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Current Status of Liver Diseases in Korea:
Report from the Epidemiology Study Group of the KASL

Current status of liver diseases in Korea: Hepatitis B

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= Abstract =

Hepatitis B virus (HBV) infection is the one of the most common causes of the liver diseases in Korea. Since the discovery of Australia antigen (hepatitis associated antigen, or HBsAg later), hepatitis associated antigen was tested widely. HBsAg was detected in 6.6~8.6% in 1980's. Later, it decreased to 5.7% in 1990's. Remarkably, sero-positivity of the children deceased to 0.2% after the nationwide vaccination program. Although hepatitis B vaccines are highly effective, the failure rate of perinatal prophylaxis in babies born to HBsAg positive mother was reported to be 4.25%. Treatment of chronic hepatitis B was initiated after the introduction of interferon alpha. Lamivudine opened a new era of oral antiviral agent, and it has been widely used in Korea since 1999. Adefovir was proven to have a good efficacy for lamivudine-resistant chronic hepatitis B. Newer potent antiviral agents such as entecavir, clevudine, and telbivudine are available currently. Further studies are warranted for understanding factors influencing natural history, improving treatment outcomes, and overcoming vaccine non-response.

Key words: HBsAg; Hepatitis B virus; Antiviral agents; Vaccination

Korea is an endemic area of hepatitis B virus (HBV) infection. Although the prevalence of chronic HBV infection is decreasing, it is still a major etiology of liver cirrhosis and hepatocellular carcinoma in Korea. Herein, changing epidemiology and natural history of chronic HBV infection will be reviewed based on the

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past and current data. Also, we would like to discuss how the diagnostic tests have been utilized, how the treatments of chronic hepatitis B have been challenged, and how the prophylactic measures for HBV infection have been applied in this country.

1. Epidemiology

Hepatitis B surface antigen (HBsAg) represents HBV infection, whether acute or chronic. In 1980s, HBsAg was detected in 6.6~8.6% of Korean and this increased with age from the 2nd to the 5th decade, then decreased with age thereafter.[1-3] In 1990s, the overall prevalence of HBsAg was 5.7% with a similar pattern according to age, but decreasing prevalence in general (Table 1).[4,5]

HBsAg positivity was not affected by socioeconomic status, but by gender. It was prevalent in male.[1-3,6] Serum HBsAg was detected in 73% of the chronic hepatitis and liver cirrhosis patients, and in 79% of primary liver cancer,[7-9] which denotes hepatitis B is a major cause of chronic liver disease. HBsAg positivity among the mothers of patients with chronic liver diseases was 40~80%, and that among the siblings of the patients was 33~67%. These data highly suggest that vertical transmission of HBsAg from the mother to the infant is an important cause of the high occurrence rate of HBsAg among the Korean population.[10-12]

In children and adolescent, before a nationwide vaccination, the positive rate of HBsAg was 4~5%.[13,14] After a nationwide vaccination program, seropositivity gradually decreased from 3.2% in 1988, 2.6% in 1993 to 1.7% in 1997.[15,16] Recently, it decreased to 0.2%; a national population based study reported that HBsAg positivity in children aged 10 to 14 was 0.2% in 2005,[17] and that in children aged 4 to 6 was 0.2% in 2006.[18] The early development and introduction of the domestic vaccine and the successful vaccination program are regarded as the cause for the HBsAg positivity decrease in children and adolescents.[19]

Hepatitis B virus genotype C2 prevails among chronic carriers of the virus in Korea, which is known to be associated with the more severe liver disease than genotype B. This suggests that the clinical manifestations of Korean chronic B-viral patients are likely to differ from those found in other Asian countries.[20-22]

Acute hepatitis B was prevalent in the 3rd decade in 1980's, while it was prevalent in the 4th decade in the late 1990's and the early 2000's (Fig. 1). Acute exacerbation of chronic hepatitis B was also prevalent in the

