KASL clinical practice guidelines: management of chronic hepatitis B

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

Keywords: Chronic hepatitis B; Management; KASL guidelines

PREAMBLE

Aims

The clinical practice guidelines for the management of chronic hepatitis B (CHB) were first presented in 2004 by the Korean Association for the Study of the Liver (KASL), and were revised in 2007 and 2011. The American Association for the Study of Liver Diseases (AASLD) published their guidelines in 2015, the European Association for the Study of the Liver (EASL) in 2012, the Asian Pacific Association for the Study of the Liver (APASL) in 2015 and the World Health Organization (WHO) in 2015. These guidelines carry some variations due to ethnic differences and different medical environments. Therefore, there is a demand for Korean practice guidelines which reflect medical practice in Korea. Problems with emergence of drug resistant mutation are eminent in Korea and the KASL updated their guidelines regarding the management of antiviral resistant mutation in 2014.

In 2015, the objective of this manuscript was to update the recommendations for management of CHB, including epidemiology, prevention, natural history, diagnosis, treatment, monitoring, drug resistance mutations and treatment of special populations discussed herein based on current evidences or if, evidences lack, on expert opinions after deliberation.

Corresponding author: KASL (Committee chair: Kwan Sik Lee)
Room A1210 MapoTrapalace, 53 Mapo-daero, Mapo-gu, Seoul 04158, Korea
Tel: +82-2-703-0051, Fax: +82-2-703-0071
E-mail: kasl@kams.or.kr

*Clinical Practice Guidelines Committee of KASL for the Management of Chronic Hepatitis B
Kwan Sik Lee (Committee Chair, Yonsei University College of Medicine), Si Hyun Bae (Catholic University of Korea), Won Hyoek Cho (Konkuk University College of Medicine), Moon Seok Choi (Sungkyunkwan University School of Medicine), Woo Jin Chung (Keimyung University School of Medicine), Chang Wook Kim (Catholic University of Korea), Hyung Joon Kim (Chung-Ang University College of Medicine), Ja Kyung Kim (Yonsei University College of Medicine), Ji Hoon Kim (Korea University College of Medicine), Suk Bae Kim (Dankook University Medical College), Yoon Jun Kim (Seoul National University College of Medicine), Jong Eun Yeon (Korea University College of Medicine), Ki Tae Yoon (Pusan National University School of Medicine).

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Target population

The main targets of this guideline are patients both newly diagnosed with CHB and those being followed up or treated for CHB. This guideline is also intended to facilitate management of patients under the following special circumstances: malignancy, transplantation, kidney dysfunctions, co-infection with other viruses, pregnancy, and children.

Intended users

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

Developer and funding

The CHB Clinical Practice Guideline Revision Committee (CPGRC) comprising 17 hepatologists and 1 pediatrician was formed with support from the KASL. All of the required funding was provided by the KASL. Each member of the CHB-CPGRC collected and evaluated evidence, and contributed to writing the manuscript.

Conflicts of interest of the CHB-CPGRC members are summarized in Conflicts of interest.

Evidence collection

Relevant evidences obtained from a comprehensive literature search using MEDLINE (up to 2015) were systematically reviewed and selected. The languages were limited to English and Korean.

In addition to published articles, abstracts of important meetings published before 2015 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, prevention, diagnosis, treatment, antiviral resistance, and special situations.

Levels of evidence and grades of recommendation

The evidence and recommendations were graded according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system with minor modifications (Table 1). The levels of evidence were determined as 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 determined 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?
3. What is the updated knowledge on the natural course of CHB?
4. How should the infection be prevented?
5. How are patients evaluated prior to treatment?

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 recommendations | 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 |

NOTE. Of the quality levels of evidence, we excluded "very low quality (D)" from the guidelines for convenience. This was originally included in the GRADE system and indicates that the estimate of effect is highly uncertain.
6. When should treatment be considered?
7. What are the goals and endpoints of treatment?
8. What are the optimal first-line treatments for different disease status?
9. How should the treatment be monitored?
10. When can we consider stopping treatment?
11. What are the predictors of a treatment response?
12. What are the definitions of treatment failure?
13. How should we manage drug-resistant CHB patients?
14. What are the definitions of recurrence after treatment completion and how should these be managed?
15. How should we manage the following special groups:
   - acute hepatitis B
   - liver transplantation
   - chemotherapy/immunosuppression
   - chronic kidney disease
   - coinfection [with hepatitis C virus (HCV), hepatitis D virus (HDV), and/or human immunodeficiency virus (HIV)]
16. How can we reduce vertical transmission in pregnant CHB patients?
17. What is the optimal management of CHB in children?

Review of the manuscript

Drafts of the revised guideline were thoroughly reviewed at separate meetings of the committee. 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 18 specialists in CHB who are members of the KASL. The final manuscript was endorsed by the board of executives of the KASL.

Release of the guidelines

The revised CHB guidelines of KASL were released on November 26, 2015 (http://www.kasl.org).

Plan for updates

Updates or full revision will be planned when major new evidence regarding the diagnosis and/or treatment of CHB becomes available. Detailed plans for updates will be posted on the KASL website at a later date.

Epidemiology

Hepatitis B virus (HBV) infection, as a causative factor of liver disease of 240 million patients globally and death of 600 thousand patients annually, is a major cause of acute and chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. It has been recognized as an important public health problem in Korea since the 1970s and was designated a third-class communicable disease by law in 1982 and is now the target of a national vaccination program as a second-class communicable disease.

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 before commercialization of an HBV vaccine in the early 1980s; 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, in 2006 the prevalence of HBV among children aged 4 to 6 years had decreased to 0.2%. Nevertheless, according to the 2005 National Health and Nutrition Examination Survey, the HBsAg positivity rate was 4.0% at 2009. The Ministry of Health and Welfare reported that the HBsAg positivity rate was 3.4% for males and 2.6% for females, with 3.0% of the total population being infected with HBV in 2012. Positivity rates for HBsAg among pregnant females, which represents a major infection route for hepatitis B, declined steadily after 2004, as did the positivity rates among females in the childbearing period. Given that HBsAg is detected in approximately 70% of patients with chronic hepatitis or cirrhosis, and in 65–75% of HCC patients, it can be concluded that CHB infection is a matter of importance for public health in Korea. Most Korean CHB patients are infected with HBV genotype C, and tend to have lower hepatitis B e antigen (HBeAg) seroconversion rates, more rapid progression to cirrhosis and HCC, reduced efficacy of interferon treatment, and are subject to higher rates of relapse after antiviral treatment, compared to those infected with other HBV genotypes.
**Table 2. Natural course of chronic hepatitis B (CHB)**

| Clinical phase                        | Serum marker | ALT                        | HBV-DNA                        | Histology                                   |
|---------------------------------------|--------------|----------------------------|--------------------------------|---------------------------------------------|
| Immune-tolerant phase                 | HBeAg (+)    | Persistently normal        | High level of viral replication | Minimal histological disease                |
| Immune-active phase, HBeAg-positive CHB | HBeAg (+), may develop anti-HBe | Raised or intermittently raised ALT | Lower level of viral replication | Histological necroinflammatory activity present Lobular hepatitis, bridging fibrosis and fibrosis may be present |
| Immune-control phase, Inactive CHB    | HBeAg (-) anti-HBe (+) | Persistently normal ALT | Low or undetectable HBV DNA (HBV DNA levels ≤2,000 IU/mL) | Risk of cirrhosis and HCC reduced |
| Immune-escape phase, HBeAg-negative CHB | HBeAg (-), with or without being anti-HBe positive | Raised ALT (persistent or intermittent exacerbations) | Moderate to high levels of HBV replication (HBV DNA levels >2,000 IU/mL) | Older persons especially at risk for progressive disease (fibrosis/ cirrhosis) |
| HBsAg-clearance phase                | HBsAg (-) anti-HBc (+) anti-HBs (+/-) | Normal | Not detected | |

ALT, alanine aminotransferase; HBV, Hepatitis B virus; HCC, hepatocellular carcinoma.

therapy.\(^{14,15}\) HBV DNA positivity indicates an acute or chronic HBV infection, and negativity indicates resolution of infection. For this reason, the WHO decided to delete the term “hepatitis B carrier.”

The natural history of CHB is outlined below (Table 2).

**1. Immune-tolerant phase**

In cases of perinatal infection, the immune-tolerant phase is characterized by HBeAg positivity, high levels of serum HBV DNA (generally ≥10^7 IU/mL), normal levels of aspartate aminotransferase/alanine aminotransferase (AST/ALT), and mild or no liver necroinflammation.\(^{16-19}\) Elevation of ALT level was detected in 16% of patients in the immune-tolerant phase during 5 years of follow up.\(^{19}\)

This phase may continue for more than three decades in patients infected with HBV genotype C, which is common among Korean patients, and the rate of spontaneous HBeAg loss is very low.\(^{20}\) Therefore, many females infected with this genotype are in the HBeAg-positive immune-tolerant phase when they are of childbearing age. The absence of, or only mild histologic liver damage, despite high levels of HBV DNA, is attributed to immune tolerance to HBV.\(^{21}\)

**2. Immune-active HBeAg-positive CHB**

Most patients in the immune-tolerant phase will experience immune responses to HBV as they grow older, and finally reach the immune-active phase, which is characterized by HBeAg positivity, lower serum HBV DNA levels, and increased or fluctuating ALT levels.\(^{22,23}\) Histologic findings in this phase include moderate-to-severe liver inflammation and, in some patients, rapid progression of fibrosis.\(^{24}\) Such changes are due to enhancement of hepatitis B core antigen (HBcAg) or HBeAg-specific cytotoxic T-lymphocyte activity and the resulting destruction of infected hepatocytes.\(^{25}\) Sustained HBV DNA suppression occasionally accompanies HBeAg seroconversion.

Once HBeAg seroconversion occurs, the natural course of the disease may have one of three clinical features: (1) repeated HBeAg reversion and seroconversion, (2) inactive state, or (3) HBeAg-negative CHB.\(^{26,27}\) Typically, 10–40% of patients who experience seroconversion revert to HBeAg positivity and then experience recurrence of seroconversion at least once with progression of hepatitis activity.\(^{24,28,29}\) In particular, reversion frequently occurs in patients with HBV genotype C, and the rate decreases with age.\(^{30}\) Hepatic decompensation, which occurs in 5% of patients with acute exacerbation, may be fatal.\(^{30}\)

**3. Immune-control inactive CHB**

Most patients who seroconvert during the immune-active phase progress to the immune-control phase, which is characterized by HBeAg negativity, persistent normal ALT levels, and HBV DNA levels of <2,000 IU/mL.\(^{31,32}\) Typical histologic findings in 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.\(^{32}\)

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-active phase, and might experience recurring periods of reactivation and inactivation throughout their lives, which can lead to cirrhosis or HCC. This is why the ALT levels of patients in the immune-control phase must be measured at least every 6 months for life because currently there are no predictors of which patients will remain in the inactive phase and which will revert to HBeAg-negative active hepatitis.

4. Immune-escape HBeAg-negative CHB

Approximately 20% of patients who experience HBeAg seroconversion during their immune-active phase maintain HBeAg negativity and hepatitis B e antibody (anti-HBe) positivity but progress to the immune-escape phase, with findings of HBV DNA levels ≥2,000 IU/mL, increased ALT levels, and active liver necroinflammation. 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 failure to produce HBeAg. 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. Severe fluctuations of HBV DNA and ALT levels can make it difficult to differentiate these patients from those in the immune-control phase. Accordingly, for the first year after a patient is diagnosed as being in the immune-control phase, HBV DNA and ALT levels should be measured every 3 months to identify HBeAg-negative CHB patients who require antiviral treatment.

5. HBsAg-clearance phase

Patients in the immune-control phase subsequently progress to the HBsAg clearance phase at a rate of 1–2% annually. According to Liaw’s data, HBsAg loss occurs in 1.9% of CHB patients, and 0.8% of those with chronic HBV infection regardless of gender and virus genotype, with age being the only known influencing factor. It has been reported that Korean patients experience a relatively low rate of HBsAg loss (0.4% annually). 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) is detectable. HBsAg loss is associated with a reduced risk of cirrhosis but a sustained, significant risk of HCC development.

Risk factors that influence the natural history of CHB

The accumulated incidence of cirrhosis developing from CHB is generally reported to be 8–20%. 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%. The risk factors for hepatitis B progressing to cirrhosis or HCC can be divided into demographic, environmental, social, and viral factors (Table 3). Regarding demographic factors, the risk of developing HCC is

| Table 3. Risk factors associated with the development of hepatocellular carcinoma (HCC) and/or cirrhosis in persons with chronic hepatitis B |
|----------------------------------|-----------------|-----------------|
| **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**    |                  |                 |
| Alcohol                         | +                | +               |
| Aflatoxin                       | 3+               | Unknown         |
| Smoking                         | +                | +               |
| Coffee                          | Decreased risk of HCC | Slower progression of liver fibrosis |
| **Viral factor**                |                  |                 |
| 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.
Three- to fourfold higher for males than for females, 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.\textsuperscript{33,57-59} Those with a family history of HCC also have a higher risk of contracting HCC.\textsuperscript{60,61} Environmental and social risk factors for progression to cirrhosis or HCC are alcohol consumption, exposure to aflatoxin,\textsuperscript{62} and smoking.\textsuperscript{63} It is suggested that obesity, metabolic syndrome, and fatty changes in histologic tests increase the risk of CHB patients progressing to hepatic fibrosis or HCC.\textsuperscript{64,67} Many epidemiological research studies have found that coffee exerts protective effects against the development of hepatic fibrosis and HCC.\textsuperscript{68-72}

Viral factors that may influence the progression of CHB patients to cirrhosis or HCC include high levels of serum HBV DNA ($\geq$20,000 IU/mL), genotype C, BCP variants, and coinfection with other viruses.\textsuperscript{17,35,73-75} According to the Taiwanese Risk Evaluation of Viral Load Elevation and Association Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) 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\textsuperscript{7} copies/mL (cpm) at the start of observation and 10\textsuperscript{11} cpm 11 years later than among those with an entry HBV DNA level of $<10^{4}$ cpm. Likewise, the incidence of cirrhosis was significantly associated with HBV DNA levels higher than 10\textsuperscript{4} cpm at study entry.\textsuperscript{58,59} If the HBV DNA level decreased during the follow-up period, the risk of developing HCC or cirrhosis decreased. Subsequent research highlighted the clinical importance of careful evaluation of patients with an HBV DNA level $>2,000$ IU/mL who are older than 40 years (especially those HBeAg positive) for the development of fibrosis \textsuperscript{57} and HCC.\textsuperscript{76,77} Therefore, intervention with antiviral therapy should be performed when appropriate, as recommended by established practice guidelines.\textsuperscript{56}

