



Special Article



Epidemiological and Clinical History of Viral Hepatitis in Korea

Jung-Hwan Yoon ¹, Se Hyun Cho², Do Young Kim ³, Su Jong Yu ¹, and Kwang-Hyub Han ³

¹Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea

²Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

³Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

OPEN ACCESS

Received: Dec 28, 2020

Corresponding Author:

Kwang-Hyub Han, MD

Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.

Tel: +82-2-2174-2701

Fax: +82-2-393-6884

E-mail: gihankhys@yu.ac

This secondary publication is based on 'Korean Society of Infectious Diseases (KSID). Korean History of Infectious Diseases II. Seoul: Koonja; 2018. (ISBN 979-11-5955-379-0)'.

Copyright © 2021 by The Korean Society of Infectious Diseases, Korean Society for Antimicrobial Therapy, and The Korean Society for AIDS

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Jung-Hwan Yoon

<https://orcid.org/0000-0002-9128-3610>

Do Young Kim

<https://orcid.org/0000-0002-8327-3439>

Su Jong Yu

<https://orcid.org/0000-0001-8888-7977>

Kwang-Hyub Han

<https://orcid.org/0000-0003-3960-6539>

Conflict of Interest

No conflicts of interest.

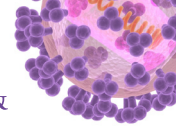
ABSTRACT

Viral hepatitis is the most important cause of acute and chronic liver disease in Korea. Particularly, hepatitis B virus (HBV) is the leading cause of liver-related mortality. Because of the nationwide vaccinations in the 1980s, hepatitis B surface antigen positive rates substantially decreased from 8% to 3%. Moreover, the introduction of potent nucleoside or nucleotide analogs led to the effective treatment of patients who had already been infected by HBV. The remaining issue has been to develop novel drugs that can cure HBV infection. Hepatitis C virus (HCV), on the other hand, is a hepatotropic virus that is parenterally transmitted. In Korea, the prevalence of HCV is estimated to be approximately 1%. Although no effective vaccine for HCV has been developed yet, highly effective and safe direct-acting antiviral therapy, which has a short treatment duration of 8–12 weeks, has made HCV eradication possible globally. Currently, the unsolved issue regarding HCV management is low disease awareness among patients and health care providers. Therefore, nationwide testing for anti-HCV would be a solution to identify patients infected with HCV but with no symptoms. Lastly, the Hepatitis A virus (HAV) is orally transmitted and results in acute hepatitis. In Korea, the young adult population is a high-risk group since this group is not vaccinated against HAV. More active vaccination and improved hygiene would be necessary to prevent HAV infection.

Keywords: Hepatitis A virus; Hepatitis B virus; Hepatitis C virus; Epidemiology

DOMESTIC OUTBREAKS AND EPIDEMICS

In Korea, research on viral hepatitis was first carried out by the United States (US) military doctors who served in the Korean War, and Professor Whan Kook Chung, who collaborated in the research as a Korean military doctor. The viral form was identified by liver biopsy of a patient with acute hepatitis in 1960 [1]. In particular, Professor Chung was the first to confirm anicteric hepatitis, which is common among Koreans, and reported a clinical type that progresses to chronic liver disease without jaundice. After the first reports of hepatitis B virus, medical treatment and research on viral hepatitis were conducted in Korea, and in 1971, acute and chronic hepatitis, cirrhosis, and liver cancer occurring in Korean adults were reported to be significantly related to the hepatitis B virus. Since then, the medical



Author Contributions

Conceptualization: KHH, JHY, DYK. Data curation: KHH, JHY, SHC, DYK, SJY. Formal analysis: JHY, DYK. Investigation: KHH, JHY, DYK. Methodology: JHY, DYK. Supervision: KHH. Validation: SHC, SJY. Writing - original draft: JHY, DYK, SJY. Writing - review & editing: KHH, JHY, SHC, DYK, SJY.

field in Korea began to differentiate between types A and B and in 1973, immunodiagnostic reagents for hepatitis A and B viruses were introduced into Korea. The use of these reagents revealed that hepatitis A is rare in adults over 10 years of age. Regarding hepatitis C, a report suspected its existence in 1979, but it wasn't until 1989, a year after the first identification of the hepatitis C virus that its presence in Korea was confirmed mainly following blood transfusion. Hepatitis C viral antibody testing subsequently became mandatory for blood donors, which significantly reduced hepatitis caused by blood transfusion [2].