Table 1. Prevalence of HBsAg according to year and age

	0~9	10~19	20~29	30~39	40~49	50~59	>60	Total
1979.3~1981.2[1]	3.2	6.6	9.8	9.9	10.3	4.8	1.4	6.6
1982.4~1983.3[2]	4.5	14.2	9.1	11.8	7.3	6.2	1.6	8.6
1984.2~1985.11[3]	0.0	3.0	11.0	7.6	7.5	9.1	0.0	8.3
1995.1~1995.12[4]		8.2*	6.9	10.3	10.4	8.4	5.0	8.3
1995.7~1997.12[5]		2.5	5.4	6.8	6.3	5.1	3.3	5.7
1996.1~1996.12[4]		3.9	8.1	6.6	5.7	5.2	3.9	4.8
1997.1~1997.12[4]		2.1	5.3	6.6	6.3	6.2	4.9	3.4
1998.1~1998.12[4]		2.6	5.1	5.8	5.8	5.1	3.5	3.4
1999.1~1999.12[4]		1.3	4.7	6.2	6.5	4.8	3.7	2.6

*Age of 6~19.

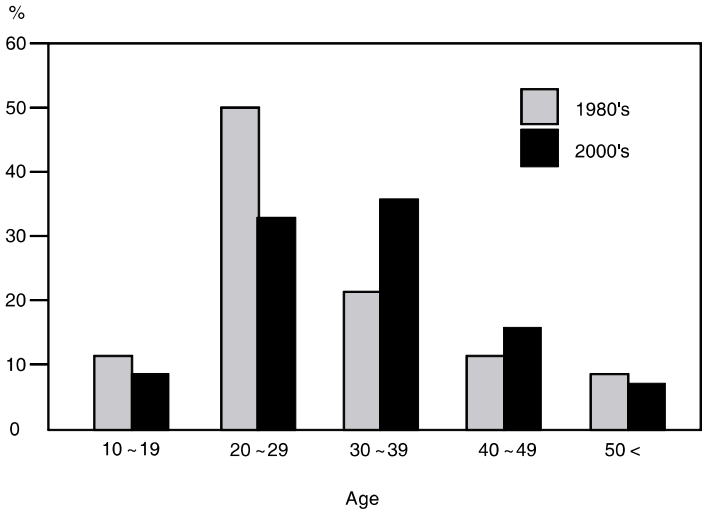

Figure 1. Age distribution of acute hepatitis B between in 2000's and in 1980's according to age. The peak age was 20~29 years old in 1980's and 30~39 years old in 2000's (Adapted from ref. 24).

Table 2. Cumulative rates in a large scaled prospective analysis

Disease status	Cumulative rate	At 5 yr	At 10 yr	At 15 yr	At 20 yr
Chronic hepatitis B	Liver cirrhosis development[26]	9%	23%	38%	48%
	Compensated cirrhosis development[27]	23%			
	Decompensated cirrhosis development[27]	5%			
	Survival[26]	97%	89%	74%	71%
	Primary cancer development[26]	3%	12%	26%	
Liver cirrhosis associated with HBV infection	Survival[27]	69%	60%	47%	
	Primary cancer development[27]	13%	26%	45%	

4th decade.[23-25]

2. Natural history

In a large scaled prospective analysis of the chronic liver disease, liver cirrhosis developed in 9%, 23%, 38%, and 48% of HBsAg positive chronic hepatitis patients in 5, 10, 15, and 20 years, respectively. The 5-, 10-, 15-, and 20-year survival rate of these patients was 97%, 89%, 74%, and 71%, respectively, and the 5-, 10-, and 15-year survival rate of B-viral liver cirrhosis patients was 69%, 60%, and 47%, respectively. Primary liver cancer developed in 3%, 12%, and 26% of HBsAg positive chronic hepatitis patients, and in 13%, 26%, and 45% of HBsAg positive liver cirrhosis patients, in 5, 10, and 15 years, respectively (Table 2).[26]

In another long term follow-up study, the rate of patients developing cirrhosis from chronic hepatitis B was 5.1%/year, and the 5-year cumulative probability of developing cirrhosis was 23%. The significant prognostic factors for developing cirrhosis were age and histologic classification. The progression rate of liver cirrhosis from chronic hepatitis B was 16% in patients under 40, while it was 38% in those aged forty or over. The rate of developing decompensated cirrhosis from chronic hepatitis B was 2.6%/year, and the 5-year cumulative probability was 5%. The rate of developing hepatocellular carcinoma from chronic hepatitis B was 0.8%/year,

and the 5-year cumulative developing rate of hepatocellular carcinoma from chronic hepatitis B was 3% (Table 2).[27]