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.\textsuperscript{78} Eight HBV genotypes have been identified, and that with the worst prognosis is genotype C, which is the most common in Korean CHB patients.\textsuperscript{73} Genotype C is associated with delayed natural seroconversion and rapid progression to liver cirrhosis and HCC. Therefore, it is an independent risk factor for HCC development. According to a cohort study in Alaska, patients infected with A-, B-, and D-genotype hepatitis B typically experience seroconversion from HBeAg to anti-HBe before the age of 20 years, whereas in those infected with the C genotype this occurs at a mean age of 47 years.\textsuperscript{26} This implies that those infected with genotype C would on average experience a much longer period of infection with high HBV viral loads, and may in part 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 the BCP and PC mutations.\textsuperscript{42,43,73,77,79} BCP mutations are A1762T and G1764A mutations in the HBV BCP regions, and multiple cross-sectional and prospective studies have indicated that they increase the risks of cirrhosis and HCC.\textsuperscript{42,43,73,77,79} According to the results of the REVEAL-HBV study, 359 and 1,149 individuals without and with BCP mutations, respectively, developed HCC among a population of 100,000,\textsuperscript{80} 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.\textsuperscript{81} Patients infected with PC mutants are characterized by HBeAg negativity and HBeAg positivity, but high levels of HBV DNA.\textsuperscript{81,82} 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 the findings of cross-sectional clinical-based studies—that the presence and absence of the PC mutation decreased and increased, respectively, the subsequent annual incidence of HCC (269 and 996 per 100,000, respectively).\textsuperscript{83}

**Prevention**

Because HBV infection is endemic in Korea, any person at high risk of liver disease or has suspected liver disease is recommended to have their HBsAg and anti-HBs statuses checked.\textsuperscript{14} CHB patients can transmit virus to others, and hence they should be counseled regarding how to modify their lifestyle so as to prevent HBV transmission. Epidemiologic studies found that the daily consumption of 40–80 g of alcohol is associated with liver damage and the progression of liver disease.\textsuperscript{83,84} and a long-term prospective cohort study of patients with chronic HBV infection showed that alcohol consumption increases the risks of liver cirrhosis and HCC development.\textsuperscript{75,79,85} No data are available on the threshold level of alcohol consumption required to significantly increase the risks of liver cirrhosis and HCC in patients with chronic HBV infection. In the general population, a daily alcohol intake of 24 g in males and 12 g in females significantly increases the risk of liver cirrhosis.\textsuperscript{85} So, abstinence or a very limited consumption of alcohol is recommended in patients with chronic
HBV infection. According to a long-term prospective study of patients with chronic HBV infection, smoking also increases the risks of liver cirrhosis and HCC, and so non-smoking is recommended in patients with chronic HBV infection. Vertical infection is the most important route of HBV transmission. Following initiation of the HCV vaccination program, the HBsAg positivity rate among pregnant females was 3.32% (308/9281) and the vertical transmission rate was 1.59% (4/252) in 2014. Therefore, the vaccination program is effective for control of vertical transmission. HBV immunoglobulin and vaccination after delivery can prevent 90-95% of vertical transmission to newborns from HBsAg-positive mothers. Therefore, such infants should receive 0.5 mL HBIG and scheduled HBV vaccination within 12 hours of birth and after. Adding immunoglobulin is more effective than vaccination only. 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).

In patients negative for HBsAg and anti-HBs, vaccination is recommended. Isolated anti-HBc positive patients negative for HBsAg and anti-HBs should consider vaccination, especially if liver function results are abnormal. As HBV is endemic in Korea, patients negative for HBsAg and anti-HBs should be vaccinated, particularly the household members and sexual partners of patients with chronic HBV infection, as such persons are at increased risk of HBV infection. Patients with chronic HBV infection are not candidates for vaccination because of its lack of effectiveness. 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 methods, such as condoms. The three doses constituting the hepatitis B vaccine series administered intramuscularly at 0, 1, and 6 months induce a protective antibody response (anti-HBs >10 mIU/mL) in >90% of recipients. Most non-responders (44–100%) subsequently respond to a further three-dose revaccination.

Although serologic testing for anti-HBs is not necessary after routine vaccination in immunocompetent adults, post-vaccination testing of anti-HBs status is recommended in some subjects, such as newborns of HBV-infected mothers or 9-18 months old young infants whose family members has CHB. Healthcare workers, dialysis patients, workers in dialysis units and operation rooms, immunocompromised subjects (e.g., HIV infection, hematopoietic stem cell transplants, patients with chemotherapy), and sexual partners of patients with chronic HBV infection should be tested 1-2 months after their completion of the HBV immunization series. 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 individuals. However, an anti-HBs level of <10 mIU/mL in dialysis patients indicates an increased risk of HBV infection, and so a booster vaccination is needed if annual testing reveals an anti-HBs level of <10 mIU/mL. This also applies to immunocompromised patients. A person without protective anti-HBs exposed to HBV-contaminated blood or body fluids should receive hepatitis B immunoglobulin (HBIG, 0.06 mL/kg) and hepatitis B vaccine as soon as possible; preferably within 24 h, otherwise postexposure prophylaxis should be initiated within 7 days for percutaneous exposure or within 14 days for sexual exposure.

Coinfection with hepatitis A in HBV carriers increases the risk of mortality by 5.6- to 29-fold. Therefore, hepatitis A vaccination is recommended for persons negative for the protective hepatitis A virus antibody (anti-HAV).

**[Recommendations]**

1. HBV vaccination is recommended for persons negative for HBsAg and anti-HBs. (A1)
2. Abstinence from alcohol and smoking is recommended for patients with chronic HBV infection. (A1)
3. Newborns of HBV-infected mothers should receive HBIG and hepatitis B vaccine at delivery and complete the recommended vaccination series. (A1)
4. Hepatitis A vaccine should be given to patients with chronic HBV infection negative for anti-HAV. (A1)

**DIAGNOSIS AND INITIAL EVALUATION**

CHB is defined as the presence of HBsAg for longer than 6 months. 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, HAV, HCV, HDV coinfection, and family history of HBV infection and HCC. The causal relationship between HBV infection and liver disease has yet to be established. 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 the degree of liver injury in patients with CHB.
**Antigen/antibody test**

HBsAg immunoassay is a necessary and accurate test for diagnosis of CHB. By definition, patients who remain positive for HBsAg for longer than 6 months have progressed to chronic infection. Quantitative measurement of HBsAg is now possible and the combination of HBsAg quantification and HBV DNA level is an integral component of monitoring the response to antiviral therapy. Serologic tests, including anti-HBs and anti-HBc, can assist in screening of populations for HBV infection and differentiating among acute, chronic, and past infections. In acute HBV infection, HBsAg appears 1-10 weeks after exposure to HBsAg and disappears 4-6 months after recovering from HBV infection. Acute HBV infection is diagnosed by being HBsAg positive and anti-Hbc IgM positive. Anti-Hbc IgM is the only marker present during the window period, the interval between disappearance of HBsAg and appearance of anti-Hbs.

Anti-Hbc typically persists for life, but IgM anti-Hbc is detectable for 6 months, and anti-Hbc is detectable thereafter in patients with resolved acute HBV infection. IgM anti-Hbc can be detected at low levels during chronic HBV infection. Persistently positive anti-Hbc is shown when anti-Hbs titer from the past HBV infection becomes undetectable over time or in cases with occult hepatitis B infection. Measurement of the serum HBV DNA level might be helpful in these settings. Patients with these serologic patterns should be followed with repeated testing of HBsAg, anti-Hbs, and anti-Hbc for 3–6 months. 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 indicates a high level of viral replication, and anti-HBe positivity a low level. Serum HBV DNA and AST/ALT levels are important parameters 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 phase. 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-active 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 the PC and/or BCP regions that are unable to produce or produce only low levels of HBeAg. 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.

Acute hepatitis A co-infection in chronic hepatitis B patients can result in increased icteric manifestation, longer recovery time, and increased risk of fulminant hepatic failure. Underlying chronic liver disease is an important risk factor for fulminant hepatic failure and death in patients with acute HAV infection. 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 HAV vaccine. Laboratory tests should include tests for coinfection with HCV and/or HIV in those at risk.

**Serum HBV DNA 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 the international unit (IU) (1 IU is equivalent to 5.6 HBV DNA copies) as a recommended reporting unit for HBV DNA has facilitated standardized reporting and comparison of serum HBV DNA levels. The methods used to quantify HBV DNA levels have evolved rapidly. Real-time PCR-based assays have been introduced and demonstrate both high sensitivity and a broad linear range (10–10^9 IU/mL) of quantification. The same test should be specified each time when monitoring HBV DNA levels for a given patient in clinical practice to ensure consistency.

**HBV genotypes**

HBV genotypes appear to influence the progression of disease, risk of HCC, and response to therapy (including interferon therapy). Some studies in Asia have suggested that genotype C is associated more frequently with HBV reactivation, severe liver disease, and HCC than is genotype B. 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. In CHB, examina-
tion of genotyping is recommended selectively to help identify patients who might be at greater risk of disease progression, and routinely to determine the most appropriate candidates for peginterferon therapy.\textsuperscript{117} 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. 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 therapy.\textsuperscript{118} The ALT level is usually higher than that of AST, but the ratio may be reversed when the disease progresses to cirrhosis. HBV-infected patients with normal or mildly 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.\textsuperscript{119} ALT activity might also be affected by other factors such as body mass index, gender, abnormal lipid and carbohydrate metabolism, and uremia.\textsuperscript{119,120} 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 males and 30 IU/mL for females. Moreover, data from cohort studies indicate that the upper limit of normal (ULN) ALT and AST levels should be decreased to 30 IU/mL for males and 19 IU/mL for females.\textsuperscript{119,120} Clinical studies have shown that patients with ALT levels of 40–45 IU/mL have a high risk of significant liver disease and mortality from complications.\textsuperscript{121} According to the treatment algorithm for CHB suggested by Keeffe et al., serum ALT levels of 30 and 19 IU/mL for males and females, respectively, should be used as the ULN levels when deciding to commence treatment.\textsuperscript{117} Further prospective studies are needed to clarify this issue.

A recent prospective study in Korea involving 2,000 liver donors suggested that healthy serum ALT values should be 33 IU/L for males and 25 IU/L for females.\textsuperscript{122} Ninety thousand males and 40,000 females aged 35 to 59 years in the prospective NHS cohort exhibited upper limits of AST and ALT values for prediction of liver diseases of 31 IU/L and 30 IU/L, respectively.\textsuperscript{121}

**Liver biopsy**

A liver biopsy is recommended for determining the degree of necroinflammation and fibrosis in patients with elevated ALT, an HBV DNA positive or both, because liver histology is useful when deciding whether or not to commence treatment. A liver biopsy is invasive but the rate of serious complications is very low (1/4,000-10,000).\textsuperscript{123} Several recent 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 those older than 35–40 years.\textsuperscript{116-121,124} A retrospective study of the relationship between ALT level and fibrosis in CHB patients reported 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.\textsuperscript{125} 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 serum HBV DNA level, age, and liver histology results when deciding to commence treatment. Therefore, in HBsAg-positive patients with HBV DNA levels 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 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. This is because only a small portion of the liver is sampled, and the low intra/interobserver reliabilities. Therefore, the efficacy of noninvasive methods such as the Fibroscan device or serum markers in assessing fibrosis in CHB has increased.

**Noninvasive fibrosis test**

The severity of liver fibrosis and determination of ALT and HBV
DNA levels have essential roles in treatment decisions. Noninvasive methods to estimate liver fibrosis have been developed and used. These methods include the aspartate aminotransferase-platelet ratio index (APRI), AST/ALT ratio (AAR), Forns’ fibrosis index (age, platelets, GGT, cholesterol, FIB-4 (platelets, ALT, AST, Age)). Also, the FibroTest that uses indirect markers (α-2 macroglobulin, haptoglobin, r-globulin, apolipoprotein A1, and GGT), the FibroSpect II Enhanced Liver Fibrosis test that uses direct markers (Hepascore, FibroMeter, hyaluronic acid and tissue inhibitor of matrix metalloproteinase-1, 2) are available. The age-spleen-platelet ratio index (ASPRI) is the most accurate in predicting liver fibrosis in chronic HBV infection. APRI is useful for diagnosis of not only for liver fibrosis but also liver cirrhosis, while FIB4 is useful for mild fibrosis. However FIB4 has limitations in terms of predicting fibrosis of stage F2 and above as it has low sensitivity and specificity.

Transient elastography using Fibroscan® has a high degree of accuracy for assessment of advanced liver fibrosis. It is the most commonly used method for chronic liver diseases because of its noninvasiveness and high reproducibility.

Fibroscan® can be performed rapidly (5 min) in the outpatient clinics of hospitals and produce a result immediately after the test. However, only procedures involving ≥10 successful measurements are considered reliable. Moreover, a success rate (SR) of at least 60% and an interquartile range (IQR) of less than 30% of the median value are required (Interquartile range/median value). Fibroscan® has limitations in subjects with ascites, obesity, or narrow intercostal spaces. Moreover, the system may yield false-positive results in subjects with acute hepatitis and extrahepatic biliary tract obstruction.

Fibroscan® has greater diagnostic accuracy than APRI or FIB-4 for liver cirrhosis in a study that compared liver biopsy, AAR, APRI, Fibroscan®, and FIB-4 in patients with chronic hepatitis. Also, Fibroscan® was more predictive of liver fibrosis and liver cirrhosis in a study that compared Fibroscan® and APRI in 567 subjects with chronic hepatitis (Area under Receiver Operating Characteristic: F3 0.849 vs. 0.812, F4 0.902 vs. 0.707).

Screening for hepatocellular carcinoma

The initial evaluation of patients with CHB should include tests for HCC. Periodic surveillance is also needed in these patients to ensure early detection of HCC during follow-up. The issue of HCC is treated in detail in the “Practical Guidelines for Management of Hepatocellular Carcinoma 2014.” 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 those older than 40 years, patients with cirrhosis, those 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.

Recently developed treatments can decrease the incidence of liver diseases or delay their progression but cannot prevent all possible complications. Therefore, surveillance and screening for hepatocellular carcinoma are required at regular intervals for early diagnosis and a complete recovery.

[Recommendations]

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. A real-time PCR quantification assay is strongly recommended for quantifying the HBV DNA level. (A1)
4. An anti-HCV test is necessary to rule out coinfection with HCV. (B1)
5. An anti-HAV test is necessary in CHB patients younger than 50 years. (A1)
6. Liver biopsy is useful for determining the degree of liver in-
flammmation and fibrosis. (A1)
7. Noninvasive tests such as serum markers and liver elasticity are used for diagnosis of the degree of liver fibrosis. (B1)
8. 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 reduces the frequency of progression to liver cirrhosis or HCC. The optimal treatment result would be the loss or seroconversion of HBsAg, but since intranuclear cccDNA persists despite treatment, complete clearance of HBV is almost impossible to achieve. This is why indices such as ALT level normalization, 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. Therefore, a realistic virologic goal of antiviral therapy is the suppression of viral replication.

