBV DNA levels of less than 2,000 IU/mL.[33-35] Typical histologic findings of this phase are mild liver inflammation and fibrosis;[33] however, patients who have suffered from previous severe inflammation and fibrosis may continue to experience moderate-to-severe inflammation and fibrosis. This may result in even biochemical and histologic tests not being useful for differentiating these patients from those with cirrhosis who require antiviral treatment.[34] This phase persists for a long time in most patients, but with a relatively good prognosis; however, an estimated 20% of them will reactivate to the HBeAg-negative or HBeAg-positive immune-reactive phase, and they might experience recurring periods of reactivation and inactivation throughout their lives, which can lead to cirrhosis or HCC.[36,37] This is why the ALT levels of patients in the inactive HBV phase must be followed every 6 months for life because currently there are no predictors for whom will remain in the inactive phase or revert to HBeAg-negative active hepatitis.[19]

4) The "HBeAg negative CHB" phase: Approximately 20% of patients who experience HBeAg seroconversion during their immune-reactive phase maintain HBeAg negativity and hepatitis B e antibody (anti-HBe) positivity but progress to HBeAg-negative CHB, with findings of HBV DNA levels of 2,000 IU/mL or higher, increased levels of ALT, and active liver necroinflammation.[29] These patients show HBeAg negativity since they harbor HBV variants in the precore (PC) or basal core promoter (BCP) regions of HBV DNA, resulting in a failure to generate HBeAg.[38-40] HBeAg-negative CHB is associated with low rates of prolonged spontaneous disease remission, and most patients in this phase will experience persistent hepatocellular inflammation and progress to hepatic fibrosis and cirrhosis.[40,41] Severe fluctuations of HBV DNA and ALT levels sometimes make it difficult to differentiate these patients from those in the inactive HBV-carrier phase.[42] Accordingly, for the first year after a patient is diagnosed as being in the inactive HBV-carrier phase, HBV DNA and ALT levels should be measured every 3 months in order to differentiate HBeAg-negative CHB patients who need antiviral treatment.[19,43]

5) The "HBsAg-clearance" phase: Patients in the inactive HBV-carrier phase subsequently experience the HBsAg clearance phase at a rate of 1-2% annually. HBsAg loss occurs[42,44,45] regardless of the patient's gender and virus genotype, with age being the only known influencing factor.[46,47] It has been reported that Korean patients experience a relatively low rate of HBsAg loss (0.4% annually).[48] HBV DNA is not detectable in the serum during this phase, while hepatitis B core antibody (anti-HBc) with or without hepatitis B surface antibody (anti-HBs) are detectable. HBsAg

Table 2. Risk factors associated with the development of hepatocellular carcinoma (HCC) and/or cirrhosis in persons with chronic hepatitis B virus

Demographic	Increased risk of HCC	Increased risk of cirrhosis
Male sex	3+	+
Increasing age >40 years	3+	3+
Family history of HCC	3+	+
Social and environmental	**Increased risk of HCC**	**Increased risk of cirrhosis**
Alcohol	+	+
Aflatoxin	3+	Unknown
Smoking	+	+
Coffee	Decrease risk of HCC	Slower progression of liver fibrosis
Viral factor	**Increased risk of HCC**	**Increased risk of cirrhosis**
Genotype C	3+	2+
HBV DNA >2,000 IU/mL	3+	3+
BCP mutation	3+	+

BCP, basal core promoter; HBV, hepatitis B virus.
Modified from McMahon BJ.[57]

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loss is known to be associated with a reduced risk of cirrhosis but a sustained significant risk of HCC development.[36,44,49-54]

Risk Factors that Influence the Natural History of CHB

The accumulated incidence of cirrhosis developing from CHB is generally reported to be 8-20%.[55,56] In Korea the reported annual and 5-year accumulated incidences of cirrhosis are 5.1% and 23%, respectively, while those for HCC are 0.8% and 3%.[56]

The risk factors for chronic hepatitis B progressing to cirrhosis or HCC can be divided into demographic, environmental, social, and viral factors (Table 2).[57] Regarding demographic factors, the risk of developing HCC is three- to fourfold higher for men than for women, and the risk of HCC and cirrhosis is low among those younger than 40 years then increases exponentially with increasing age after the fourth decade of life.[27,58,59] Those with a family history of HCC also have a higher risk of HCC development.[60,61]

Environmental and social risk factors for the progression to cirrhosis or HCC are alcohol consumption, exposure to aflatoxin,[62] and smoking.[63] It remains controversial whether obesity, metabolic syndrome, and fatty changes in histologic tests increase the risk of CHB patients progressing to hepatic fibrosis or HCC.[64-67] Many epidemiological research studies have found that coffee exerts protective effects against the development of hepatic fibrosis and HCC.[68-72] Although there are no research reports on the role of coffee in hepatitis B patients, coffee may be protective in HBV since multiple studies have shown coffee intake to be protective in various liver diseases.

Viral factors that may influence the progression of CHB patients to cirrhosis or HCC include high levels of serum HBV DNA (≥20,000 IU/mL), genotype C, BCP variants, and coinfection with other viruses.[73-77] According to the Taiwanese REVEAL-HBV (Risk Evaluation of Viral Load Elevation and Association Liver Disease/Cancer-Hepatitis B Virus) study, the risk of developing HCC during the study period among subjects aged at least 40 years was significantly higher in those with an HBV DNA level of $\geq 10^4$ copies/mL (cpm) at the start of observation and 10^5 cpm 11 years later than among those with an entry HBV DNA level of $<10^4$ cpm.[74] Likewise, the incidence of cirrhosis was found to be significantly associated with HBV DNA levels higher than 10^4 cpm at study entry. When the HBV DNA level decreased during the follow-up period, the risk of developing HCC or cirrhosis reduced. Subsequent research highlighted the clinical importance of very careful evaluation of patients with an HBV DNA level of higher than 2,000 IU/mL who are older than 40 years (especially those who still have HBeAg positivity) for the development of fibrosis[76] and HCC,[75,77] and intervention with antiviral therapy when appropriate, as recommended by established practice guidelines.[57]

Unlike HCV infection, the HBV genotype exerts a profound effect on the clinical outcome but–with the exception of interferon–little effect on the treatment outcome.[78] Eight HBV genotypes have been identified, and that with the worst prognosis is known to be genotype C, which is the most common in Korean CHB patients.[79] According to a cohort study in Alaska, hepatitis B patients with genotype A-, B-, and D-infections typically experience seroconversion from HBeAg to anti-HBe before they reach the age of 20 years, whereas in those infected with the genotype C this occurs at a mean age of 47 years.[23] This implies that those infected with the genotype C would on average experience a much longer period of infection with high viral loads of HBV. This may partially explain why the risks of HCC and cirrhosis are so high in patients infected with genotype C. Two important genetic mutations of HBV that affect the natural history of CHB infection are BCP and PC mutations.[43,46,77,79-81] BCP mutations are A1762T and G1764A mutations in the HBV BCP regions, and multiple cross-sectional or prospective studies have indicated that they increase the risks of cirrhosis and HCC development.[43,46,79,80] According to the results of the REVEAL-HBV study, 359 and 1,149 individuals out of a population of 100,000 developed HCC without and with BCP mutations, respectively.[82] PC mutation typically appears near the time of HBeAg seroconversion. The mutation results in an amino-acid change that creates a stop codon at site 1896 on the HBV genome, which results in the virus being able to transcribe hepatitis B core protein but not HBeAg.[46] Patients infected with PC mutants are characterized by HBeAg negativity and HBeAg positivity, but high levels of HBV DNA.[83,84] However, the observed effects of PC mutants on the natural history of CHB have been inconsistent; a recent analysis of the role of PC in the prospective population-based REVEAL-HBV study revealed the opposite to what was found in cross-sectional clinic–based studies–that the presence or absence of the PC mutation respectively decreased or increased the annual subsequent incidence of HCC (269 and 996 per 100,000, respectively).[82] Although tests for both PC and BCP mutations are commercially available, it is premature for clinicians to place patients on antiviral therapy based on a mutational profile.[57]

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Table 3. Recommendations for HBsAg-positive person to prevent transmission of HBV to others[18]

An HBsAg-positive person should
- ensure that family members are vaccinated if their serum is negative for hepatitis B surface antibody (anti-HBs)
- ensure that sexual partners are vaccinated if their serum is negative for anti-HBs
- use barrier protection during sexual intercourse if the partner's serum is negative (or unknown) for anti-HBs
- not share a toothbrush or razor due to the potential for infection through a skin or mucosal injury
- cover open wounds
- clean blood spills using detergents or bleach
- not donate blood, blood components, organs, or sperm
An HBsAg-positive person can
- participate in school, daycare, social, and sports activities
- share foodstuffs and utensils including spoons, forks, and chopsticks
- kiss or hug others

PREVENTION OF HBV INFECTION

Because HBV infection is endemic in Korea, any person who has a high risk of liver disease or has suspected liver disease is recommended to have their HBsAg and anti-HBs statuses checked.[18] There is a risk of HBV carriers infecting others, and hence they should be counseled regarding how to modify their lifestyle so as to prevent HBV transmission to others (Table 3). Epidemiologic studies found that the daily consumption of 40–80 g of alcohol is associated with liver damage and the progression of liver disease,[85-90] and a long-term prospective cohort study of HBV carriers showed that alcohol consumption increases the risks of liver cirrhosis and the development of HCC.[74,76] No data are available on the threshold level of alcohol consumption required to significantly increase the risks of liver cirrhosis and HCC in HBV carriers. In the general population, a daily alcohol intake of 24 g in men and 12 g in women significantly increases the risk of liver cirrhosis. Therefore, abstinence or a very limited consumption of alcohol is recommended in HBV carriers.[91] Smoking also increases the risks of liver cirrhosis and HCC. Therefore non-smoking is recommended in HBV carriers.[74,76,92]

Vertical infection is the most important route of HBV transmission. Hepatitis B immunoglobulin (HBIG) and vaccine administered after birth, followed by completion of a three-dose vaccine has been demonstrated to be 90–95% effective in preventing HBV infection in infants born to HBsAg-positive women.[93-95] Therefore, such infants should receive 0.5 mL HBIG and HBV vaccination within 12 hours of birth. However, the introduction of HBV vaccination did not result in the rate of HBV infection among newborns differing between breast- and formula-feeding HBsAg-positive mothers (0% vs. 3%, respectively).[96]

Since HBV is endemic in Korea, Koreans who are negative for HBsAg and anti-HBs should be vaccinated, especially the household members and sexual partners of HBV carriers since they have an increased risk of HBV infection.[93,94,97,98] Sexual partners who have not been tested for HBV serologic markers, have not completed the full immunization series, or who are negative for anti-HBs should use barrier protection such as condoms.

The three doses constituting the hepatitis B vaccine series administered intramuscularly at 0, 1, and 6 months induces a protective antibody response (anti-HBs >10 mIU/mL) in >90% of recipients. Most nonresponders (44–100%) subsequently respond to an additional three-dose revaccination.[93,94] Although serologic testing for the anti-HBs response is not necessary after routine vaccination in immunocompetent adults, postvaccination testing is recommended in some subjects. The anti-HBs status of newborns of HBV-infected mothers, healthcare workers, sexual partners of HBV carriers, HIV-infected people, dialysis patients, and other immunocompromised subjects should be tested after they have completed the HBV immunization series.[93,94]

While anti-HBs levels can decline or disappear over several decades, vaccinated subjects remain protected against HBV infection and there is no need for booster vaccination in immunocompetent subjects. However, an anti-HBs level of <10 mIU/mL in dialysis patients indicates an increased risk of HBV infection. Therefore, a booster vaccination is needed if annual testing reveals an anti-HBs level of <10 mIU/mL;[93] this also applies to immunocompromised patients.[93,94]

A person without protective anti-HBs exposed to HBV-contaminated blood or body fluids should receive HBIG (0.06 mL/kg) and hepatitis B vaccine as soon as possible; preferably within 24 hours, otherwise postexposure prophylaxis should be initiated within 7

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days for percutaneous exposure or within 14 days for sexual exposure. Detailed recommendations for postexposure prophylaxis in both nonoccupational and occupational exposures have been developed.[93,94,99]

Coinfection with hepatitis A in HBV carriers increases the risk of mortality by 5.6- to 29-fold.[100] Therefore, hepatitis A vaccination is recommended if they are negative for the protective hepatitis A virus antibody (anti-HAV) (Table 3).[101]

[Recommendation]

1. HBV vaccination is recommended in people who are negative for HBsAg and anti-HBs (A1).
2. Abstinence or a very limited consumption of alcohol is recommended in HBV carriers (A1).
3. Non-smoking is recommended in HBV carriers (A1).
4. Newborns of HBV-infected mothers should receive HBIG and hepatitis B vaccine at delivery and the three-dose hepatitis B vaccine (A1).
5. Hepatitis A vaccine is recommended for HBV carriers who are negative for anti-HAV (A1).
6. HBV carriers should be counseled regarding how to modify their lifestyle so as to prevent HBV transmission to others (B1).

DIAGNOSIS AND INITIAL EVALUATION

CHB refers to chronic inflammation and necrosis of the liver caused by HBV infection. CHB is defined as when HBsAg is present for longer than 6 months with a serum HBV DNA level of ≥2,000 IU/mL in HBeAg-negative CHB and ≥20,000 IU/mL in HBeAg-positive CHB and persistent or intermittent elevation of AST/ALT. The condition is divided into HBeAg-positive and -negative CHB (Table 4).

The initial evaluation of CHB patients should include a thorough history-taking and physical examination, with emphasis on risk factors such as alcohol consumption or drug use, coinfection, and the family history of HBV infection and HCC. The causal relationship between HBV infection and liver disease still has to be established because not all patients with CHB have persistently elevated AST/ALT. Appropriate longitudinal long-term follow-up is crucial for patients with CHB. Serologic tests, virologic tests, biochemical tests and/or liver biopsy are used to assess HBV replication and degree of liver injury in patients with CHB (Table 5).

Serologic test

Serologic tests including of HBsAg, anti-HBs, and anti-HBc can help when screening populations for HBV infection and for differentiating among acute, chronic, and past infections. Acute HBV infection is diagnosed by positive test results for HBsAg and immunoglobulin M (IgM) anti-HBc.[102] Some people may test positive for anti-HBc but negative for HBsAg or anti-HBs. The positive finding of isolated IgM anti-HBc can occur during the window phase of acute hepatitis B,[103] while the positive finding of isolated immunoglobulin G (IgG) anti-HBc can occur for the following reasons: (1) anti-HBs has decreased to an undetectable level after recovering from a previous infection, and (2) HBsAg has decreased to an undetectable level after HBV infection (occult hepatitis B).[104-107] Measurement of the serum HBV DNA level might be helpful in these settings. Patients with these sero-

Table 4. Diagnostic criteria of HBV infection

Chronic hepatitis B (CHB)
1. HBsAg positivity for longer than 6 months
2. Hepatitis B e antigen (HBeAg)-positive CHB: serum HBV DNA ≥20,000 IU/mL [≥10^5 copies/mL (cpm)] HBeAg-negative CHB: serum HBV DNA ≥2,000 IU/mL (≥10^4 cpm)
3. Persistent or intermittent elevation of aspartate aminotransferae/alanine aminotransferase (AST/ALT)
4. Liver biopsy showing chronic hepatitis with moderate-to-severe necroinflammation (optional)
Inactive HBV carrier state
1. HBsAg positivity for longer than 6 months
2. HBeAg negativity, hepatitis B e antibody (anti-HBe) positivity
3. Serum HBV DNA <2,000 IU/mL (<10^4 cpm)
4. Persistent normal AST/ALT levels
5. Liver biopsy confirms absence of significant necroinflammation (optional)

Table 5. Initial evaluation of patients with chronic hepatitis B

1. History-taking (including alcohol consumption and drug use) and physical examination
2. Family history of liver disease and HCC
3. Laboratory tests to assess liver disease: complete blood count, AST/ALT, alkaline phosphatase, gamma-glutamyl transpeptidase, bilirubin, albumin, creatinine, and prothrombin time.
4. Serologic tests for HBV replication: HBeAg/anti-HBe and HBV DNA
5. Tests to rule out other viral coinfections: anti-HCV (hepatitis C virus), anti-HDV (hepatitis D virus) (in a person with a history of drug abuse), and anti-HIV (human immunodeficiency virus) (high-risk group).
6. Serologic tests for immunization of hepatitis A [immunoglobulin G (IgG) anti-HAV (hepatitis A virus)] in patients younger than 50 years
7. Tests to evaluate the degree of hepatic necroinflammation and stage of hepatic fibrosis: liver biopsy (optional)
8. Screening tests for HCC: ultrasound and serum α-fetoprotein

logic patterns should be followed with repeated testing of HBsAg, anti-HBs, and anti-HBc in 3-6 months in order to detect these possibilities. By definition, patients who remain positive for HBsAg for longer than 6 months have progressed to chronic infection. Patients who recover from HBV infection will test negative for HBsAg and positive for anti-HBs and anti-HBc. Patients who respond adequately to hepatitis B vaccines will test negative for anti-HBc and positive for anti-HBs, since anti-HBc emerges only after HBV infection and persists for life.