In a 3 year-retrospective, cohort study, inactive carrier state or hepatitis B e antigen (HBeAg) negative viremia with normal ALT progressed to HBeAg negative chronic hepatitis B over time, demonstrating the dynamic changing patterns of HBeAg negative chronic hepatitis B.[28]

During the natural course of chronic hepatitis B, the estimated annual incidence of HBsAg seroclearance was 0.4%.[29] The clinical course following delayed clearance of HBsAg had diverse outcomes. In patients with spontaneous HBsAg seroclearance, necroinflammation was markedly improved and liver fibrosis was unchanged or regressed despite occult HBV infection. However, HCC developed in a minority of cases.[30] Therefore, these patients also required close follow up on the possible development of hepatocellular carcinoma following HBsAg clearance. Patients who developed an acute hepatitis B tended to recover rather than become chronic.[31]

Hepatitis D virus infection in chronic hepatitis B occurred in less than 1% of the patients.[32, 33]

3. Diagnosis

From serologic to molecular testing: Since the discovery of Australia antigen (hepatitis associated antigen, or HBsAg later), hepatitis associated antigen was tested in patients with various liver diseases.[34] As of 1971, it was reported to be commonly used on the sera of subacute hepatitis (50%) and chronic active hepatitis (36.8%) in Korea.[34] Diagnostic methods for HBsAg have improved and immune adherence hemagglutination assay, which is more rapid and easier than radioimmunoassay, became available in the late 1970's.[35] Currently, several assays are in use including solid phase immunoassay, electrochemiluminescence immunoassay, and chemiluminescent microparticle immunoassay for the detection of HBsAg or HBeAg.[36] Some of these methods are also available for the quantification of HBsAg.[36]

HBeAg is a serologic marker associated with viral replication. However, in patients with negative HBeAg, recurrent appearances of HBeAg were noted during the 2 years of mean follow-up period in a study.[37] This finding suggests the spontaneous reactivation of HBV, which may be considered as a potential for the progression of hepatic injuries.

Antibody to hepatitis B core antigen (anti-HBc) appears from an early stage of HBV infection. Hence, IgM anti-HBc was considered to be the serologic marker for acute hepatitis B. However, IgM anti-HBc can be detected during the course of chronic hepatitis, cirrhosis, or hepatocellular carcinoma.[38,39] Byun et al. reported the importance of S/N (sample absorbance to negative control absorbance) ratio for IgM anti-HBc, because the cut-off level above 6 distinguished acute hepatitis B from chronic hepatitis or cirrhosis accurately.[39]

Measurement of HBV DNA is the diagnostic cornerstone for active viral replication. Cut-off values for discriminating inactive HBsAg carriers from HBeAg-negative chronic hepatitis B patients varied between 2.0×10^4 and 6.0×10^4 copies/mL from a recent data in Korea.[40,41] Among the patients in the non-replicative phase, the mean levels of HBV DNA were reported to be different between groups; 3.84, 4.10, and 3.31 log copies/ml in inactive HBsAg carriers, inactive liver cirrhosis patients, and resolved chronic HBV-infected patients with loss of HBsAg, respectively, in a study measured by sensitive real-time polymerase chain reaction (PCR).[41]

HBeAg negative subjects with higher HBV replication may have precore mutations (G to A mutation at nu-

cleotide 1896) or basal core promoter (BCP) mutations (A to T, or G to A mutation at nucleotide 1762, or 1764, respectively), which develops under immunologic pressure. Some investigators suggested the emergence of precore mutant HBV as a universal phenomenon during the natural history of chronic HBV infection and that the precore mutant did not appear to have pathogenic role.[42] In contrast, other investigators proposed the clinically important role of mutations in the progression of HBV-related liver diseases because BCP and precore mutations were more frequent in advanced liver diseases than in the other clinical statuses.[43] Pre-S mutations were also detected in advanced liver diseases, and were considered to have a clinical significance.[44]