The main cause of chronic liver diseases in Korea is the hepatitis B virus, which has the highest incidence rate, accounting for 60 – 70% of the causes of chronic liver disease and which significantly impacts the public health of Koreans, followed by hepatitis C virus. Hepatitis B virus, which proliferates only in the human body, causes inflammation in the liver when infected, and vertical infection from mother to neonate at birth is the main route of viral transmission. Until the 1970s and early 1980s, before the development of the hepatitis B vaccine, the hepatitis B surface antigen (HBsAg) positivity rate was as high as 7 – 8% in Korea's population and 14.2% in the school-age children, for which Korea was referred to as a hepatitis kingdom. Professor Chung Yong Kim identified various physical properties of these unknown antigens, and in June 1983, he, along with the Green Cross, was the first in Korea and the third in the world to develop 'Hepavax B' (Greencross, Seoul, Korea) [3]. Subsequently, with the implementation of a national vaccination program and management, the HBsAg seroprevalence has decreased significantly to around 3% of the total population.

A survey of 290,000 people that received medical checkups in Korea found that the prevalence rate of hepatitis C was about 0.8% nationwide [4]. Hepatitis C and hepatitis B are diseases that seriously threaten the health of Koreans, and comprise the third-highest causes of cirrhosis and the second-highest causes of liver cancer. Hepatitis C is an infectious disease that is transmitted through blood or body fluids. It was mainly transmitted through blood transfusions in the past, but since 1991, with the common use of hepatitis C viral screening of donated blood, the number of infections through transfusion has significantly decreased. Although it is difficult to identify the exact route of hepatitis C infection, research in Korea shows that intravenous drug abuse, injury from needle puncture, history of blood transfusion, and tattoos are significant risk factors for chronic hepatitis C infection [5]. Meanwhile, in a study of patients with acute hepatitis C in Korea, only about half of the patients had a history of exposure to contaminated blood such as acupuncture, surgery, and needle puncture, while the causes of infection in the other half of patients was unclear [6]. While hepatitis B, which is orally transmitted, is seasonal and may lead to group infections, periodic outbreaks of hepatitis C have not been reported. Since 2015, however, group infection through syringe reuse in several medical institutions has become a social problem.

Hepatitis A is closely related to hygiene and occurs more frequently in developing countries. Therefore, as socio-economic status and hygiene conditions improve, the incidence rates in many regions, including Korea are rapidly changing. Even 20 years ago, more than 90% of adults in Korea had antibodies that would provide protection against hepatitis A virus through natural infection during childhood; therefore, acute hepatitis A cases in adults were uncommon. However, due to improved hygiene conditions, the antibody positive rates due to have decreased, leading to increased numbers of adults without immunity to the virus. According to a recent report, the average age of hepatitis A patients was 29 years, with 87% of patients aged between 20 and 30 years; moreover, since 2000, the proportion of hospitalized