Laboratory tests for patients with CHB should include HBeAg and anti-HBe. HBeAg positivity generally demonstrates high viral replication, while anti-HBe positivity demonstrates low viral replication.[108] HBeAg-positive CHB patients are positive for HBeAg, negative for anti-HBe, and high levels of HBV DNA. They have increased levels of AST/ALT in the immune-reactive phase. The serum HBV DNA and AST/ALT levels are important in HBeAg-negative patients. HBeAg-negative, anti-HBe-positive patients with a normal ALT level and an HBV DNA level of <2,000 IU/mL (<10,000 cpm) may be in the inactive carrier state. These patients usually have mild or no liver necroinflammation and no or slow progression of fibrosis, but some patients with severe liver damage during the immune-reactive phase may present with a cirrhotic liver. HBeAg-negative CHB patients have an elevated ALT and an HBV DNA level of >2,000 IU/mL. HBe-negative CHB is associated with viral mutants in PC and/or BCP regions that are unable to produce or produce only low levels of HBeAg.[41] They have severe liver necroinflammation with a low rate of prolonged spontaneous disease remission and a high risk of subsequent complications such as decompensated cirrhosis and HCC.[109]

The anti-HAV seroprevalence rate in Korea was 45% for the population younger than 10 years and 90–100% in the population older than 20 years during the late 1970s and early 1980s.[110] However, it has declined markedly since the late 1990s due to improvements in the socioeconomic status and hygiene practices. A recent survey of Koreans who underwent medical checkups found that the anti-HAV seroprevalence rates were >90%, 50%, 10-20%, and <10% among people older than 40 years and in their 30s, 20s, and 10s, respectively.[111,112] Similar trends have also been observed in patients with chronic liver disease.[113] These trends result in increased icteric manifestation, longer recovery time, and increased risk of fulminant hepatic failure of acute hepatitis A. Many studies have found that underlying chronic liver disease is an important risk factor for fulminant hepatic failure and death in patients with acute HAV infection.[114-116] Therefore, CHB patients younger than 50 years should undergo testing for IgG anti-HAV, and all patients with a negative immune status for hepatitis A should receive two doses of HAV vaccine 6 to 18 months apart. Laboratory tests should include tests for coinfection with HCV and/or HIV in those at risk.

Virologic test

Serum HBV DNA testing provides a direct measure of the level of viral replication. This quantification is essential for characterizing the status of infection, diagnosing the disease, making the decision to treat, and subsequent monitoring of patients. It is also important for predicting the risks of cirrhosis and HCC. Therefore, it should be applied to all patients diagnosed with CHB. The introduction of international unit (IU) (1IU is equivalent to five or six HBV DNA copies) as a recommended reporting unit for HBV DNA has facilitated the standardized reporting and comparison of serum HBV DNA levels.[117] The methods used to quantify HBV DNA levels have evolved rapidly. Hybridization assays demonstrate reliable quantification of HBV DNA but are

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limited by their narrow range of detection (10^3–10^7 IU/mL). PCR-based assays have increased the sensitivity of HBV DNA detection to levels as low as 10^2 IU/mL. However, the quantification of many of the earlier PCR-based assays is not reliable at viral levels of >10^6 IU/mL. Real-time PCR-based assays have been introduced that demonstrate both high sensitivity and a broad linear range (10–10^8 IU/mL) of quantification.[118] The same test should be specified each time when monitoring HBV DNA levels for a given patient in clinical practice in order to ensure consistency.

HBV genotype testing

HBV genotypes appear to influence the progression of disease, risk of HCC, and response to therapy.[119-121] Some studies in Asia have suggested that genotype C is more frequently associated with HBV reactivation, severe liver disease, and HCC than is genotype B.[119,122-124] The specific genotype has also been shown to affect the response to interferon therapy, with the rate of an antiviral response to pegylated interferon (peginterferon) therapy being higher for genotypes A and B than for genotypes C and D.[125] In light of these data, foreign guidelines recommend performing genotyping selectively to help identify patients who might be at greater risk of disease progression, and routinely when wanting to determine the most appropriate candidates for peginterferon therapy.[126] However, genotyping is recommended as being unnecessary in Korea because Korean patients are almost exclusively infected with genotype C.

Biochemical test

Assessments of the severity of liver disease should include biochemical markers such as AST, ALT, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), prothrombin time (PT), and serum albumin. The ALT level is usually higher than AST levels, but the ratio may be reversed when the disease progresses to cirrhosis. A progressive decline in the serum albumin level and prolongation of the PT—often accompanied by a decrease in the platelet count—are characteristically observed after cirrhosis develops. The serum ALT level has been commonly used in assessments of liver disease and as an important criterion for defining which patients are candidates for the therapy.[127] HBV-infected patients with normal or elevated ALT levels have been thought to have mild-to-no or significant necroinflammation on liver biopsy, respectively. However, there is no correlation between the degrees of liver cell necrosis and ALT level.[128] ALT activity might also be affected by other factors such as body mass index, gender, abnormal lipid and carbohydrate metabolism, fatty liver, and uremia.[128,129] Therefore, relying solely on the finding of elevated ALT as a prerequisite for treatment candidacy has limitations. Data from clinical studies have shown that the true normal level of ALT is significantly lower than the previously established limits: 40 IU/mL for men and 30 IU/mL for women. Moreover, data from cohort studies indicates that the upper limit of normal (ULN) ALT and AST levels should be decreased to 30 IU/mL for men and 19 IU/mL for women.[128,129] Clinical studies have shown that patients with ALT levels of 20–45 IU/mL have a high risk of significant liver disease and mortality from complications.[130] According to the treatment algorithm for CHB suggested by Keeffe et al., serum ALT levels of 30 and 19 IU/mL for men and women, respectively, should be used as the ULN levels when deciding to commence treatment.[126] Further prospective studies are needed to clarify this issue.

Liver biopsy

A liver biopsy is recommended for determining the degree of necroinflammation and fibrosis in patients with elevated ALT, an HBV DNA level of >2,000 IU/mL, or both, because liver histology is very useful when deciding whether or not to commence treatment. However, its use is limited (and not mandatory) due to its invasiveness, it only sampling a small portion of the liver, and is low inter- and intraobserver reliabilities. Patients with high HBV DNA and normal ALT levels generally have less fibrosis in a liver biopsy and a poor response to antiviral therapy. Accordingly, this patient population is generally not considered for treatment. However, recent several clinical studies found that 12-43% of patients with persistent normal ALT levels had histologic evidence of significant fibrosis or inflammation in a biopsy, particularly among patients older than 35 years of age.[125-131] A retrospective study of the relationship between ALT level and fibrosis in CHB patients produced similar results: of the 59 patients with persistent normal ALT levels, 18% had stage 2 fibrosis and 34% had grade 2 or 3 inflammation, with 37% of all patients with persistent normal ALT levels having significant fibrosis and inflammation.[132] Subgroup analysis also demonstrated that most of the patients with fibrosis had high normal ALT levels. These results indicate that the ALT level in CHB patients with high normal ALT levels should be interpreted in conjunction with the level of serum HBV DNA, age, and liver histology results when deciding to commence treatment. Therefore, in HBsAg-positive patients with HBV DNA levels

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of ≥20,000 IU/mL and normal ALT levels, a liver biopsy should be considered in those older than 35 years since they are less likely to be in the immune-tolerance phase of infection. Treatment should be considered if a liver biopsy reveals fibrosis at stage 2 or greater and/or necroinflammation. When deciding whether to commence treatment in this patient population, it must be recognized that long-term therapy is likely to be needed due to the low probability of HBeAg seroconversion occurring within 1 year. A liver biopsy is also useful for evaluating other possible causes of liver disease such as nonalcoholic steatosis, steatohepatitis, or alcoholic liver disease. A liver biopsy is usually not required in patients with clinical evidence of cirrhosis or when treatment is indicated irrespective of the grade of activity or the stage of fibrosis. Although the efficacy of noninvasive methods such as using the Fibroscan device or measuring potential serum markers in assessing fibrosis in CHB has been studied in the past few years,[126,131] such methods are not yet recommended as a diagnostic or decision-making tool for treatment.

Screening for hepatocellular carcinoma

The initial evaluation of patients with CHB should include tests to screen for HCC. Periodic surveillance is also needed in these patients to ensure the early detection of HCC during follow-up. The issue of HCC is treated in detail in the "Practical Guideline for Management of Hepatocellular Carcinoma 2009".[133] Standard tools for HCC screening include measuring the α-fetoprotein level and ultrasound. Magnetic resonance imaging and computed tomography might be preferred for some patients with severe cirrhosis or obesity, since ultrasound has poor sensitivity in those conditions. Patients at a high risk of HCC include men older than 40 years, women older than 50 years, patients with cirrhosis, patients with a family history of HCC, and any carriers older than 40 years exhibiting persistent or intermittent ALT elevation, a high HBV DNA level (>2,000 IU/mL), or both.[18] Keeffe et al. recently recommend earlier screening (at 30-35 years of age or even younger) in Asian patients with presumed infection at the time of birth or in early childhood due to the higher risk of HCC in these population.[126]

[Recommendation]

1. The initial evaluation of patients with CHB should include a thorough history-taking and physical examination, with emphasis on risk factors such as coinfection, alcohol consumption, and the family history of HBV infection and liver cancer (A1).
2. Laboratory tests to assess liver disease should include the complete blood count (CBC), AST/ALT, ALP, GGT, bilirubin, albumin, creatinine, and PT (A1).
3. Tests for HBV replication include HBeAg/anti-HBe and quantitative serum HBV DNA levels (A1). A real-time PCR quantification assay is strongly recommended for quantifying the HBV DNA level.
4. An anti-HCV test is necessary to rule out coinfection with HCV (B1).
5. An IgG anti-HAV test is necessary in CHB patients younger than 50 years (A1).
6. Standard tools for HCC screening include ultrasound and serum α-fetoprotein measurement (A1).

TREATMENT GOALS

The goals of hepatitis B treatment are to decrease the mortality rate and increase the survival rate by alleviating hepatic inflammation and preventing the development of fibrosis, which ultimately decreases the progression of hepatitis to liver cirrhosis or HCC.[134-138] The result of optimal treatment would be the loss or seroconversion of HBsAg, but since intranuclear cccDNA persists despite treatment, complete clearance of HBV is nearly impossible to achieve. This is why indices such as normalization of ALT level, undetectable HBV DNA, loss or seroconversion of HBeAg, and histologic improvement are used (rather than the loss or seroconversion of HBsAg) to predict the treatment response in the clinical context.

Elevation of the ALT level beyond the normal range indicates liver injury and the persistence of such elevation increaseses the risks of mortality and developing liver cirrhosis or HCC.[130,139,140] The ALT level is a good predictor of the treatment response, and its normalization is used as a substitute index for predicting the treatment efficacy. However, the ALT level lacks specificity since it increases in liver diseases other than hepatitis B, and it might not increase even when viral replication is active in cases of immunologic tolerance or advanced liver disease. Therefore, the decision to treat cannot be made solely based on the ALT level.[74] Biopsies can be useful for predicting treatment efficacy by confirming changes in the degree of hepatic inflammation and fibrosis between before and after treatment, but they are invasive and the assessment result can vary due to the sample size, sampling location, and interobserver variation.[141,142]

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The HBV DNA level and HBeAg in CHB are indices of viral replication and active hepatitis, and patients with HBeAg-positive hepatitis B with high levels of HBV DNA have an increased risk of developing liver cirrhosis or HCC.[74-76] The loss or seroconversion of HBeAg during the natural course of hepatitis B or after IFN-α treatment indicates a favorable long-term outcome with a decreased probability of liver cirrhosis or HCC development.[29,54,143,144] Therefore, the clearance or seroconversion of HBeAg is an important goal of antiviral treatment in patients with HBeAg-positive active hepatitis. A decrease in the HBV DNA level has recently been suggested to be even more important.[74] The decrease in the HBV DNA level after antiviral treatment in active hepatitis with elevated HBV DNA results in histologic improvement, seroconversion of HBeAg, and normalization of ALT levels, and thus a slowing of the progression of hepatitis.[145,146] However, even in cases with HBV DNA levels of less than 10^4 cpm, which is considered to be inactive hepatitis, the hepatitis can still progress to liver cirrhosis and HCC.[147] Therefore, a decrease in HBV DNA to an undetectable level is recommended for patients on antiviral treatment.

Many studies into the use of HBsAg as a substitute index for the treatment response are currently underway. In the natural course of hepatitis B, a loss of HBsAg occurs in 1-2% of patients annually, and the consequent decrease in the HBV DNA level results in decreases in the rates of disease progression to liver cirrhosis and HCC.[29,44,45,148] The rate of HBsAg clearance was found to be high in cases of suppressed viral replication after IFN-α treatment[149-151] and led to a decrease in liver disease-related mortality rates, such as loss of hepatic function and occurrence of HCC. Nonetheless, the rate of HBsAg clearance remains very low.[149] The rate of HBsAg clearance was higher in the group treated with IFN than in the group treated with an oral antiviral agent.[126] However, the prolonged use of oral antiviral agents is expected to increase the HBsAg clearance rate up to IFN levels.[152] A positive correlation between the HBsAg titer and the HBV DNA level was also observed after entecavir and pegIFN treatment.[153,154] Therefore, the clearance of HBsAg and its serum titer are together expected to be a good predictor of the hepatitis B treatment response in the future.

There are no clear guidelines regarding the optimal treatment period for oral antiviral agents after viral replication has been suppressed. HBeAg-negative hepatitis mostly recurs after ending treatment, despite the cessation criteria.[155,156] In cases of HBeAg-positive hepatitis, the rate of persistent suppression of viral replication was higher when treatment was continued after seroconversion had been achieved.[157,158] Many studies about the safety and efficacy of long-term oral antiviral treatment are currently underway.[146,159,160]

[Recommendation]

1. The treatment goals in hepatitis B are to decrease the mortality rate and increase the survival rate by alleviating hepatic inflammation and preventing the development of fibrosis, which would ultimately lower the progression of hepatitis to liver cirrhosis or HCC (A1).
2. To achieve HBsAg clearance, which is the ideal treatment goal, long-term maintenance of HBV DNA at an undetectable level is recommended (B1).
3. The ultimate treatment goals in patients with HBeAg-positive hepatitis are normalization of the ALT level, undetectable HBV DNA, and the clearance or seroconversion of HBsAg and HBeAg. In patients with HBeAg-negative hepatitis the treatment goals are normalization of the ALT level, undetectable HBV DNA, and the clearance or seroconversion of HBsAg (B1).

INDICATIONS FOR TREATMENT

Indications for initiating antiviral treatment

The ultimate goal of CHB therapy is to reduce mortality by preventing progression to hepatic decompensation and HCC. However, the study durations of currently available antiviral trials are not long enough to assess the effects of treatment on long-term survival.[161]

Long-term treatment with oral nucleoside or nucleotide analogues (NUCs) ameliorates histologic abnormalities such as necroinflammation and/or fibrosis, both in HBeAg-positive[162-164] and HBeAg-negative[155,164-166] CHB. Therefore, long-term antiviral therapy may prevent disease progression and reduce the risk of liver cirrhosis.[138] A recent meta-analysis indicated that long-term use of an oral antiviral agent decreased the risks of hepatic decompensation and HCC.[167]

Previous antiviral trials targeting HBV excluded patients in the immune-tolerant phase of the disease due to the minimal histologic changes they exhibit and the benign natural course of the disease.[168]

Criteria for initiating antiviral therapy for CHB

Elevated serum ALT is an indication for antiviral therapy[37,169,170]

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because it reflects hepatic necroinflammatory activity and the risk of disease progression.[171] The previously proposed cut-off value for transaminase (> 2x ULN) has recently been challenged: a prospective cohort study performed in Korea detected an association between increased liver-related mortality and transaminase levels of ≥ 20 IU/L.[130] Moreover, ALT levels tend to decrease with age, especially in men.[129,172] In healthy individuals without hepatitis virus infection or fatty liver, the 95th percentile of the upper threshold of ALT is reported to be 30 IU/L for men and 19 IU/L for women.[128] About two-thirds of CHB patients with mildly elevated ALT (1-2x ULN) show significant hepatic fibrosis (F2 or higher),[173] and CHB patients with persistently normal ALT levels and HBV DNA levels of > 20,000 IU/mL may actually have significant fibrosis or inflammation,[132,173,174] which are indications for antiviral therapy. A cohort study in Hong Kong demonstrated that the risk of liver-related complications in CHB patients was higher for ALT levels of 0.5-1x ULN and 1-2x ULN than for ALT levels of < 0.5x ULN.[169] Thus, previous ALT criteria might exclude some patients with existing or potentially significant disease.[175,176] Since advanced age is associated with significant hepatic fibrosis and poor outcomes in CHB,[171,173,177] and defining the "inactive carrier state" according to ALT and HBV DNA levels may miss cases of histologically significant disease,[174] histologic confirmation should be considered, especially in patients with advanced age when the serum AST/ALT levels are in the upper normal range or higher.

A serum HBV DNA level of ≥ 20,000 IU/mL has been suggested as a cut-off value for HBeAg-positive CHB.[178] However, the distinction between HBeAg-negative CHB and inactive carriers is not clear due to the fluctuating course of HBeAg-negative CHB.[178] A population-based cohort study revealed increased risks of liver cirrhosis and HCC when the serum HBV DNA level exceeds 2,000 IU/mL,[74,76,109] and therefore this level is widely accepted as the cut-off for indicating antiviral therapy.