Most guidelines state that antiviral treatment is required for patients with acute liver failure, decompensated liver cirrhosis or in the acute phase of severe chronic HBV hepatitis regardless of HBV DNA and ALT levels, and the treatment has almost no complications, although few controlled studies have been performed. Antiviral therapy decreases the rate of recurrence of viral infection in patients who require liver transplantation. The HBV DNA and HBeAg levels in CHB are indices of viral replication and active hepatitis, respectively, and patients with HBeAg-positive hepatitis B with high levels of HBV DNA have an increased risk of developing liver cirrhosis or HCC.

Patients with disappearance or conversion of serum HBeAg have a low risk of liver cirrhosis and hepatocellular carcinoma, and so have a good prognosis.

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. Therefore, 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. The decrease in the HBV DNA level after antiviral treatment in active hepatitis with elevated HBV DNA levels results in histologic improvement, seroconversion of HBeAg, and normalization of ALT levels, and thus a slowing of the progression of hepatitis. However, even in cases with HBV DNA levels of less than 10^5 copies/mL, which is considered to be inactive hepatitis, the hepatitis can still progress to liver cirrhosis and HCC. Therefore, a decrease in HBV DNA to an undetectable level is recommended for patients on antiviral treatment.

TREATMENT INDICATIONS AND STRATEGIES

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 improvement of survival. Since eradication of HBV infection is rarely achieved with currently available drugs, long-term treatment is necessary in most cases. Treatment protocol 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 as local availability, cost, and reimbursement policy. The durations of currently available antiviral trials are insufficient to assess the effects of treatment on long-term survival. Long-term treatment with oral nucleos(t)ide analogs (NAs) ameliorates histologic abnormalities such as necroinflammation and/or fibrosis, both in HBeAg-positive and HBeAg-negative CHB. Therefore, long-term antiviral therapy may prevent disease progression and reduce the
risk of liver cirrhosis.\textsuperscript{145}

**Immune tolerance phase**

Antiviral therapy is not indicated for patients in the immune-tolerant phase despite HBeAg positivity and a high level of HBV DNA, because of the benign natural course of the disease and such treatment results in minimal histologic changes.\textsuperscript{159}

**Recommendations**

Patients in the immune-tolerant phase (HBeAg positive and persistently normal ALT level as recommended by this guideline rather than local laboratory ULNs) are not indicated for antiviral therapy. (B1)

**Chronic hepatitis B**

CHB patients with active viral replication and significant inflammation and/or fibrosis are appropriate targets for antiviral treatment. Early guidelines generally agreed that antiviral treatment could be recommended for CHB patients (especially those without liver cirrhosis) with serum HBV DNA level > 20,000 IU/mL and serum ALT level > 2 ULN.\textsuperscript{140,167} However, recent guidelines suggest that the indications of antiviral treatment should be expanded to those with lower serum HBV DNA levels and/or lower serum ALT levels.\textsuperscript{15,162,163}

Serum HBV DNA level is a marker of viral replication and an indicator of the 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.\textsuperscript{57,59} However, an HBV DNA level of 10^4 cpmp 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 cpmp), especially those with HBeAg negative hepatitis and/or cirrhosis, frequently show progression of liver disease and hence may need treatment.\textsuperscript{35,161,164} A serum HBV DNA level of ≥20,000 IU/mL has been suggested as the cut-off for HBeAg-positive CHB.\textsuperscript{164} However, the distinction between HBeAg-negative CHB and inactive carriers is not clear due to the fluctuating course of HBeAg-negative CHB.\textsuperscript{164} A population-based cohort study revealed increased risks of liver cirrhosis and HCC when the serum HBV DNA level exceeds 2,000 IU/mL.\textsuperscript{57,59,165} therefore this level is widely accepted as the cut-off for indicating antiviral therapy.

Serum ALT has been used as a convenient surrogate marker for liver injury, and elevated serum ALT is indicated as a risk factor for disease progression in CHB.\textsuperscript{57} A serum ALT level > 2 ULN was suggested as a suitable indication of antiviral treatment for CHB by early guidelines, especially in CHB patients without cirrhosis.\textsuperscript{162,161,166} However, an increased risk of developing liver cirrhosis and HCC has been documented in patients with mildly elevated serum ALT and even in those with serum ALT levels in the upper normal range.\textsuperscript{159,171,167} About two-thirds of CHB patients with mildly elevated ALT (1–2 ULN) show significant hepatic fibrosis (F2 or higher),\textsuperscript{168} and CHB patients with persistently normal ALT levels and HBV DNA levels of >20,000 IU/mL may actually have significant fibrosis or inflammation,\textsuperscript{125,168,169} 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 0.5–1 ULN and 1–2 ULN than for those <0.5 ULN. Thus, previous ALT criteria might exclude some patients with existing or potentially significant disease.\textsuperscript{170,171}

Liver biopsy has three major roles: diagnosis, assessment of prognosis (disease staging), and assistance in making therapeutic decisions.\textsuperscript{172} In CHB, liver biopsy is especially useful for patients who do not meet definite criteria for treatment but still have a possible risk of significant disease.\textsuperscript{35} Age of the patient, serum HBV DNA level, serum ALT level, and family history of HCC should be considered before deciding whether to perform a biopsy. ALT and HBV DNA levels may miss cases of histologically significant disease,\textsuperscript{169} and so histologic confirmation should be considered, especially in patients of advanced age with serum AST/ALT levels in the upper normal range or higher.

Peginterferon-α and NAs 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 effectiveness, safety, risk of resistance, and cost of drugs, preference of patients and physicians, and any plans for pregnancy.\textsuperscript{35}

Lamivudine and telbivudine are not preferred due to their weak antiviral potency and high frequency of drug resistance, unless a good response is predicted or the 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 the efficacy and safety of clevudine. Entecavir and tenofovir are safe agents with potent antiviral effects and low frequency of drug resistance. Due to convenience of usage, peginterferon-α is preferred over interferon-α. 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 NAs might be used in patients with good predictors of response, and can be continued or modified according to on-treatment response.

In patients treated with lamivudine, the predictive factors for a good response to therapy are increased initial serum ALT level and high histologic activity index score. During telbivudine treatment, a combination of pretreatment characteristics (low HBV DNA level; HBV DNA < 10⁷ copies/mL (HBeAg positive CHB) or HBV DNA < 10⁶ copies/mL (HBeAg negative CHB) and ALT level ≥ 2 ULN ) plus non-detectable serum HBV DNA at treatment week 24 is suggested to be the strongest predictor of optimal outcomes at 2 years. Of CHB patients receiving lamivudine or telbivudine treatment, those with a virologic response at week 24 (< 300 copies/mL) achieved a high rate of HBeAg seroconversion at week 52. Less resistance was reported in patients with low serum HBV DNA levels (< 1,000 copies/mL) at week 48 during long-term therapy with adefovir.

**[Recommendations]**

**HBeAg-positive CHB**

1. HBeAg positive CHB patients with HBV DNA ≥ 20,000 IU/mL, plus serum AST or ALT ≥ 2 ULN or significant histologic changes such as inflammation or fibrosis (≥ moderate necroinflammation; ≥ perportal fibrosis) on biopsy should be considered for treatment. (A1) Treatment can be delayed for 3–6 months if spontaneous HBeAg seroconversion is expected. (B2) However, patients with apparent or anticipated liver failure (i.e., those with jaundice, prolonged PT, hepatic encephalopathy, and ascites) should be treated promptly. (B1)

2. For those with HBV DNA ≥ 20,000 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 histologic changes such as inflammation or fibrosis on biopsy. (A1)

3. Monotherapy with tenofovir, entecavir, or peginterferon-α is preferred. (A1)

**HBeAg-negative CHB**

1. HBeAg negative CHB patients with HBV DNA ≥ 2,000 IU/mL plus serum AST or ALT ≥ 2 ULN or significant pathologic changes such as 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 pathologic changes such as inflammation or fibrosis on biopsy. (A1)

3. Monotherapy with tenofovir, entecavir, or peginterferon-α is preferred. (A1)

**Compensated liver cirrhosis**

Liver biopsy has been considered the gold standard for diagnosis of liver cirrhosis. Whereas use of liver biopsy is limited in real clinical practice; imaging studies such as CT, abdominal ultrasound, and MRI are helpful for the diagnosis of liver cirrhosis. Typical image findings of liver cirrhosis include nodular liver surface, splenomegaly, and the presence of intra-abdominal collateral vessels, which indicate increased portal venous pressure. If esophageal or gastric varices is observed in upper gastrointestinal endoscopy, liver cirrhosis can be diagnosed. With imaging studies, laboratory findings such as albumin, bilirubin, or prothrombin time and platelet values are helpful for the diagnosis of liver cirrhosis.

Patients with compensated cirrhosis and elevated serum HBV DNA (HBV DNA ≥ 2,000 IU/mL) can benefit from treatment with long-term oral NAs, because such treatment may prevent disease progression and the development of HCC. Compensated cirrhosis patients with a low viral load, although HBV DNA < 2,000 IU/mL, are at considerable risk for HCC, and antiviral treatment in these patients was suggested to reduce the risk of HCC. Antiviral therapy is recommended in CH-B patients with significant hepatic fibrosis regardless of AST/ALT levels. 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 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. Interferon-α treatment in cirrhotic patients requires careful monitoring because it may cause acute exacerbation of hepatitis, which leads to hepatic failure. 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 copies/mL) was superior in those with cirrhosis than in those without cirrhosis (35% vs. 14%, respectively). However, acute exacerbation of hepatitis (33% vs. 12%, respectively) and requirement for dose reduction (63% vs. 30%) were more common in cirrhotic patients than in noncirrhotic patients. Therefore, interferon-α can be used with caution in cirrhotic patients with preserved liver function.

In patients with decompensated liver cirrhosis, long-term lamivudine treatment significantly reduced the complications and hepatocellular carcinoma compared to placebo. However, the benefit was less in patients with lamivudine resistance. Entecavir treatment of patients with advanced hepatic fibrosis or cirrhosis for 48 weeks showed improvements in the liver histology in 57%, 59%, and 43% of patients with HBsAg-positive, HBsAg-negative, and lamivudine-resistant CHB, respectively. 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 HBV DNA was undetectable after 48 weeks of telbivudine treatment in 92.5%. 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 lamivudine-resistant CHB, respectively. 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 HBV DNA was undetectable after 48 weeks of telbivudine treatment in 92.5%. 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). A phase III clinical trial of tenofovir adopting paired liver biopsy at baseline and at week 240 revealed that, of the 96 (28%) patients with liver cirrhosis (Ishak score 5 or 6) at baseline, 71 (74%) no longer had liver cirrhosis ≥1 unit decrease in score at follow-up biopsy.

Since long-term antiviral therapy is generally required in patients with liver cirrhosis, the AASLD and EASL guidelines recommend the use of entecavir or tenofovir due to their potent antiviral efficacy and high genetic barrier to drug resistance.

Decompensated liver cirrhosis

Decompensated liver cirrhosis is defined as liver cirrhosis complicated with ascites, variceal bleeding, hepatic encephalopathy, or jaundice. Patients with decompensated liver cirrhosis should be treated at an institution that can provide appropriate management for complications of liver cirrhosis. Liver transplantation should be considered in patients with decompensated liver cirrhosis. Oral NAs may improve hepatic function and decrease the need for liver transplantation in Child-Turcotte-Pugh (CTP) class C cirrhosis. The use of interferon-α in patients with decompensated liver cirrhosis is contraindicated due to the risk of serious complications, such as infection or hepatic failure. 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. A study comparing the effects of telbivudine and lamivudine in patients with decompensated liver cirrhosis found a higher rate of HBV DNA undetectability (47% vs. 36%, respectively) and a lower viral breakthrough rate (29% vs. 39%, respectively) in the telbivudine group than in the lamivudine group. A study of 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.

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%). Entecavir therapy showed improvement of the CTP score (to ≥2) in almost half (27/55) of treatment-naïve patients with decompensated liver cirrhosis (n=55) and a 1-year transplantation-free survival rate of 87.1%.

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 for early withdrawal of drug (6.7%, 4.4%, and 9.1%, respectively) and elevation of serum creatinine (8.9%, 6.7%, and 4.5%) did not differ among the three groups. The rates of HBV DNA undetectability 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%, respectively. Because prompt treatment is required in patients with decompensated liver cirrhosis, oral antiviral therapy is the treatment of choice if HBV DNA is detectable by PCR tests. An antiviral drug with a potent antiviral efficacy and high genetic barrier to drug resistance should be used. Since clinical improvement often requires 3–6 months of antiviral therapy, progression to hepatic failure is possible even during antiviral therapy in some patients. Hence, liver transplantation should be considered together with
antiviral treatment. Pre- and post-transplantation antiviral therapy has been reported to reduce the risk of reactivation of hepatitis after liver transplantation.

[Recommendations]

Compensated liver cirrhosis
1. Antiviral therapy should be performed if HBV DNA level is ≥2,000 IU/mL regardless of AST/ALT levels. (A1)
2. Antiviral therapy can be considered when HBV DNA is <2,000 IU/mL to reduce the risk of decompensation regardless of AST/ALT levels. (C1)
3. Oral antiviral therapy is recommended. Monotherapy with tenofovir or entecavir is preferred. (A1)
4. Peginterferon-α may be used with careful monitoring of impairment of liver function and drug side effects in patients with compensated liver cirrhosis with preserved liver function. (A1)

Decompensated liver cirrhosis
1. Prompt antiviral therapy is recommended if HBV DNA is detectable by PCR test regardless of AST/ALT levels. (B1)
2. Oral antiviral therapy is recommended. Monotherapy with tenofovir or entecavir is preferred. (A1)
3. The use of peginterferon-α is contraindicated due to the risk of serious complications, such as hepatic failure. (A1)
4. Liver transplantation should be considered. (B1)

TREATMENT MONITORING

Monitoring prior to antiviral treatment

After diagnosis and 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. The HBV genotype test is not recommended in Korea because most Korean patients are known to have HBV genotype C.

Applying a quantitative HBsAg (qHBsAg) assay before or during antiviral treatment may assist prediction of the treatment response. HBsAg quantity is highest during the immune-tolerant phase (4.5–5.0 log_{10} IU/mL), starts to decrease during the immune-active phase (3.0–4.5 log_{10} IU/mL), and decreases gradually after HBeAg seroconversion. The HBsAg quantity is lowest in the immune-control phase (1.5–3.0 log_{10} IU/mL), and starts to increase in HBeAg-negative CHB (2.5–4.0 log_{10} IU/mL). During long-term lamivudine treatment, a low level before treatment and large decrement during treatment of qHBsAg were predictors of HBsAg seroconversion. Several studies reported that the decrement of qHBsAg correlated with the decrement of HBV DNA level.