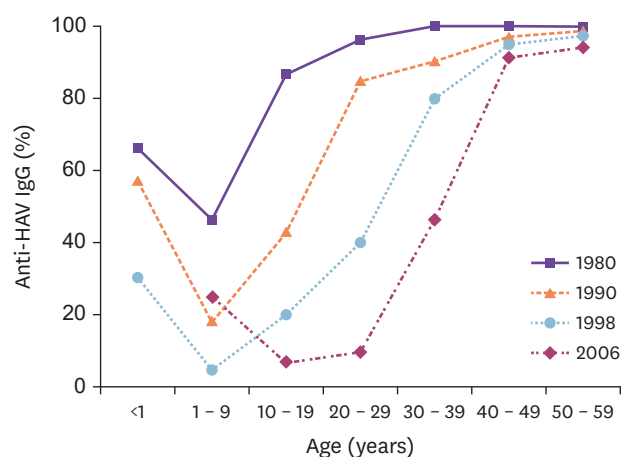


Figure 1. Changes in the epidemiology of the positive rate of hepatitis A antibodies in Korea between 1980 and 2006.
 ※ Source: The Korean Society of Gastroenterology [7].
 HAV, Hepatitis A virus.

patients has increased [7]. Since then, recognizing the importance of hepatitis A, hepatitis A vaccination has been recommended in adults under 30 years of age who are thought to have no antibodies. Subsequently, the incidence rate has been decreasing since it peaked in 2009.

The most common cause of acute viral hepatitis was hepatitis B from 1973 to 1984, with hepatitis A accounting for only 3.4%, of cases; however, the proportion increased to 49.5% from 2001 to 2003 and 94.6% from 2005 to 2007, becoming the main cause of acute viral hepatitis [8]. According to data from Korea Centers for Disease Control and Prevention, the number of reported cases of hepatitis A peaked in 2009 at 15,231, and active prevention measures led to a significant decrease to 1,129 cases 3 years later.

The changes in antibody positive rates by year in the literature are shown in **Figure 1**. Like other developed countries, Korea has shown rapid shifts in the epidemiology of hepatitis A [7].

Additionally, hepatitis D mainly occurs as a superinfection in hepatitis B patients, and hepatitis E is an acute hepatitis with similar clinical features to those of hepatitis A; however, a few cases have been reported in Korea, with infections occasionally reported after traveling abroad or among foreigners residing in Korea.

DOMESTIC CLINICAL FEATURES

Hepatitis B, C, and D viruses transmit infection via the parenteral route and have high risks of chronic progression, whereas hepatitis A and E viruses are mainly orally transmitted and manifest acute hepatitis as their major clinical form.

Hepatitis B and C are infectious diseases that require lifelong management. If not properly managed, infection could progress to chronic hepatitis, cirrhosis, liver cancer, and eventually death. Because the main route of hepatitis B is through vertical transmission at birth or in infancy, many cases have a family history. The high mortality rate from liver disease among middle-aged men in Korea is attributed to hepatitis B infection. Hepatitis C virus is transmitted horizontally and mainly affects adults. The disease gradually progresses; thus, cirrhosis

and liver cancer usually occur in patients over 60 years of age. Fortunately, it is possible to significantly reduce cirrhosis or liver cancer progression with antiviral drug treatment.

The hepatitis B treatment did not include specific antiviral drugs until the 1990s and only conservative treatment with liver supplements was possible. Even after interferon alpha was approved in 1993, it was only effective in some patients. In 1999, oral lamivudine (Zeffix[®]) (GlaxoSmithKline, London, United Kingdom) was launched in Korea and, for the first time, it was possible to suppress replication of hepatitis B virus and improve the treatment response of patients. However, limited reimbursement via national insurance and early discontinuation of the drug led to side effects and drug resistance, which worsened or continued hepatitis progression. In 2004, adefovir (Hepsera[®]) (GlaxoSmithKline, London, United Kingdom), which can inhibit lamivudine-resistant virus, was released as a second-line drug for patients in whom the first line of treatment had failed. While this solved the problem of resistance to some extent, secondary drug resistance problems such as the appearance of adefovir-resistant virus occurred. The advent of pegylated interferon alpha, which can be used once weekly, led to increased patient convenience compared to interferon, along with the advantage of shorter treatment periods; however, the therapeutic effect was insufficient compared to oral drugs. In 2007, entecavir (Baraclude[®]) (Bristol Myers Squibb, New Jersey, USA), which has superior antiviral effects and a significantly lower incidence of resistant viruses compared to the previous drugs, was released in Korea, and clevudine (Levovir[®]) (Bukwang Pharm, Seoul, Korea), which was developed by a Korean pharmaceutical company, was also expected to have better antiviral inhibitory effects than existing drugs. With telbivudine (Sebivo[®]) (Novartis, Basel, Switzerland) joining the domestic market, competition for antiviral drugs based on their efficacy and safety began. Eventually, as the problem with resistance was the most important aspect, entecavir, which showed superiority in this area, won the competition, and the use of the other two drugs gradually declined in Korea and abroad. In 2012, tenofovir (Viread[®]) (Gilead, California, USA), which was effective for both first-line therapy and resistant viral infections, was launched and is currently widely used to treat hepatitis patients in clinical practice [9]. However, the problem of long-term administration such as bone and kidney toxicity needs to be addressed.