Antiviral therapy in liver cirrhosis

Patients with compensated cirrhosis and elevated serum HBV DNA can benefit from treatment with long-term oral NUCs, because such treatment may prevent disease progression[134] and the development of HCC.[137,138,167,179-181] There is increasing evidence of the beneficial role of oral nucleoside analogs in decompensated liver disease. Oral NUCs may improve hepatic function[135] and decrease the need for liver transplantation in Child-Turcotte-Pugh class C cirrhosis.[182]

[Recommendation]

1. Patients in the immune-tolerant phase (HBeAg positive and persistently normal ALT level) are not indicated for antiviral therapy (B1).
2. HBeAg-positive CHB patients with an HBV DNA level of ≥ 20,000 IU/mL and an ALT level of ≥ 2× ULN are indicated for antiviral therapy (A1). When the ALT level is 1-2× ULN, a liver biopsy may be required to assess the need for antiviral treatment (B2). Antiviral therapy is indicated if a moderate-to-severe degree of inflammation or periportal fibrosis is present (A1).
3. HBeAg-negative CHB patients with an HBV DNA level of ≥ 2,000 IU/mL and an ALT level of ≥ 2× ULN are indicated for antiviral therapy (A1). When the ALT level is < 2× ULN, a liver biopsy may be required to assess the need for antiviral treatment (B2). Antiviral therapy is indicated if a moderate-to-severe degree of inflammation or periportal fibrosis is present (A1).
4. Patients with compensated cirrhosis are indicated for antiviral therapy if the HBV DNA level is ≥ 2,000 IU/mL, regardless of the ALT level (B1).
5. Patients with decompensated cirrhosis are indicated for antiviral therapy if HBV DNA is detectable, and liver transplantation should be considered (B1).

TREATMENT STRATEGIES

HBeAg positive and negative hepatitis

Indications for treatment

Long-term viral suppression by drugs with potent antiviral activity and high genetic barrier to resistance is a current paradigm of antiviral treatment for CHB aimed at the prevention of disease progression and improved survival. Since eradication of HBV infection is rarely achieved with currently available drugs, long-term treatment is necessary in most cases. Treatment protocol could be and should be individualized according to various factors: host factors such as mode of infection, disease status, and immunity; viral factors such as genotypes, prior antiviral treatment, mutation, and susceptibility level; and drug factors such local availability, cost, and reimbursement policy.[37]

CHB patients with active viral replication and significant inflammation and/or fibrosis are appropriate targets for antiviral treat-

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ment. Early guidelines generally agreed that antiviral treatment could be recommended for CHB patients (especially those without LC) with serum HBV DNA level > 20,000 IU/mL and serum ALT level> 2 × ULN.[183,184] However, recent guidelines suggest that the indication of antiviral treatment should be expanded to those with lower serum HBV DNA levels and/or lower serum ALT levels.[37,126,169,170]

Serum HBV DNA level is a marker of viral replication and an indicator of efficacy of antiviral treatment in individuals with CHB. Progression to cirrhosis in HBV-infected patients is reported to be strongly correlated with the level of circulating virus.[74,76] However, HBV DNA level of 10^5 cpm or 20,000 IU/mL was arbitrarily chosen by early guidelines as the cut-off level for indication of antiviral treatment. Some patients with lower serum HBV DNA levels (300–10^5 cpm), especially those with HBeAg negative hepatitis and/or cirrhosis, frequently show progression of liver disease and hence may need treatment.[37,178,184]

Serum ALT has been used as a convenient surrogate marker for liver injury, and elevated serum ALT was indicated as a risk factor for disease progression in CHB.[76] Serum ALT level > 2 × ULN was suggested as a suitable indication of antiviral treatment for CHB by the early guidelines, especially in CHB patients without cirrhosis.[183-185] However, an increased risk for developing LC and HCC has been documented in patients with mildly elevated serum ALT and even in those with serum ALT levels of upper normal range.[128,130,171]

Liver biopsy has three major roles: diagnosis, assessment of prognosis (disease staging), and assistance in making therapeutic decisions.[186] In CHB, liver biopsy is especially useful for patients who do not meet definite criteria for treatment but still have a possible risk for significant disease.[37] Age of the patient, serum HBV DNA level, serum ALT level, and family history of HCC should be considered before deciding whether or not to perform a biopsy.

Recommended antiviral agent as an initial therapy

Peginterferon-α and NUCs including lamivudine, adefovir, clevudine, telbivudine, entecavir, and tenofovir have been used for antiviral treatment of CHB. Drug of choice can differ according to various factors, including the effectiveness, safety, risk of resistance, and cost of drugs, preference of patients and doctors, and any plans for pregnancy.[37]

Peginterferon-α is preferred over conventional interferon due to its convenience of usage and high response rate. Lamivudine and telbivudine are not preferred due to their weak antiviral potency and high frequency of drug resistance, unless good response is predicted or anticipated duration of treatment is short. Adefovir is not an ideal option due to its weak antiviral activity and high frequency of drug resistance after 48 weeks. There are insufficient long-term follow-up data on efficacy and safety of clevudine. Entecavir and tenofovir are considerably safe agents showing potent viral suppression and low frequency of drug resistance. To date, there has been no report confirming the superiority of combination therapies over monotherapy in treatment-naïve patients.

Currently, monotherapy with entecavir, tenofovir, or peginterferon-α is the preferred initial therapy for CHB. Other NUCs might be used in patients with good predictors of response, and can be continued or modified according to on-treatment response. Elevated pretreatment ALT levels and/or active histologic disease were reported to be the most important predictors of lamivudine-induced HBeAg loss.[127] During telbivudine treatment, a combination of pretreatment characteristics (HBV DNA< 10^9 cpm and ALT level ≥ 2 × ULN in HBeAg-positive patients; HBV DNA< 10^9 cpm in HBeAg-negative patients) plus non-detectable serum HBV DNA at treatment week 24 is suggested as the strongest predictor for optimal outcomes at 2 years.[187] Of CHB patients receiving lamivudine or telbivudine treatment, those with virologic response at week 24 (< 300 cpm) were indicated to achieve high rate of HBeAg seroconversion at week 52.[132] Less resistance was reported in patients showing lower serum HBV DNA level (< 1,000 cpm) at week 48 during long-term therapy with adefovir.[165]

[Recommendation]

Antiviral therapy is not indicated for patients in immune tolerance phase. Spontaneous HBeAg seroconversion might be anticipated in some patients with HBeAg positive hepatitis. Serum level of AST or ALT could stabilize after transient elevation without specific treatment. Long-term treatment is necessary in a large proportion of patients receiving NUC therapy, which is associated with problems of high cost and emergence of drug resistance. Hence, careful consideration is necessary for deciding whom, when, and how to treat.

HBeAg positive chronic hepatitis B

1. HBeAg positive CHB patients with HBV DNA>20,000 IU/mL, and serum AST or ALT> 2 × ULN or significant inflammation or fibrosis (≥ moderate necroinflammation; ≥ periportal fibrosis) on biopsy should be considered for treatment (A1). Treatment can be delayed for 3–6 months if spontaneous

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HBeAg seroconversion is anticipated (B2). However, patients with apparent or concerned liver failure (i.e., those with jaundice, prolonged PT, hepatic encephalopathy, and ascites) should be promptly treated (B1).

2. For those with HBV DNA>20,000 IU/mL and serum AST or ALT = 1–2 × ULN, observation or liver biopsy can be considered. Antiviral treatment is recommended for those showing subsequent elevation of serum ALT or AST, or significant inflammation or fibrosis on biopsy (A1).
3. Monotherapy with entecavir, tenofovir, or peginterferon-α is preferred (A1). Other NUCs might be used in patients with good predictors of response, and can be sustained or modified according to on-treatment response (B2).

HBeAg negative chronic hepatitis B

1. HBeAg negative CHB patients with HBV DNA>2,000 IU/mL and serum AST or ALT> 2 × ULN or significant inflammation or fibrosis on biopsy should be considered for treatment (A1).
2. For those with HBV DNA> 2,000 IU/mL and serum AST or ALT< 2 × ULN, observation or liver biopsy can be considered. Antiviral treatment is recommended for those showing subsequent elevation of serum ALT or AST, or significant inflammation or fibrosis on biopsy (A1).
3. Monotherapy with entecavir, tenofovir, or peginterferon-α is preferred (A1). Other NUCs might be used in patients with good predictors of response, and can be sustained or modified according to on-treatment response (B2).

Compensated liver cirrhosis

The suppression of viral replication by long-term antiviral therapy may improve hepatic inflammation and fibrosis, which would stop the disease progressing to decompensated liver cirrhosis and HCC[134,164,188] Antiviral therapy is recommended in patients with CHB in whom significant hepatic fibrosis exists regardless of the AST/ALT levels.[37,169,170,189] The levels of AST/ALT should not be used as criteria for starting antiviral therapy in patients with liver cirrhosis, because they already have significant hepatic fibrosis and frequently have nearly normal AST/ALT levels.

In a cohort of HBeAg-positive liver cirrhosis patients, long-term follow-up data after interferon-α therapy showed that the HBeAg seroconversion rate was similar (67% vs. 60%, respectively) but that the ALT normalization rate (62% vs. 47%) and HBsAg loss rate (23% vs. 3%) were better in the interferon-α-treated group than in the control group.[190] Interferon-α treatment in cirrhotic patients requires careful monitoring because it may cause acute exacerbation of hepatitis that leads to hepatic failure.[191] After treating CHB patients with peginterferon-α-2b alone or in combination with lamivudine for 52 weeks, the virologic response rate (as indicated by HBeAg seroconversion and an HBV DNA level of <10,000 cpm) was superior in those with cirrhosis than in those without cirrhosis (35% vs. 14%, respectively).[192] However, acute exacerbation of hepatitis (33% vs. 12%, respectively) and requirement of dose reduction (63% vs. 30%) were more common in cirrhotic patients than in noncirrhotic patients.[192] Therefore interferon-α may be used with caution in cirrhotic patients with preserved liver function. Therefore interferon-a may be used with caution in cirrhotic patients with preserved liver function.[134]

Entecavir treatment of patients with advanced hepatic fibrosis or cirrhosis for 48 weeks produced improvements in the liver histology in 57%, 59%, and 43% of patients with HBeAg-positive, HBeAg-negative, and lamivudine-resistant CHB, respectively.[193] A study including a small number (n=40) of patients showed that telbivudine effectively decreased HBV DNA levels in patients with compensated liver cirrhosis, and the undetectablity of HBV DNA after 48 weeks of telbivudine treatment was 92.5%.[194] A study comparing the effects of clevudine treatment for 48 weeks found that the virologic response rate (HBV DNA <1,000) (87.1% vs. 71.4%, respectively) and biochemical response rate (83.9% vs. 80.9%) did not differ significantly between patients with CHB (n=21) and those with liver cirrhosis (n=31).[195] Phase-3 clinical trials of adefovir and tenofovir have included some patients with liver cirrhosis, but there has been no report on the effects of these drugs in patients with compensated liver cirrhosis.

Long-term antiviral therapy is generally required in patients with liver cirrhosis, which has led to AASLD and EASL guidelines recommending the use of entecavir or tenofovir due to their potent antiviral efficacy and high genetic barrier to drug resistance. AASLD and EASL guidelines recommend combinational use of adefovir or tenofovir to prevent the development of drug-resistant viruses in circumstances when low-genetic-barrier drugs such as lamivudine or telbivudine are selected as an initial therapy. However, there appears to be only weak evidence for supporting this approach.[37,189] Meanwhile, the APASL guideline published in 2008 recommends the use of interferon/peginterferon, entecavir, adefovir, telbivudine, or lamivudine in patients with CHB, and it seems likely that these recommendations are influenced by considerations of socioeconomic status in Asian countries.[170] In general, long-term antiviral therapy is required in patients with liver cirrhosis, therefore close monitoring about the possible development

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of drug resistance and acute flare of hepatitis, and it is necessary to differentiate the emergence of drug resistance and poor drug compliance when decompensation develops during treatment.

[Recommendation]

1. Antiviral therapy is recommended in patients with compensated liver cirrhosis if the HBV DNA level is ≥2,000 IU/mL regardless of the AST/ALT levels (B1).
2. Oral antiviral therapy using nucleoside/nucleotide analogues is recommended in patients with compensated liver cirrhosis. Long-term treatment is generally required, and hence the choice of drug is based on the general principles of hepatitis B treatment with consideration of antiviral efficacy, side effects, and genetic barriers to drug-resistant viruses (B1).
3. Peginterferon-α may be used with careful monitoring for the imparement of liver function and drug side effects in patients with compensated liver cirrhosis having preserved liver function (B2)

Decompensated liver cirrhosis

It is preferable for patients with decompensated liver cirrhosis to be treated at an institution that can provide appropriate management for cirrhosis complications. Liver transplantation should be considered in patients with decompensated liver cirrhosis. The use of interferon-a in patients with decompensated liver cirrhosis is contraindicated due to the possibility of serious complications such as infection or hepatic failure.[196] Lamivudine treatment for longer than 6 months was shown to improve or stabilize liver function and prolong the time to liver transplantation in patients with decompensated liver cirrhosis.[197-199] A study comparing the effects of telbivudine with lamivudine in patients with decompensated liver cirrhosis found that the higher HBV DNA undetectability (47% vs. 36%, respectively) and the lower viral breakthrough rate (29% vs. 39%, respectivelyy) in the telbivudine group than in the lamivudine group.[200] A study investigating the effect of adefovir in lamivudine-resistant cirrhotic patients (n=101) found that the virologic response rate was lower in decompensated cirrhotic patients (n=53) than in compensated cirrhotic patients (n=48) (50.9% vs. 83.3%, respectively), whereas ALT normalization and HBeAg loss did not differ between the two groups.[201]

A randomized study comparing the effects of entecavir (1 mg/day) and adefovir (10 mg/day) in patients with decompensated liver cirrhosis found that the rates of HBV DNA undetectability at weeks 24 and 48 were higher in the entecavir group than in the adefovir group (week 24, 49% vs. 16%, respectively; week 48, 57% vs. 20%), while HBeAg seroconversion at week 48 did not differ significantly between the two groups (6% vs. 10%).[202] Entecavir therapy improved the Child-Pugh score (to ≥2) in almost half (27/55) of treatment-naïve patients with decompensated liver cirrhosis (n=55), and the 1-year transplantation-free survival rate was 87.1%.[135]

A randomized trial comparing the effects of tenofovir (n=45), tenofovir plus emtricitabine (n=45), and entecavir (n=22) in patients with decompensated liver cirrhosis showed that the requirement of early withdrawal of drug (6.7%, 4.4%, and 9.1%, respectively) and the elevation of serum creatinine (8.9%, 6.7%, and 4.5%) did not differ between the three groups. The rates of undetectable HBV DNA at week 48 were 70.5%, 87.8%, and 72.7%, respectively, and those of HBeAg loss/seroconversion were 21%/21%, 27%/13%, and 0%/0%.[136]

Because prompt treatment is required in patients with decompensated liver cirrhosis, oral antiviral therapy is the treatment of choice if HBV DNA is detectable in PCR tests.[37,169,189] The recommended antiviral drug has a potent antiviral efficacy and high genetic barrier to drug resistance. The clinical improvement often requires 3–6 months of antiviral therapy, which can result in some patients progressing to hepatic failure even during antiviral therapy, and hence liver transplantation needs to be considered.[199] Pre- and post-transplantation antiviral therapy may reduce the risk of reactivation of hepatitis after liver transplantation.

[Recommendation]

1. Prompt antiviral therapy is recommended in patients with decompensated liver cirrhosis if HBV DNA is detectable in PCR tests regardless of the AST/ALT levels (B1).
2. The treatment of choice in patients with decompensated liver cirrhosis is oral nucleoside or nucleotide analogues that have potent antiviral efficacies and high genetic barriers to drug resistance (B1); however, long-term data about the efficacy and safety of these drugs are not available yet.
3. The use of interferon/peginterferon is contraindicated in patients with decompensated liver cirrhosis due to the possibility of serious complications such as infection or hepatic failure (A1).
4. Liver transplantation should be considered in patients with decompensated liver cirrhosis (B1).

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Combination therapy in treatment naïve patients

It has been shown that combination antiviral therapy is more effective than monotherapy in the treatment of patients with HCV or HIV infection. The potential benefits from combination therapy are additive or synergistic antiviral efficacy and reduction or delay of the occurrence of resistant viruses. Meanwhile, the possible limitations of this approach are increased toxicity and cost, drug interactions, and poor compliance. Studies investigating the effects of combination therapy of interferon/peginterferon plus lamivudine found no benefit relative to interferon/peginterferon monotherapy.[203-207] Similarly, combination therapy of interferon-α plus lamivudine was not more effective than lamivudine monotherapy in nonresponders to interferon.[208] A study found that combination therapy of peginterferon plus adefovir for 48 weeks showed higher HBeAg seroconversion (58%) and HBsAg seroconversion (15%); however, this study had limitation of the small number of patients and the absence of a control group.[209] There have been no reports on the efficacy of combination therapy of peginterferon-a plus recently developed potent oral antiviral agents.