Drug induced mutations are the major problem faced during the antiviral treatment. Early detection of the mutation is the key step in the management of antiviral resistance.[45] Recently, a matrix-assisted laser desorption/ionization time-of-flight mass spectrometry-based genotyping assay, termed restriction fragment mass polymorphism (RFMP), was developed in Korea.[46] This very sensitive method identified mixtures consistently at 1% of the relative concentration of mutant versus wild-type viruses, although line probe assay (LiPA) requires 4% of the mutants, at least.[46] However, a mere detection of YMDD mutants could not sufficiently predict the viral DNA breakthrough. Lee et al. demonstrated that a 5-fold predominance of YMDD mutants to wild-type viruses was significantly associated with the viral DNA breakthrough.[47] These advancements of the diagnostic tests enabled effective rescue therapy during antiviral treatments, which will be addressed on following section.

4. Treatment

There was a great change during the last 20 years in the field of treatment of chronic hepatitis B. Until 1999, we had only one injection drug which was approved for the treatment of chronic hepatitis B. Now, we have many choices for the treatment of chronic hepatitis B; two kinds of injections and 5 oral nucleos(t)ides analogues.

First antiviral therapy - interferon: Since the late 1980's, interferon alpha was tried as a therapeutic agent for chronic hepatitis B. It was the only one available regimen in Korea until 1999 because other trials such as adenine arabinoside were proven to have no substantial effect on chronic hepatitis B.[48] However, the treatment efficacy was not good enough compared to the data from the Western countries. Lee et al. reported that they observed a significant reduction in the interferon treatment group in terms of ALT and HBV DNA levels, but the rate of seroconversion was only 25% in the treated group (n=20) and 10% in the control group (n=10) 2 months after treatment, and the difference between them was not significant.[49] There were many trials performed for the maximum efficacy of interferon during this period, in terms of treatment methods such as a change in administration schedules and doses, targeting different patient groups, and steroid priming before interferon treatment.[50,51]

New era of oral nucleos(t)ide analogues - lamivudine and adefovir: The first oral nucleoside, lamivudine, has been available in Korea since 1999. Many studies about its efficacy and safety were reported at this time. The suppression of serum HBV DNA was sustained in 77% of the patients and the normalization of serum ALT was achieved in 80%.[52,53] The Child-Pugh score improved in 17 (65.4%) out of 26 patients after 6 months of lamivudine treatment. There were three other studies which tried to lengthen the treatment period or include the decompensated cirrhotic patients in the enrollment criteria.[54-56] Lamivudine therapy was also effective in

children.[57,58] The younger children who were younger than the age of 7 responded better.[57] One study reported the efficacy of lamivudine in children to be 42% of HBeAg seroconversion rates, 88% of ALT normalization (88%), and 53% of HBV DNA undetectability during 2 years of the mean follow up period.[58]

Long-term lamivudine therapy was associated with antiviral resistance. Kim et al. reported that cumulative rates of lamivudine resistance after one and two years of treatment were 11% and 34%.[59]

Some investigators tried to find out the answer for questions such as when they could stop the lamivudine and what factors were related to the post-treatment relapse.[60,61] A single center study reported that two-year additional administration of lamivudine could enhance the durability of lamivuidne-induced HBeAg loss.[60] In contrast, there was a contradictory thought that extended lamivudine therapy for up to 12 months did not decrease the rate of virological relapse.[61] Nevertheless, monitoring of serum HBV DNA by sensitive PCR assay was helpful in predicting post-treatment relapse.[61]

Can chronic hepatitis B be aggravated by transcatheter arterial chemoembolization (TACE) treatment? If so, does preemptive lamivudine therapy inhibit the relapse after TACE treatment? It was reported that a baseline HBV DNA level of more than 10^4 copies/mL was the only independent predictor of hepatitis due to HBV reactivation during chemo-lipiodolization.[62]