Regarding hepatitis C, the combination of oral ribavirin with interferon for 6 – 12 months increased the treatment success rate to approximately 40%. In the mid-2000s, pegylated interferon, which improved the antiviral efficacy and side effects of the existing interferon, was combined with ribavirin, which further increased the treatment success rate to 50 - 80% (70 - 90% in Koreans). In the early 2010s, direct-acting antiviral agents, which directly inhibit hepatitis C virus replication, unlike interferon, which uses the human body's immune response, was introduced and in 2015, the era of oral drug therapy without the need for interferon began in South Korea. Currently, hepatitis C has a high treatment success rate of 96 - 100% by treating for 8 - 12 weeks using various oral drugs according to the virus genotype and patient condition. Although there was a time when the use of therapeutic drugs was limited due to their high costs, insurance coverage allowed hepatitis to be easily treated with antiviral drugs.

Hepatitis A has a mild clinical course in children, but clinical symptoms are apparent in adults and can lead to serious conditions. According to data from a 2007 – 2009 survey of 4,218 hepatitis A patients conducted by the Korean Association for the Study of the Liver (KASL), patients showed atypical symptoms such as renal failure (2.73%), liver failure (0.91%), recurrent infection (0.65%), and fibrosing cholestatic hepatitis (1.92%) and 19

patients (0.45%) experienced critical conditions such as death or liver transplant [10]. Therefore, it is important to take measures to prevent hepatitis A from reaching a severe illness by ensuring rapid diagnosis.

PREVENTION AND MANAGEMENT

The first hepatitis B vaccination began in 1983. The cost was greatly reduced with the development of a vaccine in Korea and further reduced in 1985 with the development of a genetically modified vaccine. In 1987, the Program for Appropriate Technology in Health, a global organization for preventing diseases, selected Hepavax-B (Greencross, Seoul, Korea) for a large-scale hepatitis eradication project aimed at global hepatitis B eradication. In addition, to escape the stigma of Korea as the "Hepatitis B kingdom" ahead of the Seoul Olympics, the government established the "Hepatitis B eradication 5-year Plan" in 1984, which promoted a government-level preventative project for hepatitis B that became the cornerstone of the national vaccination project for infants and toddlers. The "Hepatitis B Perinatal Infection Prevention Program," aimed to protect newborns from perinatal infection (the main route of hepatitis B infection), supported the cost of immunoglobulin treatment, vaccination, and antigen and antibody testing in infants born from mothers positive for hepatitis B infection. The Korea Centers for Disease Control and Prevention successfully implemented this program in over 3,000 institutions nationwide (health care and medical institutions) with the cooperation from the related societies and associations [11].

Since then, the HBsAg positive rate has decreased significantly from 8.3% of the population in 1995 to 4.6% in 1998, 3.7% in 2005, and 3.0% in 2011. In particular, as more than 95% of infants are vaccinated nationally, the current HBsAg positive rate in adolescents has decreased significantly to less than 0.2%, considerably lowering the prevalence and mortality of chronic hepatitis.

