REVIEW ARTICLE

Reducing the mortality rate of hepatitis and liver cancer in Japan

Shinji Iwane MD, PhD | Satoshi Oeda MD, PhD | Yuichiro Eguchi MD, PhD

Liver Center, Saga University Hospital, Saga, Saga, Japan

Correspondence
Satoshi Oeda, Liver Center, Saga University Hospital, Saga, Saga, Japan.
Email: ooedasa@edu.cc.saga-u.ac.jp

Abstract
The Basic Act on Hepatitis Countermeasures issued in 2009 states the comprehensive measures that can be taken against viral hepatitis as well as the responsibility that the national government, local governments, health insurance providers, physicians, and citizens should take in these measures, thereby organically facilitating the construction of a hepatitis management system in Japan. In addition, the Committee for the Clinical Management of Hepatitis has established branches in each prefecture to create a hepatitis management network for public hepatitis screening facilities, primary care physicians, medical institutions specializing in hepatitis, and primary hospitals for cooperative medical care of liver diseases to address regional hepatitis-related issues.

KEYWORDS
Basic Act on Hepatitis Countermeasures, hepatitis screening, viral hepatitis

1 | INTRODUCTION

In Japan, more than 70% of cirrhosis cases are caused by viral infection with either hepatitis C virus or hepatic B virus (60.9% caused by HCV and 12.0% by HBV, respectively), and persistent HCV infection is responsible for approximately 70% of deaths from hepatocellular carcinoma. When untreated, viral hepatitis is likely to progress to cirrhosis and subsequently to liver cancer without giving rise to subjective symptoms; therefore, it is necessary to establish highly effective countermeasures. Japanese citizens undergo screening for hepatitis (by any cause) at least once in a lifetime and then subsequent comprehensive examination and antiviral therapy (or liver support therapy in those contraindicated for antiviral therapy) as first-line treatment for as long as possible when the screening result is positive. The current mainstream drug for HCV is direct-acting antivirals (DAAs). DAAs therapy is curative in more than 90% of chronic hepatitis C patients.

The seamless operation of this three-step (screening, diagnosis, and treatment) system is essential for the management of hepatitis and liver cancer.

In 2002, the Japanese government initiated urgent and comprehensive countermeasures against hepatitis C and hepatocellular carcinoma, including screening at health checkups conducted at milestone ages as well as at routine annual health checkups in accordance with the national Project for the Screening of Specific Infectious Diseases and the Health and Medical Service Act for the Aged. In January 2007, the Guidelines for the Establishment of a Post-screening Management System for Hepatitis C at the Prefecture Level were developed by the Council for the Clinical Management of Hepatitis C to apply community health care provided by primary care physicians as a foundation toward organizing primary hospitals for the cooperative medical care of liver diseases and specialized institutions as well as to develop a hepatitis management network in each prefecture. In February 2008, the 7-year Treatment Strategy for Hepatitis was established to provide medical care to patients with hepatitis and overcome the disease. A public subsidy system for medical expenses on antiviral treatment such as interferons and DAAs was also initiated in 2008. As demonstrated by these programs, Japan has initiated the development of groundbreaking strategies and made efforts to establishing appropriate environments around patients with viral hepatitis by promoting cooperative medical care between primary care physicians, specialists, and specialized medical institutions. Furthermore, the Basic Act on Hepatitis Countermeasures was promulgated in 2009 and was first put into force on January 1, 2010, to promote various approaches to overcoming hepatitis, for example, by honoring the human rights of individuals with
TABLE 1  The basic act on hepatitis countermeasures and the basic guidelines for the prevention and management of hepatitis (excerpt)

| Article 1: |
|---|
| This Act hereby declares the basic principles of the measures against hepatitis; clarifies, in relation to the measures, the responsibility of the national government, local governments, health insurance providers, citizens, and physicians; and promotes the measures against hepatitis comprehensively by determining the fundamental issues in the measures and establishing guidelines to promote the measures |

| Article 9: |
|---|
| The Minister of Health, Labour and Welfare shall formulate the Basic Guidelines for the Prevention and Management of Hepatitis (hereinafter, Hepatitis Prevention Guidelines) to promote the measures against hepatitis comprehensively |