Adefovir was introduced in 2004. An early article about adefovir study in Korea was about the therapeutic effects for de novo or recurrent infection of chronic hepatitis B in liver transplantation patients.[63] Adefovir was proven to have a good efficacy for lamivudine resistance chronic hepatitis B.[63] Several factors were related to good outcomes such as high ALT levels and early viral suppression.[64] However, the number of adefovir resistance patients increased as time passed. In Korea, studies for adefovir resistance were done only on patients with the previous history of lamivudine resistance, and not on naïve patients because adefovir cannot be used as the first line antiviral agent due to the current health insurance reimbursement policy. The cumulative incidence of the genotypic adefovir resistance at 12 and 24 months was 6.4% and 25.4%, respectively.[65] In another study, 10 (18%) of the 57 lamivudine resistant patients were found to have developed adefovir-resistant mutations after 48 weeks of treatment, whereas none of the 38 treatment-naïve patients developed such mutations.[66]

Which oral nuclos(t)ide will be effective for adefovir resistance chronic hepatitis B? One study shed a light on this tough question.[67] Six patients were treated with tenofovir plus lamivudine for 6 months. This combination suppressed HBV replication, and it may be the promising rescue therapy for adefovir resistance chronic hepatitis B. Does the pattern of lamivudine resistance influence the virologic response of adefovir rescue therapy? It was reported that adefovir has similar antiviral efficacy against all evaluated patterns of lamivudine resistant mutations.[68]

Advancement of antiviral therapy with more potent agents - entecavir, clevudine, and telbivudine

The phase III global study in which several Korean investigators participated showed that more patients in the entecavir group than in the lamivudine group had undetectable serum HBV DNA levels by PCR assay (67% vs. 36%, $P<0.001$).[69]

Clevudine was a thymine derivative. It was invented by a Korean scientist. Early clinical trials of clevudine were done with Korean patients. An open labeled phase II study revealed that 30 mg was safe and effective to suppress serum HBV DNA. The virus suppression effect was maintained for a 6 month observation period after withdrawal of this nucleoside.[70] Clevudine was effective in terms of virologic and biochemical response

in HBeAg positive patients after a 6 month treatment.[71] Median serum HBV DNA reductions from baseline at week 24 were 5.10 and 0.27 $\log_{10}$ copies/mL in the clevudine and placebo groups, respectively. The proportion of patients who achieved normalization of ALT was 68.2% in the clevudine group and 17.5% in the placebo group at week 24. In HBeAg negative chronic hepatitis B patients, clevudine showed similar efficacy as in HBeAg positive patients. The median changes in HBV DNA from baseline were -4.25 and -0.48 $\log_{10}$ copies/mL at week 24 in the clevudine and placebo groups, respectively. The proportion of patients who achieved ALT normalization was 74.6% and 33.3% in the clevudine and placebo groups at week 24, respectively. The therapeutic response was better sustained in HBeAg negative patients than in HBeAg positive patients.[72] Recently, clevudine was reported to be associated with myopathy, characterized by depletion of mitochondrial DNA.[73]

Fifty four of 101 patients were assigned to telbivudine treatment and 47 patients were assigned to lamivudine treatment. At week 52, significantly more patients who were treated with telbivudine than those treated with lamivudine had a therapeutic response (83% vs 62%, respectively, P=0.017), their mean serum HBV DNA levels had reduced more (6.6 vs 5.6 $\log_{10}$ copies/mL, respectively, P=0.027), and they more often achieved PCR-undetectable levels of serum HBV DNA (74% vs 34%, P<0.0001). No virologic resistance to telbivudine was detected (0% vs 18%, respectively, P=0.001).[74]

Antiviral therapy in post-transplant setting: Which clinical factors are related to HBV recurrence? The related factors are the duration of antiviral therapy before transplantation, HCC recurrence after transplantation, tumor burden, and post-op adjuvant chemotherapy.[75] Combination therapy of HBIG and lamivudine was effective for 3 years regardless of the pre-transplantation viral load.[75]