[Recommendations]

1. Chronic hepatitis (HBeAg positive or negative)
1) 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, plus HBeAg status (HBeAg and anti-HBe) should be checked every 6–12 months. (C1)
2) 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 plus HBeAg status should be checked every 2–6 months. (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 plus HBeAg status should be checked every 2–6 months. (C1)

3. Decompensated liver cirrhosis
Liver function should be tested every 1–3 months, and serum HBV DNA should be measured by real-time PCR plus HBeAg status should be checked every 2–6 months. (C1)

Monitoring during antiviral treatment

1. NAs
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 NA 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 few 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 detect treatment failure.
Peginterferon therapy resulted in a more significant reduction in qHBsAg levels than NA therapy.\textsuperscript{211,212} However, a low pretreatment qHBsAg level and greater qHBsAg decline were reported to be positive predictors of a sustained virologic response.\textsuperscript{213,214} In CHB patients receiving 10 years of NA therapy, low baseline qHBsAg levels (<1,000 IU/mL) and a greater rate of HBsAg reduction (>0.166 log\textsubscript{10} IU/mL/year) were predictive of qHBsAg seroclearance, strengthening the prognostic role of HBsAg measurements during NA therapy.\textsuperscript{213} Compliance and antiviral-resistance mutations should be monitored in patients who develop virologic breakthrough while receiving NA, and an appropriate rescue therapy should be initiated if necessary.\textsuperscript{215-219}

Most NAs are excreted through the kidney, and hence dose adjustment is required in patients with renal insufficiency (Table 4).\textsuperscript{35}

\begin{table}[h]
\centering
\caption{Nucleos(t)ide analogue dosage adjustment for adult patients with altered creatinine clearance.}\label{tab:4}
\begin{tabular}{l|l|l}
\hline
\textbf{Creatinine clearance (mL/min)} & \textbf{Recommended dose} & \\
\hline
\hline
\textbf{Nucleoside analogues} & & \\
\hline
\textbf{Lamivudine} & & \\
\textgreater{}=50 & 100 mg q 24 h & \\
30-49 & 100 mg first dose, then 50 mg q 24 h & \\
15-29 & 100 mg first dose, then 25 mg q 24 h & \\
5-14 & 35 mg first dose, then 15 mg q 24 h & \\
<5 & 35 mg first dose, then 10 mg q 24 h & \\
\textbf{Telbivudine} & & \\
\textgreater{}=50 & 600 mg q 24 h & \\
30-49 & 600 mg q 48 h & \\
<30 (not requiring dialysis) & 600 mg q 72 h & \\
\textbf{Entecavir} & & \\
\textgreater{}=50 & 0.5 mg q 24 h & 1 mg q 24 h \\
30-49 & 0.25 mg q 24 h or 0.5 mg q 48 h & 0.5 mg q 24 h or 1 mg q 48 h & \\
10-29 & 0.15 mg q 24 h or 0.5 mg q 72 h & 0.3 mg q 24 h or 1 mg q 72 h & \\
<10 or hemodialysis\textsuperscript{b} or continuous ambulatory peritoneal dialysis & 0.05 mg q 24 h or 0.5 mg q 7 days & 0.1 mg q 24 h or 1 mg q 7 days & \\
\hline
\textbf{Nucleotide analogues} & & \\
\textbf{Adefovir} & & \\
\textgreater{}=50 & 10 mg q 24 h & \\
20-49 & 10 mg q 48 h & \\
10-19 & 10 mg q 72 h & \\
<10 & No recommendation & \\
\textbf{Hemodialysis}\textsuperscript{b} & & \\
& 10 mg q 7 days following dialysis & \\
\textbf{Tenofovir} & & \\
\textgreater{}= 50 & 300 mg q 24 h & \\
30-49 & 300 mg q 48 h & \\
10-29 & 300 mg q 72-96 h & \\
<10 with dialysis\textsuperscript{c} & 300 mg q 7 days or after a total of approximately 12 h of dialysis & \\
<10 without dialysis & No recommendation & \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} Calculated using ideal (lean) body weight.

\textsuperscript{b} Administer after hemodialysis.

\textsuperscript{c} Generally once weekly assuming three hemodialysis sessions per week of approximately 4 h duration. Administer following completion of dialysis.
and regular monitoring of renal function should be performed in patients receiving adefovir or tenofovir. Several reports have associated tenofovir with bone loss in patients with HIV, although there was no consistent report during tenofovir monotherapy.\textsuperscript{220-222}

Studies of entecavir-related carcinogenicity are in progress. There have been few reports on telbivudine-related myositis; however, monitoring of the serum creatine kinase (CK) level is recommended due to the possibility of CK elevation.\textsuperscript{223-226} For clevudine prescription, CK level and related symptoms should be monitored due to clevudine-related myositis and CK elevation.\textsuperscript{223,229}

\textbf{2. Peginterferon-}\textsubscript{\textalpha{}}

The serum CBC and ALT level of patients receiving peginterferon-\textsubscript{\textalpha{}} should be tested monthly. Serum HBV DNA should be measured after 3–6 months of treatment to verify the primary response. For response prediction, qHBsAg assay can be used before the treatment and at 12 and 24 weeks of treatment. All patients treated with peginterferon-\textsubscript{\textalpha{}} should be checked for the known adverse effects of interferon at every visit.

\textbf{HBeAg-positive CHB}

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. There is a high probability of HBsAg loss if serum HBV DNA becomes undetectable during treatment. HBeAg-positive patients who achieve HBeAg seroconversion with peginterferon-\textsubscript{\textalpha{}} 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. The qHBsAg assay assists in predicting the treatment response.\textsuperscript{220,221} In case of a primary non-response (failure to achieve a 1 log\textsubscript{10} reduction in serum HBV DNA from baseline after 3 months of peginterferon-\textsubscript{\textalpha{}} treatment), peginterferon-\textsubscript{\textalpha{}} treatment should be stopped and replaced by a NA. Several studies recommend that peginterferon-\textsubscript{\textalpha{}} treatment should be stopped if qHBsAg does not decrease below 20,000 IU/mL after 24 weeks of treatment, which is predictive of non-response.\textsuperscript{220,221}

\textbf{HBeAg-negative CHB}

HBeAg-negative patients should be monitored similarly to HBeAg-positive patients during 48 weeks of treatment. A virologic response with a serum HBV DNA level of <2,000 IU/mL is generally associated with remission of the liver disease.\textsuperscript{221} 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. qHBsAg levels after 12 and 24 weeks of treatment as well as serum HBV DNA levels can be major predictive factors of a treatment response.\textsuperscript{220,223,229} Several studies recommend treatment interruption when qHBsAg after 12 weeks of treatment does not decrease, together with a < 2 log\textsubscript{10} serum HBV DNA level.\textsuperscript{234,235}

\textbf{[Recommendations]}

1. During treatment with NAs, liver function should be tested and serum HBV DNA should be measured by real-time PCR every 1–3 months, plus HBeAg status (HBeAg and anti-HBe) should be checked every 3–6 months. (C1) qHBsAg assay may assist prediction of the treatment response and identification of cases in which discontinuation of antiviral therapy may be attempted. (C1)

2. During treatment with peginterferon-\textsubscript{\textalpha{}}, CBC and ALT level should be measured monthly. Serum HBV DNA should be measured by real-time PCR at 1- to 3-month intervals, plus HBeAg and anti-HBe should be checked at 6 and 12 months during the treatment and at 6 months post-treatment. (C1) qHBsAg assay should be performed before, at 12 and 24 weeks during the treatment and at the end of treatment. (B1)

3. After identification of a complete virologic response, serum HBV DNA should be measured by real-time PCR after 3–6 months and then retesting should be performed at 2–3 months after HBeAg seroclearance is achieved. (C1)

4. Patients who develop virologic breakthrough while receiving a NA should be monitored for compliance and antiviral-resistance mutations. (A1)

5. During antiviral therapy, close monitoring for side effects of each drug is mandatory. (A1)

\textbf{Monitoring after antiviral treatment}

The response to antiviral treatment persists in some patients, while others relapse. Non-responders 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.
1. During the first year after the cessation of antiviral treatment, liver function should be monitored and serum HBV DNA should be measured by real-time PCR every 1–3 months, plus HBeAg and anti-HBe should be checked at 3–6-month intervals. Beyond 1 year after the cessation of antiviral treatment, liver function and serum HBV DNA by real-time PCR should be tested every 3–6 months to detect viral relapse. (C1)

2. For early detection of HCC, ultrasound and serum α-fetoprotein measurement should be performed regularly. (A1)

**CESSATION OF TREATMENT**

**HBeAg-positive CHB**

Although the ideal goal of treatment is to achieve HBsAg loss, 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. NA can be stopped when HBeAg seroconversion is achieved and antiviral treatment has been maintained at least for 12 months. However, cessation should be decided carefully since 40–90% of patients developed reactivation of HBeAg-positive or -negative hepatitis after HBeAg seroconversion induced by NA treatment. HBsAg should be tested at 6-month intervals after HBeAg seroconversion. HBsAg loss is rarely observed after NA therapy; however, low baseline qHBsAg levels and greater rate of HBsAg reduction were highly predictive of HBsAg seroclearance. Peginterferon-α is generally administered for 48 weeks, and its efficacy was confirmed in a recent double-blind, randomized controlled study.

**HBeAg-negative CHB**

The recommended duration of peginterferon-α treatment in patients with HBeAg-negative hepatitis is 48 weeks, but the optimal treatment duration for NA is unknown, and cessation of treatment should be individually decided according to the clinical treatment response and the baseline severity of the liver disease. Treatment with NA should be continued until the loss of HBsAg.

**LIVER CIRRHOSIS**

**DEFINITIONS OF RESPONSE AND PREDICTORS OF RESPONSE**

Definitions of treatment responses (Table 5)

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

1. NA

A primary non-response to NA 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. A 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 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 in serum that confers resistance to the antiviral agent, and phenotypic resistance is defined as the presence of HBV mutations that decrease susceptibility to antiviral drugs in an in vitro test. Cross-resistance is defined as an HBV mutation induced by one antiviral agent that confers resistance to other antiviral agents.

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

2. 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 chronic hepatitis B.

Predictors of treatment responses

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

1. NAs

Pretreatment factors predictive of HBeAg seroconversion are a low viral load (serum HBV DNA of <10\(^7\) IU/mL), high ALT level (<3 ULN), and high inflammatory activity score in a liver biopsy (at least A2)\(^{247}\). A high pretreatment ALT level is the most important

Table 5. Definitions of responses to antiviral therapy of CHB patients

| Category of response                  | Primary non-response | Partial virologic response | Complete virologic response | Virologic breakthrough | Biochemical breakthrough | Genotypic resistance | Phenotypic resistance | Cross resistance | Peginterferon alpha |
|---------------------------------------|----------------------|---------------------------|----------------------------|------------------------|-------------------------|----------------------|----------------------|-------------------|---------------------|
| Nucleos(t)ide analogues               | Decrease in serum HBV DNA <2 log\(_{10}\) IU/mL after 6 months of therapy | Decrease in serum HBV DNA of more than 2 log\(_{10}\) IU/mL but detectable HBV DNA by real-time PCR assay | Increase in serum HBV DNA of more than 1 log\(_{10}\) IU/mL compared to nadir (lowest value) | Increase in serum ALT level after ALT normalization on antiviral therapy | Detection of HBV mutations known to confer antiviral resistance during antiviral therapy | Decreased susceptibility (in vitro testing) to inhibition by antiviral drugs associated with genotypic resistance | HBV mutation selected by one antiviral agent that also confers resistance to other antiviral agents | Decrease in serum HBV DNA <1 log\(_{10}\) IU/mL after 3 months of peginterferon alpha therapy | Decrease in serum HBV DNA of less than 2,000 IU/mL after 6 months of peginterferon alpha therapy | HBeAg seroconversion in patients with HBeAg-positive chronic hepatitis B |
predictor of the outcome of treatment with lamivudine, adefovir, or telbivudine.\textsuperscript{118} 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.\textsuperscript{116,225,248} HBV genotype does not influence the response to any NA. In a study of the ability of qHBsAg assay to predict a treatment response, both HBsAg ≤ 2 log IU/mL and reduction by >1 log from baseline at the end of treatment had a 78% positive predictive value and 96% negative predictive value for a 12-month sustained post-treatment response (HBV DNA ≤ 200 IU/mL) to lamivudine in HBeAg-negative patients.\textsuperscript{248} During telbivudine treatment, a decline in serum HBsAg levels (≥ 1 log\textsubscript{10} IU/mL) in the first year was related to a greater likelihood of achieving HBsAg clearance at year 3.\textsuperscript{202} Serum HBsAg levels ≤ 2 log IU/mL at treatment week 104 are highly predictive of sustained virologic response to telbivudine at 2 years off-treatment.\textsuperscript{250}

2. 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 genotype.\textsuperscript{183,251} There is no consensus among previous reports for patients with HBsAg-negative hepatitis, but generally a pretreatment high ALT level, young age, and female gender are reported to be associated with a favorable treatment response.\textsuperscript{124,252} A decrease in serum HBV DNA to less than 20,000 IU/mL after 12 weeks of treatment is associated with a 50% probability of HBeAg seroconversion in HBeAg-positive patients and with a 50% probability of a sustained response in HBeAg-negative patients.\textsuperscript{124,252} A decrease in HBeAg at week 24 may predict HBeAg seroconversion.\textsuperscript{118,253} In HBeAg-positive patients, HBsAg levels <1,500 IU/mL at week 12 during peginterferon alfa-2a therapy were associated with high rates of posttreatment response, but treatment discontinuation is indicated in all patients with HBsAg >20,000 IU/mL at week 24.\textsuperscript{230,231} In HBeAg-negative patients, at week 12 of peginterferon-α treatment, the combination of a decline in serum HBV DNA < 2 log\textsubscript{10} copies/mL and absence of a decrease in HBsAg levels is predictive of a poor response.\textsuperscript{234,235} HBV genotypes A and B are associated with a better response to interferon-α than genotype C, in terms of HBeAg seroconversion and HBsAg loss.\textsuperscript{254,257} However, knowledge of the HBV genotype has a poor predictive value in individual cases, and currently genotype alone should not determine the choice of treatment.

**ANTIVIRAL RESISTANCE**

Both entecavir and tenofovir are highly potent antivirals with an excellent resistance profile, and to which antiviral resistance develops rarely. Nonetheless, 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 resumption of active viral replication that had been suppressed after the initiation of antiviral therapy, and can impair biochemical or histologic improvement.\textsuperscript{254} Therefore, the prevention, early diagnosis, and management of antiviral resistance may significantly affect the long-term prognosis of CHB patients undergoing antiviral therapy.\textsuperscript{141}

**Mechanism of antiviral resistance and definitions**

It is estimated that more than 10\textsuperscript{11} new virions are produced daily in a human body with active HBV replication.\textsuperscript{259} Some of the HBV mutants that emerge naturally during active replication are selected by the selection pressure exerted by the human immune system or antiviral therapy. Those mutants with maximal replication become predominant during antiviral therapy. Primary antiviral-resistant mutants usually have a low replication capacity, but recover to the level of the wild-type virus when compensatory mutations appear.\textsuperscript{260} 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.\textsuperscript{262} 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 suppression 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.\textsuperscript{262} 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 of terms associated with antiviral resistance are provided in Table 5.