In terms of hepatitis B, since its first identification 50 years ago, several countries have successfully managed the disease as an axis of national health policy in terms of prevention and treatment. Korea is one of countries that have successfully managed the disease, with the most remarkable reduction in mortality due to liver diseases in the past 30 years. However, approximately 3% of the Korean population is still infected with hepatitis B virus. To eradicate the virus, an established disease surveillance system is essential to monitor the prevalence of hepatitis B and systematically manage chronic hepatitis B patients. For this, it is necessary to establish a "hepatitis B integrated management system" that can systematically operate a preventive vaccine program, a perinatal infection prevention program, and antiviral treatment for hepatitis B patients.

Since there is no vaccine available for hepatitis C, active antiviral treatment is the most important method to manage hepatitis; however, the national medical checkup by the National Health Insurance Service does not currently include the antibody test used for hepatitis C screening. Therefore, many asymptomatic hepatitis C patients who do not undergo blood tests are unaware of their infection status. According to the "Public Liver Disease Awareness Survey" conducted by the KASL, only 10.4% of the 3,000 respondents had been tested for hepatitis C and 1.6% of all respondents tested positive. Therefore, it can be assumed that there are a large number of patients with hepatitis C who are unaware of their status because they have not had the opportunity to be tested. Accordingly, measures must

be developed to increase the hepatitis C diagnosis rate through active screening tests at the national level [11].

Epidemiological studies thus far show that unlike in the West where illegal intravenous injections are the main route of hepatitis C infection, the prevalence of hepatitis C in Korea is high among the elderly, especially in coastal areas. Exposure to needles, dental procedures, tattoos, and invasive medical practice have been identified as risk factors for infection. In addition, patients have high exposure to Oriental medicine procedures such as acupuncture, moxibustion, and cupping. Moreover, dental clinics, Oriental medicine clinics, acupuncture clinics, and tattoo parlors have low awareness of infection control and have no obligation to report infections. In the last 2 years, three episodes of hepatitis C infection occurred through medical institutions; these group infections have been attributed to the reuse of disposable syringes. Since the general population is likely to be exposed to infectious agents in medical institutions where invasive procedures are performed, realistic and overarching infection control measures for these institutions are required.

As the incidence of acute hepatitis A in adults in Korea has increased since 2000, the focus is on preventing hepatitis A through vaccination. The hepatitis A vaccination guideline for adults suggest vaccination without hepatitis A antibody testing in individuals under 30 years of age, while those over 30 years of age should be checked for the presence of hepatitis A virus immunoglobulin G antibodies through screening and vaccinated only when the result is negative. Currently, all vaccines that are widely used are inactivated vaccines, and in Korea, a booster is recommended to be administered 6 months after the first vaccination. The incidence of hepatitis A is gradually decreasing due to vaccination; however, the rate of vaccination is very low in young adults. Since hepatitis A vaccination in Korea began in 1997, most of the age groups born before 1997 do not have immunity against the hepatitis A virus. This lack of vaccination leads to a risk of developing hepatitis A. In particular, it is important to be mindful of recurrence due to the increase in the numbers of overseas travelers and people more commonly living in groups. In addition, hepatitis A is designated as a group 1 infectious disease, which requires that cases be reported to the local public health center without delay. Since 2011, the Korea Centers for Disease Control and Prevention has been continuously monitoring hepatitis A cases nationwide.

Recently, the World Health Organization (WHO) proposed a goal of reducing the incidence of new viral hepatitis cases by 90% and the mortality rate by 65% by 2030. Korea was previously designated as a representative country for managing hepatitis B by the WHO, following the introduction of an oral hepatitis C drug with excellent treatment results, identifying and treating asymptomatic hepatitis C patients to eliminate the source of infection would lead to the country to be once again recognized for excellent hepatitis C management [12]. Achieving this goal requires additional support for expensive hepatitis C treatment by expanding the government coverage and subsidizing the treatment costs.