Few reports have compared the effects of combination therapy and monotherapy in treatment-naïve patients with CHB. Combination therapy has not demonstrated better efficacy than monotherapy. Combination therapy of lamivudine plus adefovir and lamivudine monotherapy showed similar antiviral effects. Fewer lamivudine-resistant viruses developed in the combination group than in the monotherapy group (15% vs. 43%, respectively), however combination therapy could not completely prevent the development of resistant virus.[210] Another study found that combination therapy of lamivudine plus telbivudine provided no benefit relative to telbivudine monotherapy.[211] A small-sample study found that combination therapy of adefovir plus emtricitabine provided better viral suppression than adefovir monotherapy, but there was no difference in the HBeAg seroconversion rate.[212]

The patients most likely to benefit from combination therapy as the first-line antiviral treatment would be those with a high risk of developing resistant viruses (due to long-term infection, very high pretreatment HBV DNA titer, and the presence of mutant HBV prior to treatment) and in whom the emergence of resistant viruses can be life-threatening (e.g., cirrhotic and post-transplant patients).[213] AASLD and EASL guidelines recommend the combination therapy of adefovir or tenofovir to prevent the development of drug resistant virus in circumstances when low genetic barrier drugs such as lamivudine or telvbivudine are need to be selected as an initial therapeutic agent.[37,189] There is no evidence that combination therapy including low-genetic-barrier drugs is better than monotherapy at decreasing the development of resistant viruses. Moreover, there are no long-term safety data on the combination therapy of entecavir plus tenofovir, and the cost issue also needs to be addressed. Likewise, the effects of combining tenofovir with lamivudine, telbivudine, or emtricitabine require further investigation.

[Recommendation]

Combination antiviral therapy in treatment-naïve patients is not recommended since there are no data supporting the superiority of combination therapy over monotherapy (B1).

TREATMENT MONITORING

Monitoring prior to antiviral treatment

After diagnosis and the initial evaluation of patients with CHB, their serum HBV DNA, ALT, HBeAg, and anti-HBe levels should be regularly monitored until they are considered for treatment.[37,170,173,214,215] The HBV genotype test is not recommended in Korea because most Korean patients are known to have HBV genotype C.[216,217] Several studies reported that applying a quantitative HBsAg assay before or during antiviral treatment may help in predicting the treatment response.[218,219]

[Recommendation]

1. Chronic hepatitis (with HBeAg positivity or negativity)
   A. In patients with persistently normal AST/ALT levels, liver function should be tested and serum HBV DNA should be measured by real-time PCR at 2-6 month intervals, and HBeAg status (HBeAg and anti-HBe) should be checked every 6-12 months (III, C1).
   B. If AST/ALT levels increase above the normal limit, liver function should be tested every 1-3 months, and serum HBV DNA should be measured by real-time PCR and HBeAg status checked every 2-6 months (III, C1).
2. Compensated liver cirrhosis
   - Liver function should be tested every 2-6 months, and serum HBV DNA should be measured by real-time PCR and HBeAg status checked every 2-6 months (III, C1).
3. Decompensated liver cirrhosis
   - Liver function should be tested every 1-3 months, and se-

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rum HBV DNA should be measured by real-time PCR and HBeAg status checked every 2-6 months (III, C1).

Monitoring during antiviral treatment

(1) Peginterferon-α

Patients receiving peginterferon-α should be tested monthly for serum CBC and ALT level. Serum HBV DNA should be measured after 3-6 months of treatment to verify the primary response. All patients treated with peginterferon-α should be checked for the known adverse effects of interferon at every visit.

HBeAg-positive chronic hepatitis

Patients should be tested for HBeAg and anti-HBe at 6 and 12 months during the treatment, and at 6 months post treatment. After cessation of treatment, patients should be monitored for 6-12 months to check if additional treatment is required. The optimal treatment outcome is HBeAg seroconversion, ALT normalization, and serum HBV DNA of less than 2,000 IU/mL. There is high probability of HBsAg loss if serum HBV DNA becomes undetectable during treatment. HBeAg-positive patients who achieve HBeAg seroconversion with peginterferon-α require a long follow-up due to the possibility of HBeAg reversion or development of HBeAg-negative CHB. HBsAg loss should be checked at 6-month intervals after HBeAg seroconversion if serum HBV DNA is undetectable. Several studies reported that the quantitative HBsAg assay may help in predicting the treatment response. In case of a primary non-response (failure to achieve a 1 $\log_{10}$ reduction of serum HBV DNA from baseline after 3 months of peginterferon-α treatment), peginterferon-α treatment should be stopped and replaced by a nucleos(t)ide analogue (NUC).

HBeAg-negative chronic hepatitis

HBeAg-negative patients should be monitored similarly to HBeAg-positive patients during 48 weeks of treatment. A virologic response with serum HBV DNA of <2,000 IU/mL is generally associated with remission of the liver disease. Undetectable serum HBV DNA by real-time PCR is the ideal off-treatment sustained response, with a high probability of HBsAg loss in the longer term. HBsAg should be checked at 6-month intervals if HBV DNA is not detectable.

(2) NUC

In a compliant patient with a primary non-response (decrease in serum HBV DNA of <2 $\log_{10}$ IU/mL after 6 months or more of NUC treatment), changing to or adding a more-potent drug should be considered. Serum HBV DNA should be measured every 1 to 3 months for the first months to ascertain the virologic response, and then every 3 to 6 months. Serum HBV DNA reduction to an undetectable level by real-time PCR (i.e.,<10–15 IU/mL) should ideally be achieved to avoid resistance. Serum HBV DNA monitoring is thus critical to detecting treatment failure.

Compliance and antiviral-resistance mutation should be monitored in patients who develop virologic breakthrough while receiving NUC, and appropriate rescue therapy should be initiated if necessary.[220-224]

Most NUCs are excreted through the kidney, and hence dose adjustment is required in patients with renal insufficiency (Table 6),[37] and regular monitoring of renal function should be performed in patients receiving adefovir or tenofovir. Moreover, there are several reports associating tenofovir with bone loss in patients with HIV, and studies of entecavir-related carcinogenicity are in progress. There have been few reports on telbivudine-related myositis. Combination therapy of peginterferon-α plus telbivudine is not recommended due to the possibility of inducing peripheral neuritis.

[Recommendation]

1. During NUC therapy, liver function should be tested and serum HBV DNA should be measured by real-time PCR every 1-3 months, and HBeAg status (HBeAg and anti-HBeAg) should be checked every 3-6 months (III, C1).
2. During peginterferon therapy, CBC and ALT level should be measured monthly. Serum HBV DNA should be measured by real-time PCR at 1- to 3-month intervals, and HBeAg and anti-HBe should be checked at 6 and 12 months during the treatment and at 6 months post treatment (III, C1).
3. After verifying a complete virologic response, serum HBV DNA should be measured by real-time PCR at 3-6 months and then retesting should be performed at 2-3 months after HBeAg seroclearance is achieved (III, C1).
4. Patients who develop virologic breakthrough while receiving NUC should be monitored for compliance and antiviral-resistance mutation (A1).
5. During antiviral therapy, a close monitoring for side effects of each drug is mandatory (I, A1).

Table 6. Adjustment of nucleos(t)ide analogue dosagesfor adult patients with altered creatinine clearance

Creatinine clearance (mL/min)[a]	Recommended dose	
Nucleoside Analogues		
Lamivudine		
≥50	100 mg q 24 hours	
30-49	100 mg first dose, then 50 mg q 24 hours	
15-29	100 mg first dose, then 25 mg q 24 hours	
5-14	35 mg first dose, then 15 mg q 24 hours	
<5	35 mg first dose, then 10 mg q 24 hours	
Telbivudine		
≥50	600 mg q 24 hours	
30-49	600 mg q 48 hours	
<30 (not requiring dialysis)	600 mg q 72 hours	
End-stage renal disease[b]	600 mg q 96 hours	
Entecavir	*NA naavi*	*NA naavi*
≥50	0.5 mg q 24 hours	0.5 mg q 24 hours
30-49	0.25 mg q 24 hours or 0.5 mg q 48 hours	0.25 mg q 24 hours or 0.5 mg q 48 hours
10-29	0.15 mg q 24 hours or 0.5 mg q 72 hours	0.15 mg q 24 hours or 0.5 mg q 72 hours
<10 or hemodialysis[b] or continuous ambulatory peritoneal dialysis	0.05 mg q 24 hours or 0.5 mg q 7 days	0.05 mg q 24 hours or 0.5 mg q 7 days
Nucleotide Analogues		
Adefovir		
≥50	10 mg q 24 hours	
20-49	10 mg q 48 hours	
10-19	10 mg q 72 hours	
<10	No recommendation	
Hemodialysis[b]	10 mg q 7 days following dialysis	
Tenofovir		
≥50	300 mg q 24 hours	
30-49	300 mg q 48 hours	
10-29	300 mg q 72–96 hours	
<10 with dialysis[c]	300 mg q 7 days or after approximately 12 hours of dialysis	
<10 without dialysis	No recommendation	

a. Calculated using the ideal (lean) body weight.
b. Administer after hemodialysis.
c. Generally once per week assuming three hemodialysis sessions per week of approximately 4 hours duration. Administer following completion of dialysis.

Monitoring after antiviral treatment

The response to antiviral treatment persists in some patients while relapsing in others. Non-responders also should prepare for the deterioration of liver function. Therefore, regular monitoring is needed to check for the durability of the treatment response, relapse, and liver function.

[Recommendation]

1. During the first year after antiviral treatment, liver function should be monitored and serum HBV DNA should be

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measured by real-time PCR every 1-3 months, and HBeAg and anti-HBe should be checked at 3- to 6-month intervals. Beyond 1 year after antiviral treatment, liver function and serum HBV DNA by real-time PCR should be tested every 3-6 months to detect viral relapse (III, C1).
2. For early detection of HCC, ultrasound and serum a-fetoprotein measurement should be performed regularly (III, A1).

CESSATION OF TREATMENT

HBeAg-positive chronic hepatitis

The primary endpoint when treating patients with HBeAg-positive hepatitis is to achieve HBeAg seroconversion. Undetectable serum HBV DNA by real-time PCR and HBeAg seroconversion are strongly correlated with favorable biochemical and histologic responses. Peginterferon-α is generally administered for 48 weeks, and its efficacy was confirmed in a recent double-blind, randomized controlled study.[225,226] NUC can be stopped when HBeAg seroconversion is achieved and antiviral treatment has maintained at least for 12 months.[158] HBsAg should be tested at 6-month intervals after HBeAg seroconversion; however, HBsAg loss is rarely observed after NUC therapy.

HBeAg-negative chronic hepatitis

The recommended duration of peginterferon-α treatment in patients with HBeAg-negative hepatitis is 48 weeks, but the optimal treatment duration for NUC is not known, and cessation of treatment should be individually decided according to the clinical treatment response and the baseline severity of the liver disease. Treatment with NUC should be continued until the loss of HBsAg. However, treatment discontinuation can be considered if undetectable serum HBV DNA has been documented on three separate occasions 6 months apart.[170]

Liver cirrhosis

Long-term treatment is required in patients with cirrhosis. In HBeAg-positive patients with compensated cirrhosis, treatment discontinuation can be considered when NUC is administered for at least an additional 12 months after HBeAg seroconversion. Treatment discontinuation can be considered after HBsAg loss is achieved in HBeAg-negative patients. Monitoring for viral relapse and acute exacerbation of disease is mandatory after discontinuation. Long-term treatment should be planned in patients with decompensated cirrhosis, including the possibility of liver transplantation.

[Recommendation]

1. HBeAg-positive chronic hepatitis
   1) Peginterferon should be administered for 48 weeks (A1).
   2) NUC should be administered at least 12 months after serum HBV DNA is undetectable and HBeAg seroclearance or seroconversion is attained (II-2, B1).
2. HBeAg-negative chronic hepatitis

Table 7. Definitions of response to antiviral therapy of chronic hepatitis B

	Response characterization
Peginterferon-α	
Primary non-response	Decrease in serum HBV DNA of <1 $\log_{10}$ IU/mL after 3 months of peginterferon-α therapy
Virologic response	Decrease in serum HBV DNA of <2,000 IU/mL after 6 months of peginterferon-α therapy
Serologic response	HBeAg seroconversion in patients with HBeAg-positive CHB
Nucleos(t)ide Analogues	
Primary non-response	Decrease in serum HBV DNA of <2 $\log_{10}$ IU/mL after 6 months of therapy
Partial virologic response	Decrease in serum HBV DNA of >2 $\log_{10}$ IU/mL but still detectable HBV DNA by real-time PCR assay
Complete virologic response	Decrease in serum HBV DNA to an undetectable level by real-time PCR assay
Virologic breakthrough	Increase in serum HBV DNA of >1 $\log_{10}$ IU/mL relative to the nadir
Biochemical breakthrough	Increase in ALT level after ALT normalization during antiviral therapy
Genotypic resistance	Presence of HBV mutations that are known to confer antiviral resistance during antiviral therapy
Phenotypic resistance	Decreased susceptibility (*in vitro* testing) to inhibition by antiviral drugs associated with genotypic resistance
Cross resistance	HBV mutation induced by one antiviral agent conferring resistance to other antiviral agents

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1) Peginterferon-α should be administered for at least 48 weeks (B1).
2) It is not clear how long NUC should be continued, but this should be at least until HBsAg loss (A1).

3. Patients with cirrhosis need long-term treatment (II, B1).

DEFINITIONS OF RESPONSE AND PREDICTORS OF RESPONSE

Definitions of treatment responses (Table 7)

The definitions of responses to antiviral therapy vary with the type of therapy.

(1) Peginterferon-α

A *primary non-response* to peginterferon-α is defined as a decrease of less than 1 $\log_{10}$ IU/mL in serum HBV DNA from baseline after 3 months of therapy. A *virologic response* is defined as an HBV DNA level of less than 2,000 IU/mL after 6 months of therapy. A *serologic response* is defined by HBeAg seroconversion in patients with HBeAg-positive CHB.

(2) NUC

A *primary non-response* to NUC is defined as a decrease of less than 2 $\log_{10}$ IU/mL in serum HBV DNA from baseline after 6 months of therapy. A *complete virologic response* is defined as undetectable serum HBV DNA by real-time PCR. A *partial virologic response* is defined as a decrease in serum HBV DNA of more than 1 $\log_{10}$ IU/mL but with serum HBV DNA still being detectable by real-time PCR.[227] Partial virologic response should be assessed to determine whether to modify the current therapy after 24 weeks of treatment for moderately potent drugs or drugs with a low genetic barrier to resistance (lamivudine and telbivudine), and after 48 weeks of treatment for highly potent drugs, drugs with a high genetic barrier to resistance, and drugs with a late emergence of resistance (e.g., entecavir, adefovir, and tenofovir). *Virologic breakthrough* is defined as a confirmed increase in serum HBV DNA of more than 1 $\log_{10}$ IU/mL relative to the nadir serum HBV DNA during therapy. This usually precedes a *biochemical breakthrough*, which is characterized by an increase in ALT level after an initial normalization. If a virologic breakthrough develops in a compliant patient, antiviral-resistant mutations should be tested for. *Genotypic resistance* is defined as the presence of HBV mutations from a patient's serum that confers resistance to the antiviral agent, and *phenotypic resistance* is defined as the presence of decreased susceptibility of HBV mutations to antiviral drugs in an *in vitro* test. *Cross-resistance* is where HBV mutation induced by one antiviral agent confers resistance to other antiviral agents.

HBV resistance to NUCs is characterized by the presence of HBV variants with amino-acid substitutions that confer reduced susceptibility to the administered NUC. Such resistance may result in primary treatment failure or virologic breakthrough during therapy.

Predictors of treatment responses

Certain baseline and on-treatment predictors of the subsequent treatment response have been identified. The predictors of the responses for existing antiviral therapies at various time points vary with the agent.

(1) Peginterferon-α

Pretreatment factors predictive of HBeAg seroconversion in HBeAg-positive patients are a high ALT level, low viral load, a high inflammatory activity score in a liver biopsy, and HBV genotypes.[204,228] There is no consensus among previous reports for patients with HBeAg-negative hepatitis, but generally a pretreatment high ALT level, young age, and female gender are reported to be associated with a favorable treatment response.[131,229]

A decrease in serum HBV DNA to less than 20,000 IU/mL after 12 weeks of treatment is associated with a 50% chance of HBeAg seroconversion in HBeAg-positive patients and with a 50% chance of a sustained response in HBeAg-negative patients.[131,230] A decrease in HBeAg at week 24 may predict HBeAg seroconversion.[127,230] Further studies are needed to determine the usefulness of HBsAg quantification in predicting a sustained virologic response and HBsAg loss.[218]

HBV genotypes A and B have been shown to be associated with a better response to interferon-α than genotype C, in terms of HBeAg seroconversion and HBsAg loss.[203,231-233] However, knowledge of the HBV genotype has a poor predictive value in individual cases, and currently genotype alone should not dominate the choice of treatment..

(2) NUC

Pretreatment factors predictive of HBeAg seroconversion are a low viral load (serum HBV DNA of $<10^7$ IU/mL), high ALT level ($<3\times$ULN), and high inflammatory activity score in a liver biopsy (at least A2).[234] A high pretreatment ALT level is known to be the most important predictor of the treatment outcome for lamivu-

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dine, adefovir, or telbivudine.[127] During treatment with lamivudine, adefovir, or telbivudine, a virologic response at 24 or 48 weeks (undetectable serum HBV DNA by a real-time PCR assay) is associated with lower incidences of antiviral resistance (i.e., higher probability of a sustained virologic response) and HBeAg seroconversion in HBeAg-positive patients.[165,235,236] HBV genotype does not influence the response to any NUC.