**Mutations conferring resistance to antiviral agents**

Antiviral agents for the treatment of HBV infection are classified
into two groups: NAs and nucleotide analogues. Cyclopentenes (entecavir) and L-nucleoside analogues (lamivudine, telbivudine, and clevudine) are NAs, while acyclic phosphonates (adefovir and tenofovir) are nucleotide analogues.

263 The incidences of resistance to individual antiviral drugs are shown in Table 6.

1. Nucleoside analogues

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

Mutations at rtM204 are the primary resistance mutations to lamivudine, telbivudine, and clevudine.264,265 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 termed YMDD mutations, but that terminology is no longer recommended.266 rtM204V emerges during lamivudine treatment, but rtM204I can develop during the administration of lamivudine, telbivudine, or clevudine.255,225,226,269,270

An rtM204V mutant may commonly accompany rtL180M but not rtM204I.271 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.272 The mutants exhibit cross-resistance to adefovir but remain sensitive to entecavir.272

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 rtT184E/L/F/A/M/S/I/C/G, rtS202G/I/C, or rtM250V/I/L develop as primary resistance mutations to entecavir, resulting in a marked decrease in drug susceptibility.261,271 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.274

Table 6. Cumulative incidences of development of antiviral resistance according to representative studies.

| Antiviral agent | Resistance rate (%) |
|-----------------|---------------------|
|                 | Year 1  | Year 2  | Year 3  | Year 4  | Year 5  | Year 6  | Year 7  | Year 8  |
| Lamivudine†     | 24     | 42     | 53     | 70     | ≥65    |         |         |         |
| Adefovir        |         |         |         |         |        |         |         |         |
| in treatment-naïve patients‡   | 0      | 3      | 11     | 18     | 29     |         |         |         |
| in lamivudine-resistant patients† | 4.4-18 | 18.4-25 | 34.3   | 52.3   | 65.6   |         |         |         |
| Adefovir + lamivudine |         |         |         |         |        |         |         |         |
| in lamivudine-resistant patients‡ | 1      | 2      | 4      | 4      |         |         |         |         |
| Entecavir       |         |         |         |         |        |         |         |         |
| in treatment-naïve patients‡   | 0.2    | 0.5    | 1.2    | 1.2    | 1.2    | 1.2     |         |         |
| in lamivudine-refractory patients† | 6      | 15     | 36     | 47     | 51     |         |         |         |
| Tenofovir†      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       |
| Telbivudine†    | 2.7-4.4| 10.8-25.1|         |         |         |         |         |         |
| Clevudine†      | 2.3    | 2.4    |         |         |         |         |         |         |

HBeAg-negative patients.
†Emtricitabine was added in patients with detectable HBV DNA after 72 weeks of treatment.
‡Modified and updated from Lai et al. Clin Infect Dis 2003265 and Lok et al. Gastroenterology 2003.266
¶From Hadziyannis et al. Gastroenterology 2006.267
From Lee et al. Hepatology 2006268, Yeon et al. Gut 2006269, and Lee et al. Antivir Ther 2010.270
From Lampertico et al. Gastroenterology 2007.271
From Tenney et al. Hepatology 2009.272
From Lampertico P et al. J Hepatol 2015.273
From Lai et al. N Engl J Med 2007274 and Liaw et al. Gastroenterology 2009.275
From Yoon et al. J Clin Gastroenterol 2011.276
2. Nucleotide analogues

1) Adefovir
   rtN236T and rtA181V/T are the primary resistance mutations to adefovir.\textsuperscript{157,275} The levels of resistance of rtN236T and rtA181T to adefovir are 7- to 10-fold and 2.5- to 5-fold, respectively, compared to the wild-type virus.\textsuperscript{263,272} rtA181T can be detected in subjects receiving lamivudine monotherapy or combination therapy comprising adefovir plus lamivudine.\textsuperscript{276,277}

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 10-fold in the presence of rtL180M+rtM204V, according to a case study of a patient with HBV and HIV coinfection.\textsuperscript{278}

Management of antiviral resistance

Prior antiviral resistance predisposes individuals to subsequent viral mutations and limits the choice of rescue therapies due to the presence of cross-resistance.\textsuperscript{263,279} Although antiviral agents without cross-resistance may be selected, the resistance to the rescue therapy is greater than that of treatment-naïve subjects.\textsuperscript{279-281} It is therefore critical to initially choose the antiviral agent with the lowest resistance rate. Appropriate monitoring during treatment is needed to detect virologic and biochemical breakthroughs as early as possible. Antiviral resistance testing is required 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 situation deteriorates.\textsuperscript{282}

[Recommendations]

General principles of antiviral resistance management:

1. An antiviral resistance test should be performed when virologic breakthrough occurs, especially in cases with good compliance. (A1)

2. Rescue antiviral therapy should be started as soon as possible upon emergence of resistant variants, especially when viral breakthrough is detected and genotypic resistance is confirmed. (A1)

MANAGEMENT OF ANTIVIRAL-RESISTANT CHB

Management of lamivudine resistance

1. Tenofovir
   Tenofovir shows potent antiviral activity against lamivudine-resistant HBV.\textsuperscript{284-287} In a retrospective study that compared a tenofovir monotherapy group with a tenofovir-plus-lamivudine combination-therapy group for 197 patients (105 naïve patients and 92 patients resistant to lamivudine), the HBV undetectable rate (HBV DNA <20 IU/mL) was not different significantly in the HBeAg-negative group (94% vs. 96%, respectively) and HBeAg-positive group (67% vs. 83%, respectively).\textsuperscript{285} One comparative study involving lamivudine-resistant CHB patients coinfected with HIV found that the HBV DNA level after 48 weeks was <10\textsuperscript{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.\textsuperscript{284} In a study that compared a tenofovir monotherapy group with a tenofovir-plus-emtricitabine combination-therapy group including 280 patients with lamivudine-resistant HBV, the HBV undetectable rate (69 IU/mL) was not significantly different (85.8% vs. 83.5%, respectively) and tenofovir-resistant HBV was not detected in either group after 96 weeks.\textsuperscript{287} No prospective study has compared tenofovir monotherapy with tenofovir-plus-lamivudine combination-therapy. However, in a retrospective study that compared a tenofovir monotherapy group (n=71) with a tenofovir-plus-lamivudine combination-therapy group (n=54) among 125 patients with a history of antiviral treatment, the cumulative HBV undetectable rate (<20 IU/mL) differed significantly after 3 years (90.7% vs. 96.0%, respectively).\textsuperscript{286}

2. Adefovir
   Adefovir has shown antiviral activity against lamivudine-resistant HBV. The development of resistance to adefovir was significantly less frequent in the adefovir-plus-lamivudine combination-therapy group than in the adefovir-monotherapy group in long-term studies.\textsuperscript{288,289} No comparative study of tenofovir monotherapy and adefovir plus NA combination therapy has been performed. However, combination therapy with lamivudine plus adefovir results in a higher adefovir resistance rate (2.2-13.3%) compared to tenofovir (0%).\textsuperscript{290-293} Few studies of combination therapy with adefovir plus other NAs such as entecavir, telbivudine, and clevudine instead of lamivudine are available; moreover, the studies reported to date have involved small populations. One retrospective study
involving 91 lamivudine-resistant CHB patients consisted of adefovir monotherapy (n=29), adefovir and lamivudine combination therapy (n=30), adefovir and entecavir 1 mg combination therapy (n=32) found that the HBV DNA undetectable rate (<60 IU/mL) was not significantly different (48.2% vs. 76.7% vs. 87.5%, respectively) but the adefovir resistance rate differed significantly (27.6% vs. 13.3% vs. 0%, respectively) after 24 months. In a small prospective study that compared an adefovir-plus-telbivudine combination-therapy group (n=21) with an adefovir-monotherapy group (n=21), the HBV undetectable rate (<300 copies/mL) was 38.5% and 0%, respectively, and adefovir resistant virus was detected in 9.6% of patients in the adefovir-monotherapy group after 96 weeks. Two small prospective studies revealed that the reduction in HBV load was greater in the adefovir-plus-telbivudine combination-therapy group than the adefovir-plus-lamivudine combination-therapy group.

3. Entecavir
Entecavir at a dose of 1.0 mg exhibits antiviral activity in lamivudine-resistant CHB patients. In a study of monotherapy with 1.0 mg entecavir compared with adefovir-plus-lamivudine combination therapy in patients with lamivudine resistance, monotherapy showed a significantly higher viral breakthrough rate (17.6% vs. 2.0%) but comparable antiviral efficacy. Two retrospective studies of combination treatment with adefovir and entecavir 1 mg in patients with lamivudine resistance revealed a significantly lower viral breakthrough rate (0-2.6%) than adefovir combination therapy with another NA or entecavir 1 mg monotherapy.

4. Peginterferon alpha
In a study that compared a group receiving peginterferon alpha group for 48 weeks (n=155) with a group receiving adefovir for 72 weeks (n=80) among patients with compensated liver disease, the HBV DNA undetectable rate (<80 IU/mL) was lower (10.6% vs. 22.5%), but the HBeAg seroconversion rate was higher (14.8% vs. 3.8%) significantly in the peginterferon alpha group. There was no significant difference in the HBeAg seroconversion rate and HBV undetectable rate in another study that compared the efficacy of peginterferon alpha between patients with wild-type virus and lamivudine-resistant virus.

[Recommendations]
1. Switch to tenofovir or combine tenofovir with a nucleoside analogue. (A1)
2. Consider combination of adefovir and a nucleoside analogue if use of tenofovir is contraindicated. (B1)
3. Stop lamivudine and consider treatment with peginterferon-α if the patient has compensated liver function. (B2)

Management of telbivudine resistance
Few data related to telbivudine resistance are available. In a study in which telbivudine-resistant patients or viral breakthrough patients without resistance (n=68) were treated with adefovir, over 70% of patients had an HBV level of ≤300 copies/mL after 12 months. Treatment based on tenofovir could be a therapeutic option, but comparative data for telbivudine and lamivudine are insufficient. The general principles of management of telbivudine resistance are similar to those for the management of lamivudine resistance.

[Recommendation]
1. Follow the recommendations for the management of lamivudine-resistant CHB. (B2)

Management of clevudine resistance
Few data related to clevudine resistance are extant. The general principles of treatment of patients with clevudine resistance are similar to those of lamivudine resistance.

[Recommendation]
1. Follow the recommendations for the management of lamivudine-resistant CHB. (B2)

Management of adefovir resistance
The HBV mutations rtN236T and rtA181V/T result in primary resistance to adefovir. rtA181T can also be detected in subjects receiving lamivudine monotherapy or combination therapy of adefovir plus lamivudine. The double mutation (rtA181T/V and rtN236T) results in a 5.2- to 18-fold reduction in sensitivity to adefovir. Patients with persistent drug-resistant HBV viremia are more likely to suffer hepatitis flares, disease progression, and death than those without drug-resistant HBV.
The rate of adefovir-resistance is 20% and 29% after 5 years of adefovir treatment in HBeAg-positive and HBeAg-negative treatment naïve patients, respectively. The risk of genotypic resistance to adefovir increases in patients resistant to lamivudine compared to treatment-naïve patients. After 48 weeks of adefovir treatment, the rate of resistance was 18% and 0% in lamivudine-resistant and treatment-naïve patients, respectively. Moreover, the rate of adefovir resistance can reach 22-25% after 2 years of treatment in lamivudine-resistant patients.

1. Lamivudine

In vitro studies showed that the rtN236T mutant remained sensitive to lamivudine, while the rtA181T/V mutant exhibited reduced susceptibility to lamivudine.

In adefovir-resistant patients without prior exposure to lamivudine, the combination of telbivudine/ adefovir and monotherapy with entecavir was associated with virologic response rates of 73.3% and 57.1%, respectively, and HBeAg seroconversion rates of only 20% and 0%, respectively.

In patients who developed adefovir resistance in the presence of lamivudine resistance, the combination of lamivudine/ adefovir resulted in a virologic breakthrough rate of 7.3% and primary nonresponse rate of 51.2% at 1 year, and a very low virologic response rate (HBV DNA <60 IU/mL) of 12.2%.

2. Entecavir

In vitro studies have shown that HBV with adefovir-mono-resistant mutations may be susceptible to entecavir. However, HBV with lamivudine-resistance mutations have cross-resistance to entecavir. Thus, in patients resistant to both adefovir and lamivudine, entecavir monotherapy was associated with a suboptimal virologic response (42%) and high rate of additional resistance to entecavir (17%) at 1 year. In these patients, even the combination of entecavir/ adefovir resulted in a very low virologic response rate of 31.1% and 44.7% at 1 and 2 years, respectively.

3. Tenofovir

Tenofovir has about 30-fold higher antiviral efficacy than adefovir. However, in vitro studies show that HBV strains expressing the adefovir resistance-associated substitutions, rtA181T/V and/or rtN236T, demonstrate reduced susceptibility to tenofovir, ranging from 2.9- to 10-fold that of the wild-type virus. Nonetheless, several studies have suggested that tenofovir disoproxil fumarate (TDF) monotherapy is efficacious in patients with lamivudine-resistant, entecavir-resistant, adefovir-refractory, and adefovir-resistant HBV. An European trial comparing TDF and emtricitabine (FTC) plus TDF in patients with adefovir-refractory CHB demonstrated that the rate of virologic response did not differ between TDF and FTC/TDF therapies; 82% vs. 84% at 3.5 years. However, in a subgroup of patients who had double adefovir-resistance mutations; i.e., both rtA181T/V and rtN236T, the decrease in serum HBV DNA levels tended to be less in the TDF group than in the TDF/entecavir group (-3.03 log 10 IU/mL vs. -3.31 log 10 IU/mL, P=0.38).}

[Recommendations]

1. Switch to tenofovir or combine tenofovir with entecavir. (B1)
2. Combination therapy with tenofovir and a nucleoside analogue other than entecavir. (B2)
3. Consider combination of adefovir and a nucleoside analogue if use of tenofovir is contraindicated. (B2)

Management of entecavir resistance

In patients with lamivudine-resistant HBV, the rate of entecavir resistance increases to 51% after 5 years of entecavir treatment, in contrast to a 1.2% resistance rate in NA-naïve patients. The difference is because the entecavir resistance barrier is lowered by the initial selection of the lamivudine-resistance HBV mutation, rtM204V/I. In vitro studies have shown that susceptibility to entecavir is decreased by 10-250-fold when one of the entecavir resistance-associated substitutions at rtT184, rtS202, or rtM204 is present. However, in a subgroup of patients who had double adefovir-resistance mutations; i.e., both rtA181T/V and rtN236T, the decrease in serum HBV DNA levels tended to be less in the TDF group than in the TDF/entecavir group (-3.03 log 10 IU/mL vs. -3.31 log 10 IU/mL, P=0.38).