Viral hepatitis C became manageable only in the 21st century with national attention and support. Korea has been relatively successful in preventing and managing viral hepatitis through academic and government efforts. Although financial resources have been invested and national attention is focused on preventing acute infectious diseases, the management of chronic infectious disease tends to be somewhat neglected. However, viral hepatitis can be more consistently prevented and cured with effective policies, and cooperation between the medical community and government may lead to fewer people losing their health and lives due to this disease.

REFERENCES

1. Chung WK, Kim KS, Lee JK, Moon SK. Long-term follow-up studies of acute viral hepatitis. *Korean J Med* 1975;18:428-51.
2. Jeong GW, Seon HS, Jeong HG, Sin HG, Park CG, Yu JY, Di Bisceglie AM, Waggoner JJ, Hoofnagle JH. A preliminary report on the prevalence of type C hepatitis in Korea. *Korean J Med* 1990;38:750-4.
3. Kim CY. Prevention of Viral Hepatitis, Type B, by vaccination with purified hepatitis B surface antigen. *J Korean Med Assoc* 1979;22:1013-25.
4. Kim DY, Kim IH, Jeong SH, Cho YK, Lee JH, Jin YJ, Lee D, Suh DJ, Han KH, Park NH, Kang HY, Jung YK, Kim YS, Kim KA, Lee YJ, Lee BS, Yim HJ, Lee HJ, Baik SK, Tak WY, Lee SJ, Chung WJ, Choi SK, Cho EY, Heo J, Kim DJ, Song BC, Kim MW, Lee J, Chae HB, Choi DH, Choi HY, Ki M. A nationwide seroepidemiology of hepatitis C virus infection in South Korea. *Liver Int* 2013;33:586-94.
[PUBMED](#) | [CROSSREF](#)
5. Seong MH, Kil H, Kim YS, Bae SH, Lee YJ, Lee HC, Kang BH, Jeong SH. Clinical and epidemiological features of hepatitis C virus infection in South Korea: a prospective, multicenter cohort study. *J Med Virol* 2013;85:1724-33.
[PUBMED](#) | [CROSSREF](#)
6. Kim JY, Won JE, Jeong SH, Park SJ, Hwang SG, Kang SK, Bae SH, Kim YS, Lee HC. Acute hepatitis C in Korea: different modes of infection, high rate of spontaneous recovery, and low rate of seroconversion. *J Med Virol* 2011;83:1195-202.
[PUBMED](#) | [CROSSREF](#)
7. Jeong SH. Current status and vaccine indication for hepatitis A virus infection in Korea. *Korean J Gastroenterol* 2008;51:331-7.
[PUBMED](#)
8. Jung YK, Kim JH. Epidemiology and clinical features of acute hepatitis A: from the domestic perspective. *Korean J Hepatol* 2009;15:438-45.
[PUBMED](#) | [CROSSREF](#)
9. The Korean Association for the Study of the Liver. 2015 Chronic hepatitis B clinical practice guideline. Seoul: JIN & JPNC; 2015.
10. Kwon SY, Park SH, Yeon JE, Jeong SH, Kwon OS, Lee JW, Kim HS, Seo YS, Kim YS, Sohn JH, Yim HJ, Choi JY, Lee MS, Kweon YO, Cheong JY, Kim HC, Lee HJ, Baik SK, Kim DY, Lee HC, Heo J, Song BC, Kim YJ, An H, Byun KS, Lee CH. Clinical manifestations and outcome of acute hepatitis A in Korea: A multi-center study, 2007-2009. *Korean J Hepatol* 2010;16(Suppl 3):S17.
11. Korean Association for the Study of the Liver. White paper on liver diseases in Korea. Seoul: JIN & JPNC; 2013.
12. Kim DY, Han KH, Jun B, Kim TH, Park S, Ward T, Webster S, McEwan P. Estimating the cost-effectiveness of one-time screening and treatment for hepatitis C in Korea. *PLoS One* 2017;12:e0167770.
[PUBMED](#) | [CROSSREF](#)