ANTIVIRAL RESISTANCE

The development of antiviral resistance is one of the most important factors predicting the success or failure of CHB treatment. The emergence of antiviral resistance results in the resumption of active viral replication that had been suppressed after the initiation of antiviral therapy, and can impair the biochemical or histologic improvement.[237] Therefore, the prevention, early diagnosis, and management of antiviral resistance may significantly affect the long-term prognosis in CHB patients receiving antiviral therapy.[134]

Mechanism of antiviral resistance and definitions

It is estimated that more than 10^{11} new virions are produced every day in a human body with active HBV replication.[238] Some of the HBV mutants that emerge naturally during active replication are selected under specific selection pressures exerted by the human immune system or antiviral therapy. Those mutants with maximal replication become predominant during antiviral therapy. The replication fitness is determined by the replication capacity and the fold resistance (i.e., quantified as the drug concentration needed to suppress 50% of mutant virus replication or to suppress 50% of wild-type virus replication) of the mutant viruses. Primary antiviral-resistant mutants usually have a low replication capacity, but recover to the level of the wild-type virus when compensatory mutations appear.[239] In addition, a higher fold resistance to antiviral therapy allows increased replication of the mutant virus. A genetic barrier is defined as the number of genetic mutations needed to develop antiviral resistance, with a higher genetic barrier indicating a lower risk of resistance.[240] The antiviral potency of drugs also influences the development of resistance. Drugs with a lower antiviral potency or potent antiviral activity have lower risks of antiviral resistance, because the former is associated with a lower selection pressure and the latter with complete suppres-

Table 8. Cumulative incidence of antiviral resistance development in representative studies

Antiviral agent	Resistance rate (%)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Lamivudine[a]	24	42	53	70	≥65
Adefovir					
In treatment-naïve patients[*,b]	0	3	11	18	29
In lamivudine-resistant patients[c]	4.4–18	18.4–25	34.3	52.3	65.6
Adefovir + lamivudine					
In lamivudine-resistant patients[d]	1	2	4	4	
Entecavir					
In treatment-naïve patients[e]	0.2	0.5	1.2	1.2	1.2
In lamivudine-refractory patients[f]	6	15	36	47	51
Tenofovir[†]	0	0	0	0	
Emtricitabine[h]	9	18			
Telbivudine[i]	2.7–4.4	10.8–25.1			
Clevudine[j]	2.3	24.4			

[*]HBeAg-negative patients.
[†]Emtricitabine was combined in patients with detectable HBV DNA after 72 weeks of treatment.
a. modified and updated from Lai et al. Clin Infect Dis 2003[244] and Lok et al. Gastroenterology 2003[245]; b. from Hadziyannis et al. Gastroenterology 2006[165]; c. from Lee et al. Hepatology 2006[260], Yeon et al. Gut 2006[261], and Lee et al. Antivir Ther 2010[221]; d. from Lampertico et al. Gastroenterology 2007[257]; e & f. Tenney et al. Hepatology 2009[254]; g. from Heathcote et al. AASLD 2010 and Marcellin et al. AASLD 2010; h. from Gish et al. J Hepatol 2005[246]; i. from Lai et al. N Engl J Med 2007[235] and Liaw et al. Gastroenteroogy 2009[249]; j. from Yoon et al. J Clin Gastroenterol 2011.[250]

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sion of the virus. However, drugs with intermediate potency have an increased risk of resistance because residual viremia during treatment may result in selection of mutants with good replication fitness.[241] Clinically, the HBV DNA level, history of prior antiviral treatment, duration of treatment, serum drug concentration (peak and trough), and patient compliance are the most important factors influencing the development of resistance. Definitions associated with antiviral resistance are listed in Table 7.

Mutations conferring resistance to antiviral agents

Antiviral agents for the treatment of HBV infection are classified into two groups: nucleoside analogues and nucleotide analogues. Cyclopentenes (entecavir) and L-nucleoside analogues (lamivudine, telbivudine, and clevudine) are nucleoside analogues, while acyclic phosphonates (adefovir and tenofovir) are nucleotide analogues.[242] The incidences of resistance to individual antiviral drugs are summarized in Table 8.

1. Nucleoside analogues

1) L-nucleoside analogues (lamivudine, telbivudine, and clevudine)

Mutations at rtM204 are considered the primary resistance mutations to lamivudine, telbivudine, and clevudine.[243-246] The rtM204V and rtM204I mutations involve the substitution of methionine with valine and isoleucine, respectively, at codon 204 of the reverse transcriptase gene. Originally these were called YMDD mutations, but that terminology is no longer recommended.[247] rtM204V emerges during lamivudine treatment, but rtM204I can develop during the administration of lamivudine, telbivudine, or clevudine.[235,248-250] An rtM204V mutant may commonly accompany rtL180M but not rtM204I.[251] These mutants are sensitive to adefovir and tenofovir, but they exhibit cross-resistance to entecavir and show an eightfold decrease in sensitivity. The rtA181T mutation has been detected in 5% of lamivudine-resistant patients.[252] The mutants exhibit cross-resistance to adefovir but remain sensitive to entecavir.[252]

2) Cyclopentene (entecavir)

Resistance to entecavir develops via a two-hit mechanism. rtL180M and rtM204V first develop as background mutations, and then additional mutations such as rtT184L/F/A/M/S/I/C/G, rtS202G/I/C, or rtM250V/I/L develop as primary resistance mutations to entecavir, resulting in a remarkable decrease in drug susceptibility.[240,253] rtI169T is a compensatory mutation that increases the fold resistance of rtT184, rtS202, and rtM250 mutants. Since multiple genetic mutations are needed to develop high-level resistance to entecavir (high genetic barrier), the resistance rate in treatment-naïve subjects is very low. However, a resistance rate as high as 51% has been reported after 5 years of treatment in lamivudine-refractory subjects.[254]

2. Nucleotide analogues

1) Adefovir

rtN236T and rtA181V/T are the primary resistance mutations to adefovir.[165,255] The fold resistances of rtN236T and rtA181T to adefovir are 7- to 10-fold and 2.5- to 5-fold, respectively, compared to the wild-type virus.[242,252] rtA181T can be detected in subjects receiving lamivudine monotherapy or a combination therapy of adefovir plus lamivudine.[256,257]

Table 9. *In vitro* cross-resistance of frequent resistant HBV variants

HBV variant	Lamivudine	Clevudine	Telbivudine	Entecavir	Adefovir	Tenofovir
rtM204I	H	H	H	I	L	L
rtL180M+rtM204V	H	H	H	I	L	L
rtA181T/V	I	H	I	L	H	L
rtN236T	L	L	L	L	H	I
rtL180M+rtM204V±rtI169T±rtM250V	H	H	H	H	L	L
rtL180M+rtM204V±rtT184G±rtS202I/G	H	H	H	H	L	L
rtA194T	H	NA	I	L	H	H

Modified from composite data of Locarnini. Semin Liver Dis 2005[251], Qi et al. Antivir Ther 2007[252], Villet et al. J Hepatol 2008,[256] and Amini-Bavil-Olyaee et al. Hepatology 2009[296,‡].

Disclaimer: results of in vitro susceptibility tests may not be consistent, and caution might be needed in clinical applications.

H, high-level resistance (relative resistance >30-fold); I, intermediate-level resistance (relative resistance 3–30-fold); L, low-level resistance (relative resistance <3-fold); NA, not available.

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Table 10. General considerations in the management of antiviral resistance

Prevention	1. Avoid unnecessary treatment, especially in patients with a normal ALT level and no significant histologic findings.
	2. Start with an antiviral agent that shows potent antiviral activity and the lowest antiviral resistance rate.
	3. Early modification of antiviral therapy according to the initial on-treatment response is desirable.
Monitoring	1. Use the assay that is the most sensitive for monitoring antiviral responses.
	2. Check patient's compliance with the medication in the presence of virologic breakthrough.
	3. Rescue therapy should be determined according to the results of an antiviral resistance test.
Treatment	1. Start rescue antiviral therapy for antiviral resistance as soon as possible, especially when viral breakthrough occurs and genotypic resistance is confirmed.
	2. To prevent multidrug resistance, avoid sequential monotherapy.
	3. Combination therapy of a nucleoside analogue plus a nucleotide analogue that does not exhibit cross-resistance is strongly recommended.

2) Tenofovir

Clinically significant resistance mutations to tenofovir have not been reported in patients with HBV monoinfection. However, rtA194T can decrease the susceptibility to tenofovir by 10-fold in the presence of rtL180M+rtM204V, according to a case study of a patient with HBV and HIV coinfection.[258]

Management of antiviral resistance: general principles

Prior antiviral resistance predisposes individuals to subsequent viral mutations and limits the choice of rescue therapies due to the presence of cross-resistance (Table 9).[242,259] Even though antiviral agents without cross-resistance may be selected, the resistance to the rescue therapy is greater than that of treatment-naïve subjects.[259-261] It is therefore critical to initially choose the antiviral agent with the lowest resistance rate (Table 10).

Appropriate monitoring is needed during treatment in order to detect virologic and biochemical breakthroughs as early as possible. Antiviral resistance testing is needed when a virologic or biochemical breakthrough is detected in subjects with good compliance. If genotypic resistance is confirmed, rescue therapy should be initiated before the clinical manifestation deteriorates,[262] and the regimen should include a drug without cross-resistance to a prior antiviral agent. Nucleotide analogues must be combined to manage resistance to nucleoside analogues, while nucleoside analogues must be combined to manage resistance to nucleotide analogues. The combination of antiviral agents from two different groups of nucleos(t)ide analogues is expected to decrease the risk of antiviral resistance and is especially recommended in patients who need long-term antiviral therapy, those with a high viral load, and those with decompensated liver function.

[Recommendation]

General principles of antiviral resistance management:

1. An antiviral resistance test should be performed when virologic breakthrough occurs although compliance is good (A1).
2. Rescue antiviral therapy should be started for antiviral resistance as soon as possible, especially when viral breakthrough is detected and genotypic resistance is confirmed (A1).
3. Sequential monotherapy should be avoided in order to prevent multidrug resistance. Combinations of nucleoside analogues (lamivudine, telbivudine, clevudine, or entecavir) and nucleotide analogues (adefovir or tenofovir) without cross-resistance are strongly recommended (A1).

Management of antiviral-resistant CHB: individual antiviral agents

1. Management of lamivudine resistance

The drugs listed below have been found to be effective at suppressing replication in lamivudine-resistant HBV.

1) Adefovir: A pilot study that compared the efficacy of adefovir monotherapy with combination therapy of lamivudine plus adefovir against lamivudine-resistant HBV infection found comparable reductions of viral load (-4.4 vs. -3.59 $\log_{10}$ cpm, respectively) and normalizations of the ALT level (53% vs. 47%). However, a transient ALT flare was found in 37% of the patients in the adefovir-monotherapy group.[263] Therefore, switching to adefovir monotherapy or a short term (2-3 months) combination of adefovir and lamivudine at the beginning of adefovir rescue therapy to

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prevent ALT flare was considered. However, subsequent studies found that adefovir resistance emerged in patients with lamivudine resistance who were switched to adefovir monotherapy (in 18% of patients at 1 year, 25% at 2 years,[260,261] and up to 65% after 5 years[221]), suggesting adefovir monotherapy for lamivudine-resistant HBV infections has limited efficacy. On the other hand, when lamivudine-resistant HBeAg-negative CHB patients were followed up for approximately 3 years in a small prospective study, the development of resistance to adefovir was significantly less common in the adefovir-plus-lamivudine combination-therapy group than in the adefovir-monotherapy group (0% and 21%, respectively).[264] In a subsequent larger, population-based study in Italy that enrolled 588 HBeAg-negative CHB patients, the rate of virologic breakthrough (2% and 9%, respectively) and rate of adefovir resistance development (0.8% and 5%) were significantly lower in the adefovir-plus-lamivudine combination-therapy group than in the adefovir-monotherapy group, supporting the efficacy of combination therapy.[265] However, lamivudine-resistant strains (e.g., rtA181T) can continuously be detected even after combination therapy of adefovir plus lamivudine, so caution is necessary to avoid the possibility of multidrug-resistant HBV.[256,257,259,266] Other options for lamivudine resistance include adding one of the nucleoside analogues (entecavir, clevudine, or telbivudine) to adefovir.[267-270] Future studies should compare the efficacies of these regimens with that of the adefovir-plus-lamivudine combination therapy.

2) Tenofovir: Tenofovir has shown potent antiviral activity against lamivudine-resistant HBV as well as wild-type HBV.[271,272] One retrospective study involving 53 lamivudine-resistant CHB patients found that the HBV DNA level after 48 weeks was less than 10^5 cpm in 100% of patients in the tenofovir group but in only 44% of patients in the adefovir group, with the difference being statistically significant.[271] The mean change in the HBV DNA level was greater in the tenofovir group (-5.5 $\log_{10}$ cpm) than in the adefovir group (-2.8 $\log_{10}$ cpm).[271] The stronger antiviral effect of tenofovir might be due to the dose differing between the two drugs (300 mg of tenofovir vs. 10 mg of adefovir). Another retrospective study administered tenofovir to 20 patients who showed persistent HBV replication (>10^4 cpm) despite receiving adefovir treatment for longer than 15 months. HBV DNA was not detected in 95% of the patients after 3.5 months of tenofovir treatment (in a PCR assay with a lower detection limit of 400 cpm).[272] In a recent study with a longer follow-up period of up to 23 months, tenofovir monotherapy resulted in 100% DNA undetectability (in PCR assay) among lamivudine-resistant CHB patients.[273] Therefore, treatment strategies that include tenofovir seem to be more effective than those involving adefovir in overcoming lamivudine resistance. However, there is a report of tenofovir resistance in a lamivudine-resistant CHB patient who received tenofovir monotherapy, so the efficacy of tenofovir monotherapy requires further evaluation.[258] In this context, one recent study found that the reduction in the HBV DNA level among 109 lamivudine-resistant CHB patients was greater in the tenofovir-plus-lamivudine combination-therapy group (-5.3±1.8 $\log_{10}$ cpm, mean±SD) than in the tenofovir-monotherapy group (-4.7±1.5 $\log_{10}$ cpm), adefovir-monotherapy group (-2.4±2.5 $\log_{10}$ cpm), and adefovir-plus-lamivudine combination-therapy group (-2.2±1.6 $\log_{10}$ cpm).[274] More recently, combination therapy of tenofovir plus telbivudine produced a higher rate of virologic response (defined as a reduction of more than 2 $\log_{10}$ cpm in the HBV DNA level) than combination therapy of tenofovir plus lamivudine (64% vs. 45%, respectively) after 12 months of treatment.[275]

3) Entecavir: Entecavir exhibits some cross-resistance with lamivudine, which prompted a dose of 1.0 mg–which is higher than the 0.5 mg dose for treatment-naïve CHB patients–being applied to lamivudine-resistant CHB patients.[276] In a study in which HBeAg-positive CHB patients were treated with 1.0 mg entecavir for 48 weeks, 19% of patients had an HBV DNA level of <300 cpm, 8% exhibited HBeAg seroconversion, the mean change in HBV DNA levels was -5.11 $\log_{10}$ cpm, and normalization of the ALT levels occurred in 61% of patients.[277] Genotypic resistance to entecavir (7%) and accompanying virologic breakthrough (1.4%) were more frequent than in the treatment-naïve patients. When lamivudine-resistant CHB patients were treated with 1.0 mg entecavir for 2 years, HBV DNA was undetectable in 34% of patients, but an entecavir-resistant mutation that accompanied the virologic breakthrough occurred in 9% of patients.[253] A 5-year cumulative rate of genotypic resistance of 51% was recently reported, along with an accompanying virologic breakthrough of 43%.[254] Korean studies found that combination therapy of adefovir plus lamivudine showed superior antiviral efficacy over monotherapy with 1.0 mg entecavir in lamivudine-resistant CHB patients.[278,279] Although 1.0 mg entecavir monotherapy exerts an initial favorable antiviral effect against HBV, it is not recommended as an optimal treatment in lamivudine-resistant CHB patients due to the associated high rates of resistance as it is considered to be inferior to combination therapy of adefovir plus lamivudine.

4) PegIFN monotherapy: PegIFN-α treatment could be considered in lamivudine-resistant CHB patients with compensated liver disease.[280,281] One recent prospective Korean study of the effects of pegIFN found that the combined response rate (as assessed by

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HBeAg seroconversion, ALT-level normalization, and reduction of the HBV DNA level to <20,000 IU/mL) was 19% in lamivudine-resistant CHB patients and 12% in treatment-naive subjects.[280] Hence, pegIFN therapy can be considered in young patients with compensated liver disease, and it has beneficial effects in avoiding multidrug resistance caused by sequential oral nucles(t)ide analogue therapy.[259,282]

* When to change antiviral agents: When virologic breakthrough develops and genotypic resistance is found during lamivudine treatment despite good drug compliance, initiating rescue therapy is desirable before biochemical breakthrough develops.[283] A study that enrolled CHB patients with genotypic resistance to lamivudine compared the effects of adding adefovir to lamivudine when the HBV DNA level was 3–6 $\log_{10}$ cpm and greater than 6 $\log_{10}$ cpm. The rates of undetectability of HBV DNA after 3 months (100% and 46%, respectively) and 2 years (100% and 78%) were higher in the earlier adefovir add-on group.[283] A recent Korean study also found that a lower baseline HBV DNA level before initiating rescue therapy is associated with a favorable initial virologic response.[392]

[Recommendation]

The following options are recommended for the management of lamivudine resistance:

1. Add adefovir to lamivudine (A1).
2. Add tenofovir to lamivudine (B1).
3. Stop lamivudine and start adefovir or tenofovir in combination with one of the nucleoside analogues (C1).
4. Consider switching to tenofovir (B2).
5. Stop lamivudine and consider starting peginterferon if the patient has compensated liver function (B2).