1. Adefovir

No randomized trial of adefovir treatment in patients with entecavir resistance has been performed. Adding adefovir to entecavir would be more reasonable for reducing adefovir resistance and improving the antiviral efficacy. Combination therapy of adefovir plus lamivudine could also be considered. However, small retrospective cohort studies demonstrated that the virologic re-
response rate was 24-51% at 1 or 2 years of treatment with the combination of adefovir and entecavir or lamivudine.  

2. Tenofovir

Tenofovir does not show cross-resistance to entecavir in vitro and has excellent potency. A Korean multicenter randomized trial was performed in HBV patients with entecavir resistance-associated mutations comparing TDF monotherapy and TDF and entecavir combination therapy for 48 weeks. All patients had at least one entecavir-resistance mutation: rtT184A/C/F/G/I/L/S, rtS202G, and rtM250L/V, in addition to rtM204V/I. At week 48, the proportion of patients with HBV DNA <15 IU/mL, the primary efficacy endpoint, was not significantly different between the TDF and TDF+entecavir groups (71% vs. 73%; P=0.81). Virologic breakthrough occurred in one patient on TDF, which was attributed to poor drug adherence. At week 48, six and three patients in the TDF and TDF+entecavir groups, respectively, retained their baseline resistance mutations (P>0.99). None developed additional resistance mutations. Safety profiles were comparable in the two groups.

[Recommendations]

1. Switch to tenofovir or combine tenofovir with entecavir. (B1)
2. Consider combination of adefovir and a nucleoside analogue if use of tenofovir is contraindicated. (B2)

Management of tenofovir-resistance

No tenofovir-resistant patients have been reported to date. A prospective study found no HBV strain resistant to TDF after up to 8 years of treatment. An in vitro study reported that A194T in combination with lamivudine resistance mutations, rtL180M and rtM204V, might account for TDF resistance in HBV. However, other in vitro studies have reported inconsistent results.

Management of multiple drug resistance

Multidrug resistance is defined as resistance to two or more groups of antiviral drugs; i.e., L-nucleoside (lamivudine, telbivudine, clevudine), cyclopentane (entecavir), or nucleotide analogue (adefovir and tenofovir).

Interferon has not been used for the management of patients with multidrug-resistant HBV. However, there is also no suggestion that such patients have decreased susceptibility to interferon.

In vitro clonal analyses showed that multidrug-resistance mutations usually reside in the same viral genome, and replicating clones with lamivudine- and adefovir- associated mutations had >50-fold reduced susceptibility to combination of lamivudine and adefovir. In fact, a cohort study demonstrated that in patients with HBV resistant to lamivudine and adefovir, combination therapy with these two drugs was not effective and indeed was inferior to entecavir monotherapy in terms of suppressing HBV DNA. However, the response to entecavir monotherapy was not optimal. Entecavir was markedly less effective in patients refractory to both lamivudine and adefovir than in those with lamivudine monoresistance, or treatment-naive patients.

In patients with multidrug-resistant HBV, a combination of the two most potent drugs, TDF and entecavir, would likely prevent the emergence of resistance to TDF. However, two randomized trials in patients with resistance to entecavir and/or adefovir in addition to lamivudine resistance showed no difference in virologic response between TDF monotherapy and TDF and entecavir combination therapy, and no emergence of additional resistance mutations. Based on their comparable antiviral efficacy, extremely low risk of TDF resistance, lower cost, and potentially better safety profile, TDF monotherapy would be a reasonable option for the treatment of entecavir-resistant patients.

[Recommendations]

1. Switch to tenofovir or combine tenofovir with entecavir. (B1)
2. Consider combining adefovir with a nucleoside analogue if use of tenofovir is contraindicated. (B2)

RESPONSE-GUIDED THERAPY DURING ORAL ANTIVIRAL DRUG TREATMENT FOR CHB

Once antiviral-resistant HBV mutants have been selected, they are persistently archived (retained in the virus population) in ccc-DNA in the nucleus of infected cells, even if treatment is stopped, which can limit future therapeutic options. Preventing the development of resistance is important to ensure long-term therapeutic efficacy. Persistence of viral replication during antiviral treatment is associated with the emergence of drug resistance. Therefore, evaluation of the treatment response using sensitive PCR assays to measure serum HBV DNA levels every 3-6 months is recommended. The response patterns of oral antivirals during treatment are
classified as complete response, partial response and primary non-response. Complete response is defined as undetectable serum HBV DNA by PCR during treatment. Partial virologic response is defined as detectable serum HBV DNA with a more than 2 \( \log_{10} \) IU/mL reduction in HBV DNA level from baseline. A primary non-response is defined as a reduction in the serum HBV DNA level of less than 2 \( \log_{10} \) IU/mL at week 24. Virologic breakthrough is defined as an increase in serum HBV DNA level of more than 1 \( \log_{10} \) IU/mL from nadir. Although virologic breakthrough is generally associated with emergence of resistance mutations, up to 30% of the cases of virologic breakthrough in clinical trials are related to medication noncompliance. Therefore, compliance should be checked in all patients with a sub-optimal response.

In patients with a complete virologic response, treatment should be continued until the endpoint is achieved, which should be evaluated by measuring the serum HBV DNA level every 3–6 months. Primary non-response is very rare in oral antiviral therapy, with the exception of adefovir. Therefore, few studies of primary non-response patients have been performed. In patients with primary non-response with good compliance, switching to a drug with a high genetic barrier is indicated if the patient is taking a drug with a low genetic barrier, due to the possibility of imminent resistance. However, a recent study of entecavir for treatment-naïve CHB reported a primary non-response rate of 1.3–1.7%, and all patients achieved a virologic response after continuing entecavir therapy during follow up. Therefore, if the patient is taking a drug with a high genetic barrier, such as entecavir or tenofovir, treatment could either be switched to another high-genetic-barrier drug or be continued using the same high genetic barrier drug with monitoring for virologic response at 3-6-month intervals in patients with primary non-response.

The rate of emergence of lamivudine or telbivudine-resistant HBV was directly proportional to the HBV DNA level after 24 weeks of treatment. 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 \( \log_{10} \) or higher, respectively, after a median follow-up of 29 months. Although few studies on this issue have been conducted, a partial response should be evaluated at 6 months after therapy and switching to a drug with a higher genetic barrier should be considered if lamivudine or telbivudine is used. A prospective study of switching to entecavir 1 mg in patients with a partial response to lamivudine reported a virologic response rate of 67.6% and a resistance rate of 3% at 96 weeks. However, a history of exposure to lamivudine is associated with a high rate of emergence of entecavir resistance during entecavir therapy. Therefore, switching to entecavir should be considered carefully. The response to tenofovir monotherapy was influenced by neither a previous history of lamivudine treatment nor resistance. The incidences of adefovir resistance at 114 weeks of adefovir therapy in patients with an HBV DNA level of less than 1,000 copies/mL, 10^3–10^6 copies/mL or more than 10^6 copies/mL at 48 weeks of adefovir therapy were 4%, 26% and 67%, respectively. A partial virologic response to adefovir should be evaluated at 12 months after adefovir therapy and switching or adding antivirals is recommended for patients with a partial virologic response. Although a prospective controlled study reported that the virologic response rates were 81% and 88% after 12 months of therapy with adding lamivudine or telbivudine in patients with a partial virologic response to adefovir at 48 weeks, these combination therapies have a substantial risk of emergence of resistance during long-term treatment. Switching to entecavir 1.0 mg needs to be done with utmost caution since the incidence of entecavir resistance was as high as 25.7% in patients with adefovir resistance. In a prospective controlled study of treatment-naïve CHB patients, the virologic response rate during adefovir therapy at 48 weeks was 63% but increased to 90% after switching to tenofovir for a further 48 weeks. Tenofovir is an effective alternative for patients with a suboptimal response to adefovir and adefovir resistance mutations, and no report of tenofovir resistance has been published.

Partial virologic response to entecavir and tenofovir (which have a high genetic barrier) should be evaluated at 12 months after therapy due to the high potency and low incidence of resistance. Although some studies suggested that a partial virologic response to entecavir could be defined as a serum HBV DNA level of 1,000 IU/mL or 35 IU/mL at 12 months after therapy, it is generally defined as detectability of HBV DNA by PCR. The incidence of a partial virologic response to entecavir has been reported to be 10% to 28% and that of a virologic response to maintenance entecavir therapy after a partial virologic response have been reported to be 45% to 95%. Although switching therapy to tenofovir in 14 patients with a decline in HBV DNA level of less than 1 \( \log_{10} \) during more than 6 months of entecavir therapy achieved a virologic response in all patients during a mean of 50 weeks of tenofovir therapy, further studies are needed to determine the optimal treatment strategy for patients with a partial virologic response to entecavir. Although a partial virologic response has been found in patients with a high genetic barrier, continuing the antiviral agent, especially in cases with a continuous decrease
in HBV DNA level, could be recommended as the incidence of resistance during long-term treatment is low. However, switching to another high genetic barrier antiviral is another option.

[Recommendation]

1. In patients with a complete virologic response, treatment should be continued until the treatment endpoint is achieved, and monitored by measuring the serum HBV DNA level every 3–6 months. (B1)
2. Drug compliance should be checked thoroughly in patients with a partial virologic response or primary non-response. For patients treated with a drug with a low genetic barrier, treatment should be switched to a drug with a higher genetic barrier. (B1) For patients treated with a drug with a high genetic barrier, treatment could either be switched to another drug with a high genetic barrier or be continued with monitoring for a virologic response at 3-6-months intervals. (C1)
3. In the event of viral breakthrough, rescue therapy should be implemented according to the genotypic resistance profile. (A1)
4. The treatment strategy should follow the recommendations for treating drug-resistant HBV when genotypic resistant mutations are identified. (A1)

TREATMENT OF SPECIAL POPULATIONS

Acute hepatitis B

Acute hepatitis B resolves spontaneously and does not progress to the chronic stage in more than 95% of patients, so antiviral therapy is generally not recommended. Early initiation of antiviral therapy has been reported to interfere with the normal protective immune response and suppresses production of neutralizing antibodies against hepatitis virus, increasing the risk of chronic hepatitis. However, acute hepatitis B infection seldom progresses to serious hepatitis and may lead to hepatic failure. According to a randomized controlled trial in 71 patients with severe acute hepatitis B, HBV DNA levels were significantly lower in the lamivudine-treated group (n=31, 3.7 log_{10} copies/mL) compared with the control group (n=40, 4.2 log_{10} copies/mL) after 4 weeks. However, the rate of HBsAg loss after 12 months was similar in the two groups (93.5% in the lamivudine group and 96.7% in the placebo group). In this study, the rate of development of protective anti-HBs after 1 year was 67.7% in the lamivudine group and 85% in the placebo group; the difference was not significant. A recent, small, prospective, controlled study also reported no significant benefit of lamivudine in severe acute hepatitis B. In contrast, Tillman et al. reported that lamivudine is safe in patients with severe acute or fulminant hepatitis B, leading to rapid recovery with the potential to prevent liver failure and liver transplantation when administered sufficiently early. However, only a few case reports of antiviral agents as treatment for acute hepatitis B other than lamivudine have been published to date.

[Recommendation]

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

Liver transplant patients

In the past, severe liver damage and a low survival rate due to HBV recurrence after liver transplantation in HBV-related liver disorder patients were major problems. However, in an extensive cohort study of 372 patients who received liver transplants in the early 1990s and were positive for HBsAg, the study group treated with HBIG therapy for more than 6 months showed a significantly lower rate of hepatitis B recurrence than the group treated with HBIG therapy for less than 6 months or those who were not treated. The study group also had a higher long-term survival rate than the other groups. 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.

Lamivudine and HBIG combination therapy reduces the rate of HBV recurrence to less than 10% after 1–2 years and is superior to high-dose HBIG therapy with respect to cost and effectiveness. In a meta-analysis of six independent studies, lamivudine and HBIG combination therapy was found to reduce the rates of HBV recurrence and death 12-fold compared with HBIG therapy alone. A meta-analysis of 46 studies in which 2,161 HBV-infected patients received liver transplants found that adeovir and HBIG combination therapy significantly reduced the rate of hepatitis B recurrence to 2% compared to 6% with lamivudine and HBIG combination therapy.

In patients who received lamivudine monotherapy without

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HBIG, the hepatitis B recurrence rate after 4 years of liver transplantation was ~40%. In contrast, a study of lamivudine and adefovir combination therapy reported no recurrence in CHB patients during the 22-month observation period. In patients who received entecavir monotherapy without HBIG, the rate of HBsAg loss was 88-91% and negative viremia was maintained in more than 98% during a 26-53-month follow up; moreover, the rate of HBV recurrence was lower than that with lamivudine monotherapy.

In a meta-analysis of 19 studies, lamivudine or adefovir with HBIG significantly reduced HBV recurrence compared to monotherapy with either lamivudine or adefovir. However, in a meta-analysis of 17 studies with 519 patients, those treated with lamivudine and HBIG (6.1%) combination therapy showed a rate of HBV recurrence comparable to that of those treated with either entecavir or tenofovir monotherapy (3.9%, P=0.52), and significantly higher than that of those treated with the combination of HBIG and either entecavir or tenofovir therapy (1%, P<0.001).

To date, few studies regarding entecavir or tenofovir monotherapy for the prevention of HBV recurrence after liver transplantation have been reported. Therefore, the combination of an antiviral and HBIG is recommended to prevent HBV recurrence after liver transplantation.

To reduce the cost of HBIG, studies of low-dose HBIG in combination with an antiviral or conversion to antiviral monotherapy after short-term HBIG combination therapy have been performed. 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 a moderate cost, as the 5-year recurrence rate of hepatitis B was 4%. Furthermore, patients with HBV DNA levels of less than 2.5 pg/mL before liver transplant and treated with lamivudine and HBIG (2,000 IU) combination therapy for 1 month after liver transplant were randomly assigned to either a combination therapy maintaining group or lamivudine monotherapy group. The rates of HBV recurrence and patient survival did not differ between the two groups. Two other retrospective studies reported no recurrence of HBV when lamivudine and HBIG combination therapy or HBIG therapy alone for 2 years after liver transplantation was replaced with lamivudine monotherapy. 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 showed similar rates of hepatitis B recurrence.