5. Prevention

Immunization strategy for hepatitis B: In 1983, the domestically developed plasma-derived hepatitis B vaccine was first approved in Korea. In 1984 and 1985, the government recommended the general population to be vaccinated against the hepatitis B infection, and consequently, about 6 million doses of hepatitis B vaccines were used for the immunization. In 1985, the government changed its strategy on the vaccination for hepatitis B and began to focus the target of immunization on mainly infants and children. In 1988, the mass catch-up vaccination campaign of hepatitis B with school-aged children and adolescents was performed by the government.[76]

The Korean Pediatric Society has also recommended the hepatitis B vaccine as a routine vaccine since 1991. According to the Communicable Disease Prevention Act reformed in 1995, the government included hepatitis B vaccine in the National Immunization Program.[77] The current coverage rate of hepatitis B vaccine is about 95% of all infants.[19]

The government in conjunction with the Korean Medical Association has carried out a 'Hepatitis B Perinatal Transmission Prevention Program' since July 2002. This program has provided all the expenses required for hepatitis B immunoglobulin, three doses of vaccine, and a serological test to verify the outcome of perinatal prophylaxis in all infants born from HBsAg positive mothers, including non-citizens.[76]

The immunization for hepatitis B is conducted in accordance with a 0-, 1-, 6-months schedule, and the first dose is recommended to be given at birth (within 24 hours). The booster dose of the vaccine, which was given

every 5 years, has not been recommended since 1997.[77]

History of hepatitis B vaccine: The first domestically developed hepatitis B vaccine was licensed in 1983, quickly following the first licensed hepatitis B vaccine developed on a worldwide basis in 1981. There were two plasma-derived vaccines, Hepavax-B® (Korea Green Cross Co., Yongin) and Hepaccine-B® (CJ Jeiljedang Co., Icheon), which were inactivated with formalin and heat, respectively. A large quantity of these vaccines was exported to numerous developing countries through UNICEF. However, the production of these two vaccines were stopped in 1996 and 2004 due to the insufficient supply of HBsAg-positive blood pool, the theoretical risks of blood-transmitted infectious diseases, and high production costs.[77]

Beside the plasma-derived vaccines, two recombinant vaccines utilizing yeast, Euvax B® (LG Bioscience, Seoul) and Hepavax-Gene® (Korea Green Cross Co., Yongin), were developed and used from 1992 and 1997, respectively.[77] The seroconversion rate of these two domestic recombinant hepatitis B vaccines were 97.1% and 96.8% in Korean adults, respectively.[78,79] Similar results have been demonstrated in babies and adults in foreign countries.[80,81]

Prevention of perinatal hepatitis B infection: In one study, the family history of hepatitis B infection was evaluated in children with chronic hepatitis B. Seventy five (83.3%) out of 90 children had a family history of chronic hepatitis B. Among the 75 children, 66 children (88%) had mothers with chronic hepatitis B infection. This result suggested that the most common mode of transmission of chronic hepatitis B in Korea is the perinatal infection.[82]

A serosurvey of pregnant women was conducted between 1990 and 1995, which suggested an annual average HBsAg positive rate of 3.4%, 25.5% of which was HBeAg positive.[83] According to a survey conducted in 2003, more than 99.7% of delivery-related hospitals tested HBsAg as part of their antenatal care, and the HBsAg positive rate in pregnant women was 3.2%.[84] On the reference of 'Hepatitis B Perinatal Transmission Prevention Program' from 2002 to 2007, the failure rate of perinatal prophylaxis in 34,828 babies born to HBsAg positive mother was 4.25% (1,480 babies).[76]

Several studies about the mechanism or the prevention of perinatal prophylaxis failure, which involves the surface gene variant,[85] maternal DNA titers,[86] HLA systems,[87] and the trial of double dose hepatitis B immunoglobulin[88] have been established.

6. Future directions

Not much information is available on what leads the patients in the immune tolerance phase to the immune clearance phase, what makes HBV reactivate, and what factors lead to the resolution of disease activity during the natural history. Hence, studies on factors related to the immunologic response to HBV are needed for the Korean patients. For the treatment of chronic HBV infection, appropriate indication, the best antiviral agent, optimal duration, and long term safety, as well as efficacy need to be determined in the future studies. In addition, strategies to overcome vaccine non-response need to be warranted.

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