2. Management of telbivudine resistance

Few data related to telbivudine resistance are available. A recent study found that adefovir rescue therapy is effective at reducing serum HBV DNA levels in telbivudine-resistant HBV infection.[284] Tenofovir could be a therapeutic option, and its combination with nucleoside analogues would have the desirable effect of preventing subsequent antiviral resistance. The general principles for the management of telbivudine resistance can refer to the management of lamivudine resistance.

[Recommendation]

Telbivudine resistance: Refer to the management of lamivudine-resistant CHB (C1).

3. Management of clevudine resistance

At present it seems reasonable to treat clevudine resistance according to the principles of lamivudine resistance. A recent multicenter study in Korea compared the antiviral efficacies of adefovir monotherapy, combination therapy of adefovir plus lamivudine, combination therapy of clevudine plus adefovir, and entecavir monotherapy in clevudine-resistant CHB patients, and found that adefovir monotherapy showed the lowest antiviral efficacy at 12 weeks.[285] However, long-term follow-up data are lacking. It is considered that the general treatment principles of clevudine resistance can follow those of lamivudine resistance.

[Recommendation]

Clevudine resistance: Refer to the management of lamivudine-resistant CHB (C1).

4. Management of adefovir resistance

The drugs listed below have been found to be effective at suppressing replication in adefovir-resistant HBV.

1) Tenofovir: Tenofovir significantly suppresses HBV replication in patients exhibiting lamivudine resistance who have failed to respond adequately to adefovir, and in patients who are resistant to both lamivudine and adefovir.[286] However, reduced sensitivity to tenofovir was demonstrated in adefovir-resistant HBV infections, indicating potential cross-resistance.[273] Therefore, adding emtricitabine or lamivudine to tenofovir would be a more-appropriate therapeutic strategy than tenofovir monotherapy in patients exhibiting adefovir resistance. Indeed, the addition of emtricitabine led to a further decrease in the serum HBV DNA level in patients exhibiting adefovir resistance and a suboptimal response to tenofovir therapy.[287] When combination therapy of lamivudine plus tenofovir was given to CHB patients who had previously failed in both lamivudine and subsequent adefovir therapy, 64% achieved an undetectable level of HBV DNA (<15 IU/mL) after 96 weeks of treatment.[286]

2) Entecavir: Recent studies have found that entecavir is effective at suppressing the replication of HBV in patients exhibiting adefovir resistance. Entecavir has been shown to be effective against both rtA181T/V and rtN236T mutant HBV strains,[256,288-290] as entecavir does not share cross resistance with adefovir.[252] A

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recent Korean study found that the mean reduction in serum HBV DNA levels was significantly greater in the entecavir-monotherapy group than in the lamivudine-plus-adefovir combination-therapy group among patients with sequential lamivudine-adefovir resistance (-3.47 vs. -1.49 $\log_{10}$ IU/mL, respectively; $P<0.01$).[291] However, combination therapy of adefovir plus entecavir is considered a better therapeutic option because the selection of lamivudine-resistant strains during entecavir monotherapy can result in subsequent entecavir resistance.[267] Combination therapy of entecavir and tenofovir can also be considered for multidrug-resistant HBV infections that include adefovir resistance.[292]

3) Lamivudine: The rtN236T mutant was found to remain sensitive to lamivudine, while the rtA181/V mutant exhibited reduced susceptibility to lamivudine.[252] When adefovir resistance develops in patients who received adefovir as an initial antiviral agent, switching from adefovir to lamivudine can be considered, but this may lead to subsequent lamivudine resistance. Therefore, combination therapy of lamivudine plus adefovir is recommended.

4) Telbivudine and clevudine: No study has evaluated telbivudine or clevudine as a rescue therapy for adefovir. However, it is thought that these drugs can be used in patients who do not exhibit resistance to nucleoside analogues because the rtN236T mutant remains sensitive to telbivudine or clevudine.[252] However, telbivudine or clevudine is not recommended for the rtA181T/V mutant due to the possibility of cross-resistance.[252]

[Recommendation]

The following options are recommended for the management of adefovir resistance:

1. When adefovir has been used as the second drug after failure of L-nucleoside analogues
   1) Stop adefovir and start combination therapy of tenofovir plus a nucleoside analogue (lamivudine or entecavir 1 mg) (B1).
   2) Adding entecavir 1 mg to adefovir can be considered (B2).
2. When adefovir has been used as a first-line therapy
   1) Stop adefovir and start combination therapy of tenofovir plus a nucleoside analogue (lamivudine or entecavir) (B1).
   2) Consider adding a nucleoside analogue. If rtA181T is detected, adding entecavir is preferred (C1).

5. Management of entecavir resistance

The drugs listed below have been found to be effective at suppressing replication in entecavir-resistant HBV.

1) Adefovir: There are few data on the use of adefovir for treating entecavir resistance. Entecavir-resistant HBV is associated with lamivudine-resistant mutations, so treatment options may not differ in treatment-naïve patients and in lamivudine-resistant patients before the initiation of entecavir. Entecavir-resistant HBV maintains the susceptibility to adefovir, which could be considered as an initial treatment option, and a clinical case indicated that adefovir was effective in suppressing the entecavir-resistant mutant.[293,294] Adding adefovir to entecavir would be more reasonable for reducing adefovir resistance and improving the antiviral efficacy.[267] Combination therapy of adefovir plus lamivudine could be considered as another option, since a small study showed that the short-term efficacy of this combination was similar to that of combination therapy of adefovir plus entecavir.[295]

2) Tenofovir: Tenofovir has not been fully evaluated in the treatment of entecavir resistance. However, it is expected that it will be very effective once it becomes available in Korea, since tenofovir does not show cross-resistance to entecavir *in vitro* and has excellent potency.[273]

[Recommendation]

Entecavir resistance: Add a nucleotide analogue (tenofovir or adefovir) (B1).

6. Management of tenofovir resistance

There have been very few reports of clinical cases of tenofovir resistance. An *in vitro* study found that replication of the rtA194T mutant was suppressed effectively by entecavir and intermediately by telbivudine.[296]

7. Management of multidrug resistance

Multidrug resistance is defined as resistance to two or more groups of antiviral drugs. Sequential monotherapy is associated with the development of multidrug resistance.[259,282,293] For example, multidrug resistance may emerge if additional antiviral resistance develops in cases of (1) re-administration of lamivudine to prior lamivudine-resistant CHB patients receiving adefovir due to newly developed resistance to adefovir, (2) administration of entecavir to patients exhibiting lamivudine resistance, and (3) administration of lamivudine to patients exhibiting adefovir resistance, even in the absence of prior lamivudine treatment. In these situations, pre-existing antiviral resistant mutations may reappear and become co-located with newly developed resistant mutations on the same viral genomes.[259,293]

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Combination therapy of tenofovir plus entecavir can be considered for resistance to both lamivudine and adefovir.[243,297] Combination therapy of adefovir plus entecavir could be another option.[267] If resistant mutations to lamivudine, entecavir, and adefovir are detected at the same time, combination therapy of tenofovir plus entecavir might be the best option.[292,297]

[Recommendation]

The following options are recommended for the management of multidrug resistance:

1. Combine tenofovir and entecavir 1 mg (B1).
2. Consider combining adefovir and entecavir 1 mg (B2).

Response-Guided Therapy During Oral Antiviral Drug Treatment for Hepatitis B

Once antiviral-resistant HBV mutants have been selected, they are persistently archived (retained in the virus population) in cccDNA in the nucleus of infected cells, even if treatment is stopped, and thereby potentially limiting future therapeutic options.[298,299] Preventing the development of resistance is important to ensure the long-term therapeutic efficacy. The persistence of viral replication during antiviral treatment is associated with the emergence of drug resistance.[235,300,301] Therefore, evaluating the treatment response by using sensitive PCR assays to measure serum HBV DNA levels every 3 months is recommended.

The rate of emergence of lamivudine-resistant HBV was directly proportional to the HBV DNA level after 24 weeks of treatment.[235,300,301] Yuen and colleagues found that these rates were 8%, 13%, 32%, and 64% for patients with 24-week HBV DNA levels of <200, 3 $\log_{10}$, 4 $\log_{10}$, and 4 $\log_{10}$ cpm or higher, respectively, after a median follow-up of 29 months.[300] This finding has been supported by several subsequent studies. Fukai and colleagues found that patients who achieved an undetectable HBV DNA level in PCR tests at week 24 of lamivudine treatment exhibited a substantially lower rate of virologic breakthrough.[301] The importance of HBV DNA suppression at week 24 has also been shown in a phase-3 multicenter trial with telbivudine (the GLOBE trial).[235] Therefore, an on-treatment strategy for patients receiving oral NUC therapy will produce better viral suppression and lower drug resistance by measuring serum HBV DNA levels at 24 weeks (Fig. 1).

Patients with primary treatment failure–defined as a reduction in the serum HBV DNA level of less than 2 $\log_{10}$ IU/mL at week 24 with good drug compliance–should be tested for the presence of genotypic resistance mutations. If such mutations are not found, switching to a drug with a high genetic barrier is indicated if the patient is taking a drug with a low genetic barrier.[289,302]

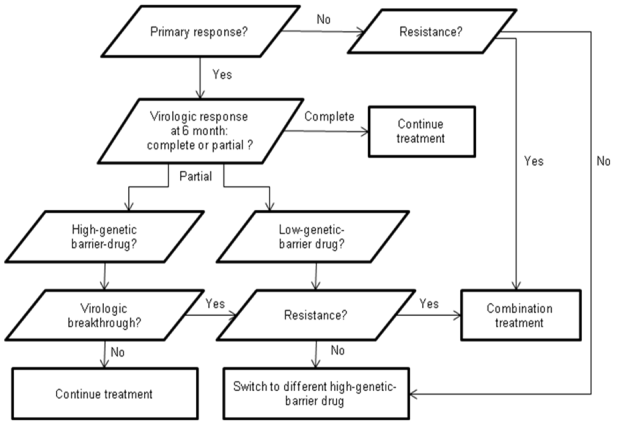

Figure 1. Flow chart of treatment recommendations based on the virologic response during oral antiviral therapy. Refer to Table 7 for definitions of virologic responses. Low-genetic-barrier drugs include lamivudine, telbivudine, clevudine, and adefovir. High-genetic-barrier drugs include entecavir and tenofovir.

The risk of resistance development in patients with a complete virologic response–defined as an HBV DNA level that is undetectable in PCR tests (less than 60 IU/mL or 300 cpm) at week 24–is low during long-term treatment.[235,300,301] Thus, treatment should be continued until the treatment endpoint is achieved, with the serum HBV DNA level being measured every 3-6 months.[126,303]

A partial virologic response is defined as detectable HBV DNA without primary treatment failure at week 24. Up to 30% of the cases of virologic breakthrough observed in clinical trials are related to medication noncompliance.[304] Thus, compliance should be ascertained before testing for genotypic resistance.

A recent European multicenter cohort study found that the antiviral efficacy of entecavir did not differ between patients who did not develop lamivudine resistance following lamivudine treatment and lamivudine-naive patients.[289] A recent Korean multicenter clinical trial also showed that switching patients with insufficient suppression of HBV replication (HBV DNA ≥60 IU/mL) to entecavir (1 mg/day) resulted in a significantly higher proportion of patients with serum HBV DNA levels that were undetectable in real-time PCR at week 48 relative to those who continued lamivudine (77.3% vs. 8.7%, respectively). No patients in the entecavir-switch group developed resistance, while genotypic resistance emerged in 60.9% (14/23) of patients in the lamivudine-maintained group during the 48 weeks of treatment.[302] The response to tenofovir monotherapy was not influenced by the presence of lamivudine re-

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sistance.[273,287,305,306] Most NUC-naïve patients with detectable HBV DNA during entecavir or tenofovir therapy achieved undetectable levels of HBV DNA after prolonged continuation of entecavir or tenofovir monotherapy, and none of them developed additional drug resistance.[159,306,307] Therefore, three options should be considered for patients with a partial virologic response: (1) if the patient is taking a drug with a low genetic barrier (e.g., lamivudine, telbivudine, clevudine, or adefovir), he/she should be switched to a high-genetic-barrier drug (e.g., entecavir or tenofovir); (2) if the patient is taking a drug with a high genetic barrier, treatment should be continued with regular monitoring for viral breakthrough; and (3) if viral breakthrough is detected, a rescue therapy should be implemented according to the results of the genotypic resistance analysis. In any case, the treatment strategy should follow the recommendations for drug-resistant HBV when genotypic resistance mutations are identified.

[Recommendation]

1. Patients with primary treatment failure and good drug compliance should be tested for the presence of genotypic resistance mutations. In the absence of genotypic resistance mutations, switching to a drug with a high genetic barrier is indicated if the patient is taking a drug with a low genetic barrier (B1).
2. In patients with a complete virologic response at week 24, treatment should be continued until the treatment endpoint is achieved, with the serum HBV DNA level being measured every 3-6 months (B1).
3. For patients with a partial virologic response at week 24 and good drug compliance, the following three options should be considered:
   1) If the patient is taking a drug with a low genetic barrier (e.g., lamivudine, telbivudine, clevudine, or adefovir), treatment should be switched to a high-genetic-barrier drug (e.g., entecavir or tenofovir) (B1).
   2) If the patient is taking a drug with a high genetic barrier, treatment should be continued with regular monitoring for viral breakthrough (B1).
   3) In the event of viral breakthrough, a rescue therapy should be implemented according to the results of the genotypic resistance analysis (A1).
4. The treatment strategy should follow the recommendations for drug-resistant HBV when genotypic resistance mutations are identified (A1).

TREATMENT OF SPECIAL POPULATIONS

Acute hepatitis B

It is well known that acute hepatitis B recovers spontaneously and does not progress to chronic stage in more than 95%, so antiviral therapy is generally not recommended.[308,309] There have been reports showing early initiation of antiviral therapy interferes with normal protective immune response and suppresses production of neutralizing antibodies against hepatitis virus, therefore increasing the risk of chronic hepatitis.[310,311] However, acute hepatitis B infection seldom progress to serious hepatitis and may even fall into hepatic failure.[309]

According to a randomized controlled trial in 71 patients with severe acute hepatitis B, HBV DNA levels were significantly lower in lamivudine treated group (n=31, 3.7 $\log_{10}$ copies/mL) compared with control group (n=40, 4.2 $\log_{10}$ copies/mL) after 4 weeks. However, negative conversion rate of HBsAg after 12 months was similar between the two groups (93.5% in lamivudine group and 96.7% in placebo group).[312] In this study, development of protective anti-HBs after 1 year, was 67.7% in the lamivudine group and 85% in the placebo group, but it was not statistically significant. Tillman et al reported that lamivudine is safe in patients with severe acute or fulminant hepatitis B, leading to fast recovery with the potential to prevent liver failure and liver transplantation when administered early enough.[313] There have been only a few case reports of antiviral agents as treatment for acute hepatitis B other than lamivudine so far.[314-316]

[Recommendation]

In patients with acute hepatitis B, oral antiviral therapy should be considered in cases of persistent serious hepatitis or acute liver failure. (C1)

Liver Transplant Patients

For most patients with liver disorders related to HBV, the recurrence of HBV causes severe liver damage. Moreover, the survival rate of such patients has been low in the past.[317-324] In an extensive cohort study of 372 patients who received liver transplants in the early 1990s and were positive for HBsAg, the test group treated with hepatitis B immunoglobulin (HBIG) therapy for more than 6 months showed a significantly lower recurrence rate of hepatitis B than the group treated with HBIG therapy for less than

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6 months or those who were not treated with this therapy. The test group also had a higher long-term survival rate than the other groups.[325] Since then, several studies have reported hepatitis B recurrence rates ranging from 16% to 35% after liver transplantation in groups receiving high-dose HBIG (10,000 IU) therapy.[326-328] For the patients who received lamivudine monotherapy, the recurrence rate of hepatitis B was approximately 40% 4 years after liver transplantation, and the emergence of lamivudine resistance mutants has also been reported. Therefore, the effectiveness of therapy using only lamivudine is limited.[329,330] On the other hand, a study using lamivudine and adefovir combination therapy reported no recurrence in patients with hepatitis B during a 1-year observation period, although these studies had limited scope. In this study, lamivudine resistance was also prevented.[331] Further studies are therefore required on combination therapy using antiviral agents to prevent the recurrence of hepatitis B. Lamivudine and HBIG combination therapy could reduce the recurrence of HBV to less than 10% in 1–2 years and is superior to high-dose HBIG therapy with respect to cost and effectiveness.[332-335] In a meta-analysis of 6 independent studies, lamivudine and HBIG combination therapy was found to reduce the recurrence rate of HBV and relevant death rate by 12 times compared with HBIG therapy alone.[336] In a study of 147 patients who received liver transplants, Gane et al. showed that lamivudine and low-dose HBIG (400–800 IU) combination therapy effectively suppressed the recurrence of hepatitis B at moderate cost, since the 5-year recurrence rate of hepatitis B was only 4%.[337]

Furthermore, the patients whose HVB DNA was less than 2.5 pg/mL before liver transplant were randomly assigned to continuing combination therapy and lamivudine monotherapy groups after administering lamivudine and HBIG (2,000 IU) combination therapy after liver transplants for 18 months, resulting in no difference in the rates of HBV recurrence and patient survival during a median follow-up of 83 months between the two groups in this prospective study.[338] Two other retrospective studies have reported no recurrence of HBV when lamivudine and HBIG combination therapy or HBIG therapy alone for 2 years after liver transplantation were replaced with lamivudine monotherapy.[339,340] In a recent study by Angus et al., lamivudine and low-dose HBIG (800 IU) combination therapy was continued for at least 12 months after liver transplantation. The group in which HBIG was replaced by adefovir and the group in which HBIG was continuously administered did not show a difference in the recurrence rate of hepatitis B.[341] These results suggest the possibility of reducing the period of high-dose HBIG administration, which is expensive. However, it is estimated that the combination therapy would be applied to clinical cases provided that its long-term effects are recognized through extensive future research.