Lamivudine and adefovir combination therapy with initial short-term low-dose HBIG (400-800 IU) did not show HBV recurrence during the 57-month follow-up period. Few studies with a small number of patients have evaluated entecavir- or tenofovir-based therapy to reduce HBIG usage. The HBV recurrence rate was reported to be 10% (1/10) and 0% (0/11) when combination entecavir and HBIG therapy was converted to entecavir monotherapy; there was no HBV recurrence after converting to tenofovir monotherapy in 9 patients and 17 patients.

The rates of recurrence were 5.9% (1/17) and 4.8% (1/21) in a study of conversion to tenofovir and emtricitabine (Truvada®); however, HBIG withdrawal had an economic benefit. Although these studies suggested the possibility of reducing the dose and duration of HBIG treatment, further work is needed to determine the optimal duration, amount and type of antiviral treatment.

If hepatitis B recurs after preventive HBIG therapy following liver transplantation, lamivudine therapy could effectively inhibit the virus. However, it has been reported that long-term lamivudine therapy is associated with a resistance rate of >50% after 3 years. Such lamivudine resistance causes inflammatory changes and hepatic fibrosis in the transplanted liver; indeed, death following hepatic failure is possible in severe cases. A few studies have reported the effects of tenofovir and entecavir on hepatitis B recurrence after liver transplantation; however, further research is required. Several studies have reported relatively good efficacy of lamivudine and adefovir in 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 rate of reduction in HBV DNA was 65%, whereas the rate of lamivudine resistance at 96 weeks after the initiation of therapy was 2%. Although these studies were conducted for a short period in small groups, it was recently reported that tenofovir is effective against mutants with lamivudine resistance. However, a high rate of emergence of entecavir resistance has been reported when entecavir is administered as a rescue therapy to patients with lamivudine resistance. Therefore, entecavir is not recommended in patients with lamivudine resistance after liver transplantation.

If HBsAg seronegative patients receive liver transplants from positive anti-HBc donors, ~50% will develop new hepatitis B. When HBIG therapy was administered to these patients after liver transplantation, hepatitis B occurred in ~20%. However, when lamivudine therapy was applied, hepatitis B developed only in 2–3% of patients. Nevertheless, lamivudine and HBIG combination therapy had no additional preventive effects compared to lamivudine monotherapy.

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mivudine therapy alone.\textsuperscript{415-417} The protective effect against HBV recurrence was similar between lamivudine and entecavir or tenofovir.\textsuperscript{414} Lamivudine was more cost-effective than entecavir or tenofovir according to a Markov model.\textsuperscript{419}

[Recommendation]

1. Pre-transplant therapy with a NA is recommended for all HBsAg-positive patients undergoing liver transplantation to achieve the lowest possible level of HBV DNA before transplantation. (A1)

2. Antiviral therapy before liver transplantation should comply with the guidelines for chronic hepatitis B therapy. (B1)

3. Therapy with a NA and HBIG should be administered for the lifetime of the patient to prevent recurrence of hepatitis B after liver transplantation, until more evidence regarding alternative treatment regimens is accumulated. (B1) If serum HBV DNA becomes negative before the liver transplant, withdrawal of HBIG may be considered in certain patients after long-term monitoring. (B1)

4. In case of HBV recurrence after liver transplantation, a potent NA with a high barrier to resistance is recommended. (B1) Upon emergence of drug-resistant variants, the CHB treatment guidelines should be followed. (B1)

5. When an HBsAg-negative recipient receives an HBsAg-negative but anti-HBc-positive graft, the recipient should take oral antivirals indefinitely. (B1)

Immunosuppression and chemotherapy

The clinical course of individual patients with chronic hepatitis B is affected by the interaction between the virus and the host immune system. Impaired host immunity due to chemotherapy or immunosuppressive treatment increases the risk of HBV reactivation.\textsuperscript{493} Previously, HBV reactivation referred to the reappearance of necroinflammatory disorders in patients with either inactive CHB or with resolved hepatitis,\textsuperscript{441} and was commonly defined as an increase in the serum HBV DNA of $>10^4$ IU/mL together with elevated serum ALT (higher than 3× ULN or an absolute increase of $>100$ IU/L).\textsuperscript{424,425} However, most studies of HBV reactivation used their own definition of HBV reactivation, and so the exact incidence of HBV reactivation during immunosuppressive therapy or chemotherapy was unclear. In addition, several terms such as “preventive”, “prophylactic” and “preemptive” were used but not clearly defined, which resulted in confusion in scientific communications. In this guideline, “prophylactic” therapy means starting antiviral therapy simultaneously with initiation of immunosuppressive therapy or chemotherapy. Meanwhile, “preemptive” therapy means deferring antiviral therapy until the HBV DNA level increases. We prefer the term “preventive” therapy, which means not only starting antiviral therapy upon initiation of immunosuppressive therapy or chemotherapy but also deferring antiviral therapy until the HBV DNA level increases.

Two definitions of HBV reactivation are in use.\textsuperscript{424} One is exacerbation of chronic HBV infection, and the other is relapse of past HBV infection. Exacerbation of chronic HBV infection is defined as a $2\log_{10}$ increase of HBV DNA level from the baseline level or a new appearance of HBV DNA to a level of $\geq 100$ IU/mL. Relapse of past HBV infection is defined among HBsAg negative, IgG anti-HBc positive and HBV DNA negative patients as reappearance of HBsAg or detectable HBV DNA. 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 to be 20-50%, although the ranges varied among studies. Many patients with HBV reactivation are asymptomatic, but the clinical course varies widely from jaundice to decompensation or even death.\textsuperscript{422,425-427} 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.\textsuperscript{428-430} Predictive factors for HBV reactivation include the pretreatment HBV DNA level, HBeAg positivity, cccDNA in hepatocytes and PC/BCP mutation as viral factors, type of malignancy, male and young age as host factors, and type or intensity of immunosuppression or chemotherapy and hematopoietic stem cell or organ transplantation as environmental therapeutic factors.\textsuperscript{431}

The reported reactivation rate in lymphoma patients ranges from 24% to 67%, possibly due to intense chemotherapeutic regimens against lymphoma and higher HBsAg positivity rates in these patients.\textsuperscript{426,432-434} Rituximab, which is commonly administered with corticosteroid for lymphoma, further increases the risk of HBV reactivation.\textsuperscript{435,436} One retrospective study reported a 27.8% (45/162) HBV reactivation rate among HBsAg-positive lymphoma patients, with a lower rate of HBV reactivation in the preventive antiviral therapy group compared to the non-preventive antiviral therapy group (22.9% [32/140] vs. 59.1% [13/22]; $P<0.001$).\textsuperscript{431} In this study, entecavir reduced the rate of HBV reac-
tivation to a greater degree than lamivudine (6.3% vs. 39.3%; P<0.05). In HBsAg negative/anti-HBc positive patients, the rate of HBV reactivation was 2.4% in this retrospective study. Another prospective study of HBsAg negative/anti-HBc positive lymphoma patients reported a higher rate of HBV reactivation and hepatitis aggravation (10.4 and 6.4 per 100 person-years, respectively) during rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy. In this study, close monitoring of HBsAg and HBV DNA with immediate antiviral therapy usually overcame the complications of HBV reactivation; however, some cases showed marked aggravation and progression of severe hepatitis, which was associated with reappearance of HBsAg compared to reappearance of HBV DNA without HBsAg (100% vs. 28%). A rituximab-containing regimen increased the risk of HBV reactivation among HBsAg-positive and HBsAg-negative/anti-HBc-positive lymphoma patients (relative risk 2.14, 95% CI 1.42–3.22, P=0.0003), especially in HBsAg-negative/anti-HBc-positive lymphoma patients (relative risk 5.52). Preventive antiviral therapy in lymphoma reduced the rate of HBV reactivation significantly compared to a non-preventive group (13.3% vs. 60%). Pretreatment screening for HBsAg and anti-HBc before R-CHOP chemotherapy in lymphoma and preventive antiviral therapy enhanced survival and cost-effectiveness by reducing the rate of HBV reactivation.

The risk of reactivation is also elevated when high-intensity chemotherapy is applied prior to hematopoietic stem-cell transplantation in hematologic malignancies. Similarly, preventive antiviral therapy with lamivudine or entecavir reduced the rate of HBV reactivation. Although the reactivation rate was 14-21% in solid tumors, higher rates of 41-70% were reported in breast cancer, possibly related to the use of high-dose chemotherapy with anthracycline agents and steroids. The rate of HBV reactivation during transcatheter arterial chemoembolization (TACE) as a therapeutic option for HCC was 4-40%. Preventive lamivudine therapy compared to non-preventive group reduced the rates of HBV reactivation (2.8% vs. 40.5%), hepatitis aggravation (2.8% vs. 29.7%) and hepatic failure (0% vs. 8.1%) significantly. Preventive antiviral therapy can be considered in cases undergoing TACE for HCC treatment to reduce HBV reactivation; however, the rates of HBV reactivation during TACE differed according to procedure method, interval, frequency and the TACE agents. Therefore, further studies are required to elucidate the criteria for preventive antiviral therapy in TACE. Sorafenib, which was approved for advanced HCC, seems not to cause HBV reactivation but this should be confirmed in further investigations. Steroids can suppress the host immune system but also induce HBV replication directly, which increases the risk of HBV reactivation. Other risk factors for reactivation include the use of anti-TNF agents for inflammatory bowel diseases or rheumatologic diseases (e.g., infliximab, etanercept, and adalimumab), the HBV genotype or specific mutations in the HBV genome, and recovery from neutropenia. The rate of HBV reactivation was 12.3% among HBsAg-positive patients receiving an anti-TNFα antibody or disease-modifying antirheumatic drug (DMARD), which are used in rheumatologic diseases. Other study reported a rate of HBV reactivation of 39% among HBsAg-positive patients and 5% among isolated anti-HBc-positive patients receiving anti-TNFα antibody therapy. Preventive antiviral therapy decreased the rate of HBV reactivation significantly (23% vs. 62%, P=0.003).

Because HBV reactivation is associated with the risk of hepatic failure and death, prevention is of utmost importance. This necessitates screening for HBsAg and IgG anti-HBc. Vaccination should be considered if there is no evidence of (past) HBV infection (i.e., negative for both HBsAg and IgG anti-HBc). Preventive antiviral therapy is recommended in HBsAg-positive patients regardless of the serum HBV DNA level. Preventive lamivudine therapy has significantly reduced the rates of HBV reactivation, hepatic failure, and mortality in randomized controlled studies of lymphoma patients in Hong Kong and Taiwan. Therefore, it is recommended that preventive antiviral therapy be started simultaneously with the initiation of chemotherapy rather than deferring until the HBV DNA level increases, and should be maintained for a certain period after the termination of chemotherapy (e.g., at least 6 months). However, evidence that can be used to determine the duration of preventive antiviral therapy remains limited. Elevated risk of reactivation was reported with cessation of preventive lamivudine therapy at 3 months following the termination of chemotherapy, especially in cases with a high HBV DNA level before chemotherapy (≥2,000 IU/mL). Therefore, the duration of preventive antiviral therapy could be determined based upon treatment guidelines for CHB if the pre-treatment HBV DNA level is high. In contrast, attention should be paid 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 preventive treatment with other antiviral agents—such as adefovir, telbivudine, clevudine, entecavir, and tenofovir—these agents could be administered for preventive purpose considering their mechanisms of action and therapeutic results. Since resistance was reported in preventive lamivudine therapy, other antiviral agents with lower resistance rates should be considered.
in cases with prolonged treatment (e.g., >1 year). A retrospective study reported that the risks of hepatitis and chemotherapy disruption due to HBV reactivation in lymphoma patients were lower for entecavir than for lamivudine. However, data on the relative efficacy and cost-effectiveness of antiviral agents are scarce. Prospective studies to determine the appropriate antiviral agents and optimal treatment duration in various types of malignancy are needed, as most previous studies involved only lymphoma patients. If cost is ignored, entecavir and tenofovir are appropriate choices based on their potency and resistance rate. Interferon-α is contraindicated for preventive use due to its bone marrow suppression and exacerbation of underlying hepatitis.

In some cases, HBV reactivation occurs not only in HBsAg-positive patients but also in IgG anti-HBc-positive patients without HBsAg. 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. The rate of HBV reactivation is higher in patients with isolated anti-HBc than in patients with both anti-HBc and anti-HBs. IgG anti-HBc-positive patients (HBsAg-negative) have a risk of HBV reactivation irrespective of anti-HBs, but a uniform treatment recommendation cannot be provided because the effects of the type of malignancy or immunosuppressive/chemotherapeutic agents used on the reactivation risk are unclear. However, preventive therapy should be started if serum HBV DNA is positive in high-risk groups such as patients with lymphoma undergoing hematopoietic stem cell transplantation; preventive treatment may be started together with immunosuppressive/chemotherapy or 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. It is recommended to screen for HBsAg and IgG anti-HBc prior to initiation of immunosuppressive treatment or chemotherapy. If either is positive, serum HBV DNA should be tested. (A1)
2. Patients without evidence of HBV infection should be vaccinated. (B1)
3. Consider preventative antiviral therapy simultaneously with the initiation of immunosuppressive treatment/chemotherapy if HBsAg or HBV DNA is positive. (A1) Although selection of a NA requires consideration of the serum HBV DNA level, the intensity and duration of immunosuppressive treatment/chemotherapy and the cost, entecavir or tenofovir can be preferentially considered if the baseline HBV DNA level is high or long-term treatment is anticipated. (C1)
4. If IgG anti-HBc is positive without HBsAg or HBV DNA, irrespective of anti-HBs, serum HBV and HBsAg should be tested regularly and preventative antiviral therapy should be considered if reappears during immunosuppressive treatment/chemotherapy. (A1) Preventive antiviral therapy in patients with isolated anti-HBc can be initiated in high-risk groups such as patients with lymphoma undergoing rituximab-containing regimen or those with leukemia who undergo hematopoietic stem cell transplantation. (B2)
5. Serum HBV DNA should be monitored periodically during and after preventative antiviral therapy. (A1)
6. Preventive antiviral therapy should be maintained for at least 6 months after the termination of immunosuppressive treatment/chemotherapy. (C1)

Patients with chronic kidney disease and under dialysis

Patients under dialysis are relatively prone to being exposed to HBV infection, which might exert a negative influence on their long-term prognosis. Exacerbation of hepatitis B is of particular importance for immunosuppression after renal transplantation. Fortunately, the incidence of HBV infection in dialysis patients has decreased due 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 0-6.6% in Western countries, and ~5% in Korea in recent reports. The prevalence of occult HBV infection was higher than the HBsAg-reactivity rate in one report, but this was not the case in Korea. The standard precautions to avoid nosocomial transmission are of the highest priority for preventing new HBV infections in dialysis patients. Vaccination against HBV is widely recommended in these patients; the efficacy is higher with earlier vaccination because the antibody production rate is 50-60% compared with ~90% in the general population, and decreases as residual renal function declines. Data on antiviral treatment in dialysis patients are insufficient. Although a randomized controlled study of interferon-α in HBV-infected patients with glomerulonephritis has been performed, it is difficult to recommend its use due to the increased adverse events in this popula-
tion due to pharmacodynamic changes. Several small studies have reported the effectiveness of lamivudine. Resistance to lamivudine was 39% at 16.5 months of treatment, which was similar to the rate in patients with normal renal function. Entecavir or tenofovir may be preferentially used, given their potency and resistance profile in patients with normal renal function. Careful dose adjustment is required for adefovir and tenofovir due to their potential nephrotoxicity in patients with residual renal function. Tenofovir is less nephrotoxic than adefovir. Two of 426 patients with chronic hepatitis B who underwent tenofovir therapy for 144 weeks showed elevation of serum creatinine to >0.5 mg/dL compared to baseline with no reduction in glomerular filtration rate to <50 mL/min.