A meta-analysis of 46 studies in which 2,161 HBV-infected patients received liver transplants found that adefovir and HBIG combination therapy significantly reduced the recurrence rate of hepatitis B to 2% compared to 6% with lamivudine and HBIG combination therapy. A preliminary study that was conducted recently has confirmed the good results of HBIG combination therapy with entecavir or tenofovir, which has strong anti-viral effects and less drug resistance. Consequently, it is expected that these drugs will be used more efficiently in the future.[342]

Meanwhile, a study by Grellier et al. has indicated that when lamivudine therapy is administered from 4 weeks before liver transplantation, the recurrence of HBV after the transplant is effectively prevented.[343] A recent prospective study found that in 57 patients with lamivudine-resistant HBV who were treated with lamivudine plus adefovir, only two (3.5%) had HBV recurrence for a median of 9 months with a survival rate of 87%.[344] However, the impacts of entecavir and tenofovir therapy before liver transplantation on the recurrence of HBV after liver transplants remain unreported, and thus require further examination.

When hepatitis B recurs even after preventive HBIG therapy after liver transplantation, lamivudine therapy could effectively inhibit the virus. However, it has been reported that lamivudine resistance was over 50% over 3 years when lamivudine therapy is administered over a long term.[345-347] It is known that such lamivudine resistance causes inflammatory changes in the transplanted liver and hepatic fibrosis, and severe impacts, including death, by hepatic failure.[346,348,349] A few studies have reported the effects of tenofovir and entecavir on hepatitis B recurrence after liver transplantation; however, more studies on these drugs need to be performed.[350]

Several studies have reported the relatively good effects of lamivudine and adefovir on patients with recurrent hepatitis B who exhibit lamivudine resistance after liver transplantation. The most extensive study administered the combination therapy to 241 patients with recurrent hepatitis B. The HVB DNA reduction rate was 65%, whereas lamivudine resistance 96 weeks after therapy started was 2%.[344] Although these studies were conducted for a short period with small groups, it was recently reported that tenofovir is effective against mutants with lamivudine resistance.[349] However, high emergence rate of entecavir resistance have been reported when entecavir is administered as rescue therapy for patients who had lamivudine resistance.[254] Therefore, entecavir is

not recommended if patients have lamivudine resistance after liver transplantation.

It is known that if negative HBsAg patients receive liver transplants from positive anti-HBc donors, approximately 50% will have new hepatitis B.[351] When HBIG therapy was administered to these patients after liver transplantation, hepatitis B affected over 20%. However, when lamivudine therapy was applied, hepatitis B affected only 2-3% of patients. Nevertheless, lamivudine and HBIG combination therapy had no additional preventive effects compared to lamivudine therapy alone.[351-353] There has been no research on anti-viral drugs other than lamivudine.

[Recommendation]

1. For patients whose serum is positive for HBV DNA and who have had a liver transplant, the serum HBV DNA value should be minimized before liver transplantation by administering oral anti-viral drugs (A1).
2. The anti-viral therapy before liver transplantation complies with the chronic hepatitis B therapy guidelines (B1).
3. Oral anti-viral drugs and HBIG therapy should be administered throughout life to prevent the recurrence of hepatitis B after liver transplantation (B1). However, if serum HBV DNA is positive before the liver transplant, HBIG may not be administered to the patients after long-term monitoring (B2).
4. In case of HBV recurrence after liver transplantation, anti-viral drugs that strongly suppress viruses and have low drug resistance are recommended (A1). In case of drug resistance, the chronic hepatitis B therapy guidelines are followed (B1).

Immunosuppression and Chemotherapy

Impaired host immunity due to chemotherapy or immunosuppressive treatment increases the risk of HBV reactivation.[354] HBV reactivation refers to the reappearance of necroinflammatory disorders in patients with either inactive carrier or resolved hepatitis,[355] and is commonly defined as a rise in the serum HBV DNA of more than 10 times of the baseline level or an absolute level of higher than 100 IU/mL along with elevated serum ALT (higher than 3 X ULN or an absolute increase of more than 100 IU/L).[356,357] The diagnosis of HBV reactivation requires the exclusion of other conditions such as chemotherapy-related hepatic injury, hepatic metastases, and other types of viral hepatitis. The reactivation rate has been reported as 20-50%, although the ranges were diverse in various reports. Many patients with HBV reactivation are asymptomatic, but the clinical courses are varied widely from jaundice to decompensation or even death.[356,358-360] In typical cases, HBV DNA appears in the serum during immunosuppressive treatment, followed by elevation of ALT after treatment cessation. If HBV reactivation occurs during chemotherapy, treatment disruption or premature termination may adversely affect the outcome of chemotherapy.[361-363]

Predictive factors for HBV reactivation include the pretreatment HBV DNA level, type of malignancy, and type or intensity of immunosuppression or chemotherapy. The reported reactivation rate in lymphoma patients has ranged from 24% to 67%, possibly due to intense chemotherapeutic regimens against lymphoma and higher positivity rates for HBsAg in these patients.[359,364-366] Rituximab, which has been commonly administered with corticosteroid for lymphoma, further increases the risk of HBV reactivation.[367,368] The risk of reactivation is also elevated when high-intensity chemotherapy is applied prior to hematopoietic stem-cell transplantation in hematologic malignancies.[369,370] Although the reactivation rate has been known as 14-21% in solid tumors, higher rates of 41-56% were reported in breast cancer which is possibly related to the use of high dose chemotherapy and anthracycline agents.[371,372] Sorafenib, which was approved recently for advanced HCC, seems not cause HBV reactivation,[373] but this needs to be confirmed in further investigations. Corticosteroid increases the risk of HBV reactivation via immune suppression as well as direct stimulation of HBV replication. Other risk factors for reactivation include the use of anti-TNF-α antibody for inflammatory bowel diseases or rheumatologic diseases (e.g., infliximab), the HBV genotype or specific mutations on the HBV genome, and recovery from neutropenia.[374-383] In rare cases, HBV reactivation occurs not only in HBsAg-positive patients but also in anti-HBc IgG-positive patients without HBsAg.[384] The latter cases correspond to either occult HBV infection in which HBV DNA is detected in the hepatocytes or even in the serum, or reverse seroconversion (seroreversion) of HBsAg in which HBV replication resumes after immunosuppression with reappearance of HBsAg.[356,385,386]

Because HBV reactivation is associated with the risk of hepatic failure or even death once it occurs, prevention is of utmost importance. This makes screening for HBsAg and anti-HBc IgG is necessary. Vaccination should be considered if there is no evidence of (past) HBV infection (i.e., negative for both HBsAg and anti-HBc IgG). Preemptive antiviral therapy is recommended in HBsAg-positive patients regardless of the serum HBV DNA level.[376] Preemptive lamivudine therapy has significantly reduced the rates of HBV reactivation, hepatic failure, and mortality in random-

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ized controlled studies of lymphoma patients in Hong Kong and Taiwan.[365,370,387,388] From these results, it is recommended that preemptive antiviral therapy should be started with the initiation of chemotherapy rather than deferring until the HBV DNA level increases, and should be maintained for certain period after the termination of chemotherapy (e.g., at least 6 months).[388,389] However, evidence to determine the duration of preemptive antiviral therapy remains limited. Elevated risk of reactivation was reported with cessation of preemptive lamivudine therapy after 3 months following the termination of chemotherapy, especially in cases of a high HBV DNA before chemotherapy (≥2,000 IU/mL).[390] Therefore, the duration of preemptive antiviral therapy could be determined based upon treatment guidelines for CHB if the pre-treatment HBV DNA level is high. In contrast, special attention should be paied to reports of reactivation after more than 6 months irrespective of the pre-treatment HBV DNA level. Although there is limited information about the efficacy of preemptive treatment with other antiviral agents such as adefovir, tenofovir, entecavir, telbivudine, or clevudine, these agents could be administered for preemptive use considering their mechanisms of action and therapeutic results. Since resistance was reported in preemptive lamivudine therapy, other antiviral agents with lower resistance rate need to be considered in cases with prolonged treatment period (e.g., longer than 1 year).[365] A recent retrospective study demonstrated that the risks of hepatitis and chemotherapy disruption due to HBV reactivation in lymphoma patients were lower for entecavir than for lamivudine.[391] However, data on the relative efficacy and cost-effectiveness of antiviral agents are scarce. Prospective studies of the appropriate choice of antiviral agents and optimal treatment duration in various types of malignancies are urgently needed, since most of the previous studies only included lymphoma patients. If cost is ignored, entecavir and tenofovir will be safer choices based on their potency and resistance rate. Interferon-α is contraindicated for preemptive use due to its bone marrow suppression and exacerbation of underlying hepatitis. Anti-HBc IgG-positive patients (HBsAg-negative) have a risk of HBV reactivation, but a uniform treatment recommendation cannot be provided because the effects of the types of malignancies or immunosuppressive/chemotherapeutic agents used on the reactivation risk has not been clarified. However, preemptive therapy should be considered if serum HBV DNA is positive in high-risk groups such as patients with lymphoma under a rituximab-containing regimen or those with leukemia who undergo hematopoietic stem cell transplantaion; the need for preemptive treatment may be determined with periodic monitoring (e.g., every 1-2 months) of the HBV DNA level in patients with no detectable serum HBV DNA at baseline.

[Recommendation]

1. Check HBsAg and anti-HBc IgG before starting immunosuppressive treatment or chemotherapy. (A1)
2. Vaccinate if there is no evidence of HBV infection. (B1)
3. Consider preemptive antiviral therapy with the initiation of immunosuppressive treatment/chemotherapy if HBsAg is positive. (A1) Although the choice of antiviral agent requires consideration of the serum HBV DNA level, intensity and duration of immunosuppressive treatment/chemotherapy and cost, entecavir or tenofovir can be preferentially considered if the baseline HBV DNA level is high or long-term treatment is needed. (C1)
4. The serum HBV DNA should be monitored periodically during and after preemptive antiviral therapy. (A1)
5. Preemptive antiviral therapy has to be maintained for at least 6 months after terminating immunosuppressive treatment/chemotherapy. (C1)
6. In anti-HBc IgG-positive patients, preemptive therapy should be considered if serum HBV DNA is detectable in high-risk groups (C1). The need for preemptive treatment may be determined by periodic monitoring of the HBV DNA level in patients with no detectable serum HBV DNA at baseline. (C2)

Dialysis Patients

Dialysis patients are relatively prone to being exposed to HBV infection, which might exert negative influence on their long-term prognosis. Exacerbation of hepatitis B is of particular importance to immunosuppresion after renal transplantation.[392] Fortunately, the incidence of HBV infection in dialysis patients has reduced thanks to surveillance of blood products, enhanced infection control, and widespread use of erythropoietin. The prevalence of HBV infection based on HBsAg positivity in this population is known as 0-6.6% in Western countries, and approximately 5% in Korea in recent reports.[393-395] Prevalence of occult HBV infection was higher than HBsAg-positive rate in some reports,[396] but this was not the case in Korea.[397]

The standard precaution to avoid nosocomial transmission is of the highest priority for preventing new HBV infections in dialysis patients.[398] Vaccination against HBV is widely recommended in these patients; the efficacy is higher with eariler vaccination because antibody production rate is as low as 50-60% compared

with about 90% of general population and it is lower as residual renal function declines.[399-401]

Data on the antiviral treatment based in dialysis patients are insufficient. Although there is a randomized controlled study on interferon-α in HBV-infected patients with glomerulonephritis,[402] it appears difficult to recommend its use considering the increased adverse events in this population due to pharmcodynamic changes.[403,404] Several small studies reported the effectiveness of lamivudine.[405-407] Resistance to lamivudine was as high as 39% at 16.5 months of treatment which was similar to patients with normal renal function,[408] and adefovir can be added for lamivudine resistance.[409,410] Entecavir or tenofovir may be preferentially used, given their potency and resistance profile in patients with normal renal function.[37] Careful dose adjustment is required for adefovir and tenofovir due to their potential nephrotoxicity in patients with residual renal function.[411-414]

[Recommendation]

1. Vaccination is necessary in dialysis patients without anti-HBs. (A1)
2. Oral anvitiral agents are recommended rather than interferon in dialysis patients. (B1) Entecavir and tenofovir are preferentially considered according to the residual renal function. (B1)

Co-infection with other viruses

HCV Co-infection

In patients with CHB the rate for anti-HCV antibody positivity varies from 0.1% to 22%, depending on the region,[415-418] with it being very low in Korea (0.1%).[416] Patients with HBV/HCV co-infection are known to have an increased risk of severe or fulminant infection, and high incidences of cirrhosis and HCC.[419-422] The scarcity of data makes it impossible to recommend the treatment of HBV/HCV co-infection.[423-425] However, it is necessary to determine which virus is dominant by means of serologic or virologic tests. It is recommended that CHB patients who are positive for HCV RNA are treated with combination therapy of pegIFN-α-2a plus ribavirin which has been shown to be equally effective in patients with HCV mono-infection and HBV/HCV co-infection.[426] The HBV treatment should be added when HBV reactivates, which can reportedly occur during or after the standard treatment for HCV.[427]

[Recommendation]

1. Apply serologic or virologic tests to determine which virus is dominant (B1).
2. CHB patients with detectable HCV RNA should be treated with combination therapy of pegIFN-α-2a plus ribavirin (B1).
3. HBV treatment should be added when HBV reactivates, which can occur during or after the standard treatment for HCV (B1).

HDV Co-infection

It is estimated that approximately 20 million people are infected with HDV worldwide.[428] HDV infection is prevalent in Mediterranean countries, the Middle East, central Africa, and South America.[429] The HDV co-infection rate in CHB patients has been reported to be 0-3.6% in Korea.[430-432] The incidences of cirrhosis and HCC are known to be higher in patients with HBV/HDV coinfection than in those with HBV monoinfection.[433,434]

HDV infection can be diagnosed by detecting anti-HDV antibody or HDV RNA in the patient's serum or by detecting HDV antigen in liver tissue by immunohistochemistry. The treatment goals are to inhibit HDV replication, normalize ALT, and improve histology findings. IFN-α (conventional or pegylated) is the only drug that can inhibit HDV replication.[435-439] The biochemical, virologic, and histologic responses were found to be better for high-dose IFN-α therapy (9 MU, three times per week) than for the conventional dose of IFN (3 MU, three times per week), with the high-dose therapy producing an HDV RNA negativity rate of 43% at 6 months after the end of 48 weeks of treatment.[438] PegIFN-α showed HDV RNA negativity rates of 17-43% at 6 months after the end of 48 or 72 weeks of treatment.[435,439,440] No head-to-head comparison trial between high dose IFN-α and pegIFN-α therapies has been performed and hence either pegIFN-α or high-dose IFN-α therapy for longer than one year is recommended for patients with HBV/HDV co-infection.[441] The treatment response can be evaluated by measuring the serum HDV RNA level at week 24. Both lamivudine and adefovir were found to be ineffective at inhibiting HDV replication.[442,443] Combination therapy of lamivudine plus IFN-α was not superior to IFN-α monotherapy,[444] and adefovir plus pegIFN-α therapy also did not improve the response rate relative to pegIFN-α monotherapy.[443]

[Recommendation]

1. CHB patients with HDV co-infection should be treated with pegIFN-α or high-dose IFN-α (9 MU, three times per week) for longer than one year (B1).

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HIV Co-infection

The incidences of cirrhosis and HCC are reportedly higher in patients with HBV/HIV coinfection than in those with HBV monoinfection.[445,446] Treating HBV should be considered in HBV/HIV-coinfected patients who exhibit ALT elevation due to HBV. Before such treatment it is necessary to determine whether or not treatment against HIV is also required.[447] Patients who are not indicated for HAART should receive the standard treatment for CHB. In that case the antiviral agents should be chosen (e.g., IFN, adefovir, or telbivudine) on the basis that they will not affect HIV proliferation, in order to prevent the future development of HIV cross-resistance. Patients who need treatment for both HIV and HBV should be treated with antiviral agents that are effective against both viruses, such as lamivudine, tenofovir, or emtricitabine.[448-450] When HAART regimens are altered, antiviral agents that are effective against HBV should be included to avoid HBV reactivation, except in patients who meet the criteria for discontinuation of anti-HBV treatment.

[Recommendation]

1. HBV/HIV-coinfected patients who exhibit ALT elevation due to HBV should be considered for HBV treatment (B1).
2. Patients who are not indicated for HAART at present or in the near future should receive the standard treatment for CHB. In that case the antiviral agents should be chosen on the basis that they will not affect HIV proliferation, in order to prevent the futuredevelopment of HIV cross-resistance (B1).
3. Patients who need treatment for both HIV and HBV should be treated with antiviral agents that are effective against both viruses (B1).

Female patients of childbearing age

Treatment before pregnancy

When planning the treatment for women of child-bearing age, special considerations for the fetus and the duration of treatment are needed in addition to the aforementioned general considerations. For example, IFN preparations are preferred in female patients who are planning pregnancy since the period of treatment is more clearly defined. However, the IFN side effect of fetal malformations makes it contraindicated during pregnancy, and so it must be recommended in combination with contraception.

Treatment during pregnancy

Changes in the maternal immune system during pregnancy such as a shift in the Th1-Th2 balance toward a Th2 response lead to an increase in the HBV DNA level and a reduction in the ALT level.[451] These immune responses are restored after delivery, thereby causing a reduction of the HBV DNA level and ALT elevation, and so careful monitoring is needed.

The optimal antiviral treatment strategy during pregnancy is based on the aforementioned general principles for the treatment of CHB. However, all decisions about the timing and duration of treatment in pregnancy should include an analysis of the risks and benefits for both the mother and fetus. In addition, pregnant women often experience worsening of liver disease unrelated to HBV infection (e.g., acute fatty liver of pregnancy), which is difficult to discriminate from an HBV flare-up. Thus, antiviral treatment should be considered when the liver disease is present (e.g., jaundice or prolongation of PT), and the HBV DNA level meets general criteria for antiviral treatment.

When starting antiviral therapy during pregnancy, Category B drugs (which, according to the results of animal studies, carry no teratogenic or embryogenic risk and for which there have been no controlled human studies or for which animal studies may indicate a risk, but controlled human studies refute the findings) are recommended. Among oral antiviral agents, telbivudine, tenofovir, and emtricitabine are Category B drugs, while lamivudine, adefovir, and entecavir are Category C drugs (drugs that exert teratogenic or embryocidal effects in animals and for which there are no controlled studies in humans).[19] The safety data of antiviral agents during pregnancy can be found at the Antiretroviral Pregnancy Registry (APR; http://www.apregistry.com). The APR is an international, voluntary, prospective registry that reports the rate of birth defects of newborns born to mothers receiving antiretroviral therapy, and it contains a considerable amount of data on lamivudine and tenofovir. According to the APR, the rates of birth defects among women exposed to lamivudine and tenofovir in the first trimester (3.1% and 2.4% of live births, respectively) are similar to that in the general population (2.7%), as reported by the CDC birth defect surveillance system. There are only a few reported cases related to other drugs such as telbivudine and entecavir. However, since the APR is designed to report onlydefects identified at birth, it is possible that it does not contain accurate data on developmental anomalies (e.g., cardiac or neurologic defects).

Oral antiviral agents may cause mitochondrial toxicity by inhibiting mitochondrial DNA replication. It is difficult to estimate their effects on the fetus especially in the developmental stages.[452] Thus, based on considerations of fetal safety it is desirable to avoid the administration of oral antiviral agents, especially in the

first trimester of pregnancy. However, the decision about whether to discontinue drugs in patients who are already been treated with oral antiviral agents should be individualized; such patients may be considered for temporary drug discontinuation when the degree of liver disease is mild and the HBV DNA level is <60 IU/mL, but in that case they should be carefully monitored for HBV reactivation. Meanwhile, women who become pregnant while on Category C drugs should change to Category B drugs. Since little is known about whether or not antiviral agents are secreted into breast milk, breast-feeding is currently not recommended.

Prevention of vertical transmission with antiviral drugs

A high maternal HBV DNA level is known to be associated with a high failure rate of neonatal passive-active immunoprophylaxis.[453,454] In a double-blind, randomized controlled trial, pregnant women with high serum HBV DNA levels [>10^3Meq/mL (~10^9cpm)] were given lamivudine from week 32 of gestation to week 4 postpartum in addition to neonatal passive-active immunoprophylaxis.[455] HBsAg positivity was present in 18% and 39% of 1-year-old infants from lamivudine- and placebo-treated mothers, respectively (P=0.014). No safety concerns were noted in the lamivudine-treated mothers and their newborns. However, these data should be interpreted with caution due to the high dropout rates, especially in the placebo group (13% in the lamivudine group and 31% in the placebo group). A prospective controlled study included pregnant women with high serum HBV DNA levels (>10^7cpm) who were treated with telbivudine from weeks 20 to 32 of gestation to week 4 postpartum in addition to neonatal passive-active immunoprophylaxis.[456] HBsAg positivity was present in none of the 6-month-old infants from telbivudine-treated mothers, whereas it was present in 8% of those from placebo-treated mothers. The prevalence of safety issues did not differ significantly between the two groups. These studies imply that antiviral medication in the late stage of pregnancy is likely to reduce the vertical transmission rate. However, the decision about whether or not to treat should be individualized in patients who are not indicated for the treatment of HBV, based on the treatment duration, stopping point, possible appearance of drug-resistant strains, and the patient's preferences.

[Recommendation]

1. PegIFN is preferred in female patients who are planning pregnancy since the period of treatment is more clearly defined (C1). However, the side effects of fetal malformations make pegIFN contraindicated during pregnancy, and so it must be recommended in combination with contraception (A1).
2. When antiviral treatment is needed during pregnancy, Category B drugs such as telbivudine or tenofovir are recommended (B1).
3. The antiviral treatment strategy during pregnancy is based on the general principles of treatment of CHB; however, decisions should be based on analysis of the risks and benefits for both the mother and fetus (C1).
4. Breast-feeding is not recommended in women who are treated with antiviral agents (C1).

Children and adolescents

Providing HBIG and HBV vaccine to newborns of HBsAg-positive mothers within 12 hours of birth can prevent 90-95% of cases of perinatal infection. Ninety percent of infants infected as a neonate progress to chronic infection. Most children remain in the immune-tolerant phase until late childhood or adolescence. However, some children progress to the immune-reactive phase. A Taiwanese study found that the annual spontaneous HBeAg seroconversion rates were 2% and 4-5% in children younger than 3 years and older than 3 years, respectively.[457] Children who are in the immune-reactive phase–with increased ALT levels and histologic findings of liver inflammation and fibrosis–are usually asymptomatic. The goals of therapy are to suppress viral replication, reduce liver inflammation, reverse liver fibrosis, and prevent cirrhosis and HCC.

Treating children in the immune-tolerant phase is not beneficial, and there is a high risk of the development of drug resistance, which would limit the treatment options in later life. Children with a persistent elevated serum ALT should be evaluated for viral active replication, including measurement of HBV DNA levels. HBeAg-positive children should be considered for treatment when their serum ALT levels are above 2× ULN for at least 6 months and their HBV DNA levels are above 20,000 IU/mL.[458] Acute elevation of the liver enzymes with an ALT level of >5× ULN may be followed by spontaneous HBeAg seroconversion. It is therefore reasonable to delay treatment for an observation period of at least 3 months if there is no concern about hepatic decompensation. Children with moderate-to-severe necroinflammation or periportal fibrosis in a liver biopsy are recommended for treatment. The decision to treat is based on factors such as age, liver biopsy findings,

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and family history of HBV-associated cirrhosis or HCC. In obese children it is important to remember that ALT elevations may be due to fatty liver disease.[459] The responses to interferon-α and lamivudine are better in children with higher activity scores in a liver biopsy.[460,461] There are few data on the drugs prescribed to children and adolescents younger than 18 years. Drugs that have been shown to be effective in randomized controlled trials are interferon-α, lamivudine, and adefovir. Entecavir is labeled for those aged 16 years and older.

A randomized controlled trial of interferon-α therapy involving children aged 1 to 17 years found that 36% of treated children whose baseline ALT was at least 2× ULN became negative for HBeAg at the end of treatment. HBsAg seroconversion occurred in 10% of the children in the treatment group.[460] Factors that are predictive of a positive response among children are being younger than 5 years,[462] having a low serum HBV DNA level, and having active inflammation in a liver biopsy.[460] After 5 years of observation the rate of HBeAg seroconversion did not differ between the treatment and control groups. However, loss of HBsAg occurred in 25% of children who responded during treatment, but in none of the children in the nonresponse and control groups.[463] The recommended treatment regimen for interferon-α is 6 MU/m^2 three times per week by subcutaneous injection for 6 months. Interferon-α is approved in children older than 12 months, and its advantages include the finite duration of treatment and no development of viral resistance. The adverse effects include fever, flu-like symptoms, bone marrow suppression, depression, and transient growth suppression. Interferon-α is contraindicated in children with decompensated cirrhosis and autoimmune disease. There are no published reports on clinical trials of peginterferon in children with CHB. However, the efficacy and safety of peginterferon were demonstrated for treating children with chronic hepatitis C, and a recent update of the Swedish national recommendations for the treatment of CHB recommends the use of peginterferon (100 μg/m^2 weekly) in children.[464]

A randomized controlled study of lamivudine involving children aged 2-17 years found that loss of HBeAg at 52 weeks of treatment occurred in 34% of children whose baseline ALT level was at least 2× ULN, and that the resistance rate was 18%.[465] The HBeAg seroconversion rate after 2 years of therapy was 54% in children without lamivudine-resistant viruses. The resistance rate was 64% in children who received lamivudine for 3 years. Lamivudine treatment over 3 years did not significantly increase seroconversion rates and it increased the incidence of viral resistance.[466] Studies of Korean children found that the HBeAg seroconversion rates after 2 and 3 years of treatment were 65% and 70%, respectively.[467,468] Loss of HBsAg was observed in 20% of children after 2 years of lamivudine treatment, and the resistance rates at 1 and 2 years of treatment were 10% and 23%, respectively. Factors associated with a response were elevated baseline ALT, high baseline histology-activity-index score,[461] and being younger than 7 years.[467] Long-term durability of HBeAg seroconversion was observed in more than 90% of the subjects after they had taken lamivudine for at least 2 years.[469] Lamivudine is orally administered at a dose of 3 mg/kg/day, with a maximum of 100 mg/day. Adefovir could be added if there is incomplete suppression after 24 weeks of therapy, or the treatment could be changed to off-label entecavir.[459] Lamivudine treatment should be continued for at least 1 year, and it is desirable to continue treatment for 1 year after HBeAg seroconversion. Adefovir should be added when lamivudine resistance develops.

Another randomized controlled study of HBeAg-positive children aged 2-17 years showed undetectable HBV DNA and a normal ALT level after 48 weeks of adefovir treatment in 23% of the 12- to 17-year-old subjects, but there was no statistical difference between adefovir and placebo in the subjects aged 2-11 years.[470] No subject developed adefovir resistance.

Entecavir and tenofovir are potent HBV inhibitors with a high barrier to resistance. Pediatric clinical trials of entecavir and tenofovir are currently underway, and if the final results are positive they will be suitable for use in therapies. Entecavir is considered a first-line therapy for adolescents aged 16 years and older. Therapeutic options for children are currently limited, and a prudent decision should be made based on the drug adverse effects and the potential for viral resistance to affect future therapies.

[Recommendation]

1. Children with HBeAg-positive CHB should be considered for treatment when the serum HBV DNA level is >20,000 IU/mL and the AST or ALT level is >2× ULN for at least 6 months, or moderate-to-severe necroinflammation or periportal fibrosis is shown in a liver biopsy (A1).
2. Lamivudine or interferon-α is considered the first-line therapy in children with CHB, while entecavir is the first-line therapy in those aged 16 years and older (B1). Data on peginterferon, entecavir, and tenofovir are currently scarce, but the use of these drugs in children can be based on the results obtained in studies involving the treatments administered to adults (C1).

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3. If lamivudine resistance develops, adefovir should be added (A1).

Conflicts of Interest

The authors have no conflicts to disclose.

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Appendix 1. Disclosure of conflict of interests for the past 2 years

Joong-Won Park: advisory board member for Bayer Healthcare, Pfizer, and Taiho pharm. Co; honoraria from Bayer Healthcare, Taiho Pharm. Co., and BMS Pharmaceutical Korea.
Jae Sung Ko: none.
Geum-Youn Gwak: honoraria from Handok Pharmaceuticals Co., JW Creagene, and MSD Korea.
Jin-Wook Kim: none.
Hwi Young Kim: none.
Sang Hoon Park: advisory board member for Bukwang Pharm. Co, Roche Korea, JW Pharmaceutical, BMS Pharmaceutical Korea, JW Creagene; honoraria from Daewoong Pharmaceutical Co., Handok Pharmaceuticals Co., Celltrion, and Roche Korea.
Si Hyun Bae: honoraria from BMS Pharmaceutical Korea, Bayer Healthcare, Gilead Sciences, Bukwang Pharm. Co, and MSD Korea; advisory board member for GlaxoSmithKline Korea and Bayer Healthcare.
Yong Han Paik: advisory board member for GlaxoSmithKline Korea; honoraria from Bayer Healthcare, Handok Pharmaceuticals Co., BMS Pharmaceutical Korea.
Byung-Cheol Song: advisory board member for BMS Pharmaceutical Korea; honoraria from Novartis Korea and Handok Pharmaceuticals Co.
Ju Hyun Shim: none.
Sang Hoon Ahn: honoraria from BMS Pharmaceutical Korea; honoraria from and advisory board member for Bayer Healthcare, BMS Pharmaceutical Korea, Gilead Sciences, GlaxoSmithKline Korea, Roche Korea, Handok Pharmaceuticals Co., Merck Korea, Novartis Korea.
June Sung Lee: honoraria from Bayer Healthcare, Handok Pharmaceuticals Co., Bukwang Pharm. Co., and GlaxoSmithKline Korea.
Young-Suk Lim: honoraria from GlaxoSmithKline Korea, BMS Pharmaceutical Korea, Roche Korea, Bayer Healthcare, and MSD Korea.
Hyung Joon Yim: honoraria from GlaxoSmithKline Korea, BMS Pharmaceutical Korea, Handok Pharmaceuticals Co., and Bukwang Pharm. Co.; advisory board member for BMS Pharmaceutical Korea and Handok Pharmaceuticals Co.
Moon Suk Choi: honoraria from Roche Korea, BMS Pharmaceutical Korea, GlaxoSmithKline Korea, MSD Korea, and Handok Pharmaceuticals Co.
Won Young Tak: honoraria from Roche Korea, GlaxoSmithKline Korea, MSD Korea, Bukwang Pharm. Co., Bayer Healthcare, BMS Pharmaceutical Korea, and Handok Pharmaceuticals Co.; advisory board member for MSD Korea, Roche Korea, and Bayer Healthcare.

Appendix 2. Process of the revision of 2011 KASL clinical practice guideline for the management of chronic hepatitis B

2004, November: Release of 2004 KASL practice guideline for the management of chronic hepatitis B (CHB)
2007, November: Release of 2007 KASL practice guideline for the management of CHB
2010, October: The KASL board of directors suggested revision of CHB guideline.
2010, November: The KASL board of trustees approved revision of the guideline.
2010, December: The KASL board of directors approved the CHB Clinical Practice Guideline Revision Committee (CPGRC), which represents the position of the KASL.
2011, January 14: Opening meeting of CHB-CPGRC at KASL office
Chairman: Byung Chul Yoo (President of KASL, Sungkyunkwan University)
Chief Director: Joong-Won Park (National Cancer Center)
Members: Jin-Wook Kim (Seoul National University), June Sung Lee (Inje University), Won Young Tak (Kyungpook National University), Sang Hoon Park (Hallym University), Si Hyun Bae (Catholic University), Moon Suk Choi (Sungkyunkwan University), Young-Suk Lim (University of Ulsan), Yong Han Paik (Sungkyunkwan University), Byung-Cheol Song (Cheju National University), Hyung Joon Yim (Korea University), Sang Hoon Ahn (Yonsei University), Geum-Yeon Gwak (Sungkyunkwan University), Hwi Young Kim (National Cancer Center), Ju Hyun Shim (University of Ulsan), Jae Sung Ko (Seoul National University)
2011, Feburary 13: Workshop of the committee at Seoul National University Cancer Research Institute.
2011, April 30: The CHB-CPGRC meeting on the 1st version manuscript at Seoul National University Cancer Research Institute.
2011, June 11: The CHB-CPGRC meeting on the 2nd version manuscript at Sheraton Grande Walkerhill hotel.
2011, July 16: The CHB-CPGRC meeting on the 3rd version manuscript at Seoul National University Cancer Research Institute.
2011, August 25: Advisory board meeting on the 4th version manuscript at Millennium Seoul Hilton hotel.
Advisory board: Young Oh Kweon (Kyungpook National University), Dae-Ghon Kim (Chonbuk National University), Dong Joon Kim (HallymUniveristy), Kwan Soo Byun (Korea University), Seung Kew Yoon (Catholic University), Kwan Sik Lee (Yonsei University), Yung Sang Lee (University of Ulsan), Young Sok Lee (Catholic University), Heon Young Lee (Chungnam National University), Sung Won Cho (Ajou University), Sung Kyu Choi (Chonnam National University), Kwang-Hyub Han (Yonsei University)
2011, September 8: Public hearing on the 4th version manuscript at Clinical Research Institute Auditorium, Seoul National University Hospital.
2011, October 7: The CHB-CPGRC meeting on the 5th version manuscript at T-Won, Seoul Station.
2011, October 31: The KASL board of directors reviewed and approved the 6th version (final) manuscript of CHB guidelines.
2011, December 1: Release of the 2011 KASL Clinical Practice Guideline on the Management of CHB (Korean version) at the general meeting of KASL annual conference at ICC, Jeju Province.
2012: The English version of the 2011 CHB guideline is released on The Clinical and Molecular Hepatology.

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