[Recommendation]

1. Vaccination is recommended for patients under dialysis negative for HBsAg and anti-HBs. (A1)
2. Oral NAs such as entecavir and tenofovir are preferable to interferon therapy in patients under dialysis. (B1) NAs should be dose-adjusted according to residual renal function. (A1)

CO-INFECTION WITH OTHER VIRUSES

HCV Co-infection

In patients with CHB the anti-HCV antibody positivity rate varies from 0.1% to 22%, depending on the region with being very low in Korea (0.1%). Patients with HBV/HCV co-infection have an increased risk of severe or fulminant infection, and high incidences of cirrhosis and HCC. The scarcity of data makes it impossible to recommend a treatment for HBV/HCV co-infection. However, it is necessary to determine which virus is dominant by means of serologic or virology tests. If HCV RNA is positive with a low or undetectable serum HBV DNA level, HCV infection should be considered dominant and the patient treated as for HCV monoinfection. Combination therapy of pegIFN-α-2a plus ribavirin is equally effective in patients with HCV monoinfection and HBV/HCV co-infection. HBV treatment should be added when HBV reactivates, which can reportedly occur during or after combination therapy of pegIFN-α plus ribavirin for HCV. The role of direct-acting agents (DAAs) in HBV/HCV co-infection needs to be elucidated.

[Recommendations]

1. After confirming the dominant cause of liver disease in HBV/HCV coinfection, treatment following the same strategy as that for the dominant virus is recommended. (B1)
2. HBV treatment should be initiated when HBV proliferation is identified during or after treatment for HCV. (B1)

HDV Co-infection

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

HDV infection can be diagnosed by detecting anti-HDV antibody or HDV RNA in the 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. The biochemical, virologic, and histologic responses to high-dose IFN-α therapy (9 MU, three times per week) were better than those to the conventional dose of IFN-α (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. PegIFN-α showed HDV RNA negativity rates of 17-43% at 6 months after the end of 48 or 72 weeks of treatment. 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 1 year is recommended for patients with HBV/HDV co-infection. 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 in terms of inhibiting HDV replication.

Combination therapy of lamivudine plus IFN-α was not superior to IFN-α monotherapy, and adefovir plus pegIFN-α therapy did not improve the response rate compared to pegIFN-α monotherapy. In addition, the rates of HDV DNA negativity at 24 weeks after therapy with the combination of adefovir plus pegIFN-α or pegIFN-α monotherapy for 48 weeks were superior to those following adefovir monotherapy for 48 weeks (26%, 31% and 0%, respectively).
**HIV Co-infection**

The incidences of cirrhosis and HCC are reportedly higher in patients with HBV/HIV coinfection than in those with HBV monoinfection. HBV should be treated in HBV/HIV-coinfected patients who exhibit ALT elevation due to HBV. Before such treatment it is necessary to determine whether treatment for HIV is also required. Patients who are not indicated for HAART should receive the standard treatment for CHB. In such cases antiviral agents (e.g., IFN, adefovir, or telbivudine) that do not affect HIV proliferation should be selected, to prevent the future development of HIV cross-resistance. Entecavir or tenofovir monotherapy should not be used in patients with HBV/HIV co-infection due to the development of resistant HIV. Patients who need treatment for both HIV and HBV should be treated with antiviral agents that are effective against both viruses, such as tenofovir/emtricitabine, tenofovir or lamivudine, as highly active anti-retroviral therapy (HAART). 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.

**Female patients of childbearing age**

1. **Treatment before pregnancy**
   - When planning treatment for females 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 as 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 during the therapy and until 6 month after cessation of therapy. Females who want to be pregnant should be treated with antiviral agents that belong to 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). Tenofovir and telbivudine belong to pregnancy category B, while entecavir, adefovir and lamivudine belong to pregnancy category C drugs (drugs that exert teratogenic or embryocidal effects in animals and for which there are no controlled studies in humans).^5^

2. **Treatment during pregnancy**
   - Pregnant females with chronic HBV infection are usually in the immune-tolerance phase, and changes in the maternal immune system during pregnancy, such as a shift in the Th1-Th2 balance after delivery, thereby causing a reduction in 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 regarding 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 females 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 liver disease is present (e.g., jaundice or prolongation of PT), and the HBV DNA level meets the general criteria for antiviral treatment.
   - When starting antiviral therapy during pregnancy, category B drugs are recommended. 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.

1. CHB patients with HDV co-infection should be treated with peginterferon-α or high dose interferon-α (9 MU, three times per week) for >1 year. (B1)

2. Patients who are not indicated for HAART at present or in the near future should receive the standard treatment for CHB. In such cases, NAs that do not affect HIV proliferation should be used to prevent the future development of HIV cross-resistance. (B1)

3. Patients who need treatment for both HIV and HBV should be treated with HAART agents effective against both viruses; e.g., tenofovir/emtricitabine or tenofovir plus lamivudine. (B1)
and it contains a considerable amount of data on lamivudine and tenofovir. According to the APR, the rates of birth defects among females 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. Few cases related to other drugs such as telbivudine and entecavir have been reported. However, since the APR is designed to report only defects identified at birth, it may 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. Thus, based on considerations of fetal safety oral antiviral agents should not be administered, especially in the first trimester of pregnancy. However, the decision about whether to discontinue drugs in patients receiving treatment with oral antiviral agents should be individualized. One retrospective study showed that ~14% of pregnant females with active chronic hepatitis B without antiviral therapy can progress to hepatic failure and have a risk of maternal or fetal death, so appropriate antiviral therapy should be considered in pregnant females in the active phase of chronic hepatitis B.

In childbearing females who require treatment with an oral antiviral agent against HBV, pregnancy category B drugs such as tenofovir can be considered if the patient wants to become pregnant. In females already receiving antiviral therapy with a category C drug who want to become pregnant, the category C drug should be changed to a category B drug, such as tenofovir.

In the first trimester of pregnancy, pregnant females with mild chronic hepatitis B and undetectable HBV DNA (<60 IU/mL) may be considered for temporary drug discontinuation with careful monitoring for HBV reactivation. Meanwhile, females who become pregnant while on category C drugs should change to category B drugs if continuous antiviral therapy is needed.

As little about whether or not antiviral agents are secreted into breast milk is known, and the effects on babies of antiviral agents in breast milk is unclear, breast-feeding is not currently recommended.

Prevention of vertical transmission with antiviral drugs

A high maternal HBV DNA level is associated with a high rate of failure of neonatal passive-active immunoprophylaxis. In a double-blind, randomized controlled trial, pregnant females with high serum HBV DNA levels (>10³ cpm) were given lamivudine from week 32 of gestation to week 4 postpartum in addition to neonatal passive-active immunoprophylaxis. 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 study included pregnant females with HBeAg-positive and high serum HBV DNA levels (>10⁷ copies/mL) who were treated with lamivudine from week 24 to week 32 in addition to neonatal passive-active immunoprophylaxis as the treatment group. The HBsAg-positivity rates of infants at 1 year after birth were significantly different: 0% (0/94) in the treatment group and 7.7% (7/91) in the placebo group. Another prospective study included pregnant females with high serum HBV DNA levels (>10⁶ copies/mL) treated with telbivudine from week 12–30 to birth in addition to neonatal passive-active immunoprophylaxis as the treatment group. The HBsAg-positivity rates of infants at 6 months after birth were significantly different: 0% (0/54) in the treatment group and 8.6% (3/35) in the placebo group. Another prospective controlled study included pregnant females with high serum HBV DNA levels (>10⁷ copies/mL) treated with tenofovir from weeks 20 to 32 of gestation to week 4 postpartum in addition to neonatal passive-active immunoprophylaxis. HBsAg positivity was present in none (0/132) of the 6-month-old infants from telbivudine-treated mothers, whereas it was present in 8% (7/88) of those from placebo-treatment mothers. Another prospective study included pregnant females with high serum HBV DNA levels (>10⁷ copies/mL) treated with tenofovir or lamivudine from week 32 to week 4–12 postpartum in addition to neonatal passive-active immunoprophylaxis as the treatment group. The HBsAg-positivity rates of infants at 9 months after birth were significantly different: 1% (1/87) in the treatment group and 20% (2/10) in the placebo group. 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 rate of vertical transmission. However, the decision about whether or not to treat should be individualized in patients 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.
Children and adolescents

Providing HBIG and HBV vaccine to newborns of HBsAg-positive mothers within 12 h 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. The spontaneous HBeAg seroconversion rate in immune-tolerant Korean children was 4.6%, 7.1%, and 28.0% for patients aged <6, 6-12, >12 years, respectively. A Taiwanese study reported an annual spontaneous HBeAg seroconversion rates of 2% and 4–5% in children younger than 3 years and older than 3 years, respectively. Children who are in the immune-reactive phase—with increased ALT levels and histologic findings of liver inflammation and fibrosis—are usually asymptomatic. Long-term treatment in children with CHB is expected, and a prudent decision should be made based on the adverse effects of the drugs and the potential for viral resistance to affect future therapies. The treatment window should not be missed because cirrhosis can occur in their 20s and HCC later in life. 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 development of drug resistance, which would limit treatment options in later life. Children with a persistent elevated serum ALT level 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 and their HBV DNA levels are above 20,000 IU/mL. Acute elevation of 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 regarding 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, 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. The responses to interferon-α and lamivudine are better in children with higher activity scores in a liver biopsy. A randomized controlled trial of interferon-α therapy involving children aged 1 to 17 years found that 36% of those with a baseline ALT level of at least 2 ULN became negative for HBeAg at the end of treatment. HBSAg seroconversion occurred in 10% of the treated children. Factors predictive of a positive response among children are being younger than 5 years, having a low serum HBV DNA level, and having active inflammation in a liver biopsy. 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 to treatment, but in none of the children in the nonresponse and control groups. The recommended treatment regimen for interferon-α is 6 MU/m² 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. Clinical trials of peginterferon in children with CHB are ongoing. The efficacy and safety of peginterferon were demonstrated in children with chronic hepatitis C, and an update of the Swedish national recommendations for the treatment of CHB recommends the use of peginterferon (100 μg/m² weekly) in children.

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 those with a baseline ALT level of at least 2 ULN, and that the resistance rate was 18%. The HBeAg seroconversion rate after 2 years of therapy was 54% in children.
without lamivudine-resistant virus. The resistance rate was 64% in children who received lamivudine for 3 years. Lamivudine treatment for >3 years did not significantly increase seroconversion rates and increased the incidence of viral resistance. The studies of Korean children found that the HBV DNA level after 2 and 3 years of treatment were 65% and 70%, respectively. 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, and being younger than 7 years. Long-term durability of HBsAg seroconversion was observed in more than 90% of the subjects after they had taken lamivudine for at least 2 years. Lamivudine is orally administered at a dose of 3 mg/kg/day, with a maximum of 100 mg/day. Lamivudine treatment should be continued for at least 1 year, and it is desirable to continue treatment for 1 year after HBsAg seroconversion. If lamivudine resistance develops, it should be treated in accordance with the guidelines for antiviral resistance management in adults.

A randomized controlled study of 173 HBsAg-positive children aged 2–17 years showed undetectable HBV DNA and a normal ALT level after 48 weeks of adefovir treatment in 23% of 12- to 17-year-old subjects, but there was no significant difference between adefovir and placebo in those aged 2–11 years. The HBsAg seroconversion rate in the adefovir group and placebo group was 16% and 5%, respectively (P=0.051). No subject developed adefovir resistance. Continuation of adefovir treatment for a further 4 years was safe. Resistance to adefovir was observed in one child. Entecavir and tenofovir are potent HBV inhibitors with a high barrier to resistance. Entecavir is considered the first-line therapy in children older than 2 years and tenofovir in those older than 12 years. A randomized controlled trial of tenofovir in adolescents aged 12 to 17 years reported that the rate of a virologic response (HBV DNA <400 copies/mL) at week 72 was significantly higher in patients (n=52) who received tenofovir than those (n=54) who received placebo (89% vs. 0%). No resistance to tenofovir developed through week 72. The rate of grade 3/4 adverse events was higher among patients treated with placebo (24%) than those treated with tenofovir (10%). In a randomized controlled study involving 180 children aged 2 to 17 years with HBsAg-positive CHB, the HBsAg seroconversion and HBV DNA <50 IU/mL rates at week 48 were significantly higher with entecavir than placebo (24.2% versus 3.3%). The cumulative probability of entecavir resistance at 1 and 2 years was 0.6% and 2.6%, respectively. Entecavir showed no difference in safety compared with placebo.

[Recommendations]

1. HBsAg-positive CHB children with an HBV DNA level >20,000 IU/mL and HBsAg-negative CHB children with an HBV DNA level >2,000 IU/mL should be considered for treatment when the AST or ALT level is >2 ULN for at least 6 months, or moderate-to-severe necroinflammation or periportal fibrosis is evident in a liver biopsy. (A1)

2. Tenofovir, entecavir or interferon-α is the first-line therapy in children with CHB. (B1) Data on peginterferon are currently scarce, but its use in children can be based on the results of studies involving adults. (C1)

3. If antiviral resistance develops, it should be treated in accordance with the guidelines for antiviral resistance management in adults. (B1)

Conflicts of Interest

Potential conflicts of interests are as the followings.

Kwan Sik Lee: Consulted Gilead
Si Hyun Bae: Consulted BMS, Yuhan, Bayer and received honorarium from MSD.
Won Hyeok Choe: Nothing to disclose
Moon Seok Choi: Received honoraria from Roche, BMS, GSK, MSD, Gilead and consulted Gilead.
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Chang Wook Kim: Received honoraria or grant and consulted BMS, Gilead, Yuhan, Handok, Daewoong, PharmaKing, Pharmicell, KT&G, Roche, Dong-A, Hanmi
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Yoon Jun Kim: Consulted or received grants/ honoraria from JW creagene, Ildong, Daewoong, Roche, LG, Bayer, PharmaKing, Gilead, MSD, BMS, Samil, Yuhan.

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