(2) The basic issues in the Hepatitis Prevention Guidelines are as follows:

(i) The prevention of hepatitis and the promotion of the treatments
(ii) Matters concerning the preventive measures against hepatitis
(iii) Matters concerning the improvement of the hepatitis screening system and the capability
(iv) Matters concerning the establishment of a system to provide treatment for hepatitis
(v) Matters concerning the fostering of human resources for the prevention and treatment of hepatitis
(vi) Matters concerning the survey and research on hepatitis
(vii) Matters concerning the research and development of drugs for treating hepatitis
(viii) Matters concerning the education and dissemination of knowledge about hepatitis and the respect for human rights in care of patients with hepatitis
(ix) Other important matters concerning measures for the prevention of hepatitis

(2), Paragraph 2; (i), Item 1; (i), Item 1; (ii), Item 2; (iii), Item 3; (iv), Item 4; (v), Item 5; (vi), Item 6; (vii), Item 7; (viii), Item 8; (ix), Item 9.

hepatitis viral infection and of patients with hepatitis while also providing high-quality, appropriate medical care. This has led to the nationwide practice of measures against hepatitis and liver cancer, in order to realize the early detection and early treatment of hepatitis.

Article 1 of the Basic Act on Hepatitis Countermeasures declares that the Act aims to promote the measures against hepatitis comprehensively by clarifying the responsibility that the national government, local governments, health insurance providers, physicians, and citizens should take; by establishing guidelines for the promotion of the measures; and by specifying the fundamentals of the measures (Table 1).

Paragraph 1 of Article 9 states that the Minister of Health, Labour and Welfare should establish the Basic Guidelines for the Promotion of Hepatitis Preventive Measures to comprehensively promote the measures against hepatitis. Of the nine guideline items in Paragraph 2 Article 9, items 1, 3-5, and 8 relate to healthcare systems. Therefore, in line with these guidelines, this article will discuss the future challenges and directions of the hepatitis management system and cooperative medical care system (Table 1).

We review the latest polices of hepatitis in this article.

1.1  |  Prevention, care, and treatment of hepatitis, cirrhosis, and liver cancer caused by hepatitis viruses (written as “hepatitis management” in the guidelines)

In Paragraph 2 of Article 9, Item 1 generalizes the contents of items 2-9. It is important to follow this idea to proceed seamlessly with the above-mentioned three steps: screening, diagnosis, and treatment (Table 1).

First, Japanese citizens should be screened for hepatitis at least once. The risk factors for infection by HBV and HCV are family history, a history of blood transfusion or surgery, and the use of blood products. However, it is unwise to limit consideration to only these risk factors, due to the involvement of other factors in previous cases of HBV and HCV infection. Therefore, it is important for all prefectures to establish a screening system for hepatitis and urge residents to undergo screening. As of December 2015, hepatitis screening is provided free of charge in every prefecture, city with a public health center, and Tokyo special ward (Table 2).

In 1990, Saga Prefecture pioneered a prefectural project for the screening of liver diseases. However, as of 2010, only about 50% of residents have been screened for hepatitis, with especially problematically low rates among residents in their fortieths to fifties. Since 2002, hepatitis screening has been a part of routine annual health checkups across Japan. However, a survey of approximately 300 residents of Saga Prefecture between July and November 2012 revealed that while approximately 70% of residents were aware that infection with hepatitis virus is a cause of liver cancer, only 30% knew that hepatitis screening was essentially free of charge. This suggests that the announcements of hepatitis screening on newsletters and official Web sites by individual prefectural and local governments do not serve as sufficient information sources on hepatitis to the general public. Therefore, it will be necessary to develop a channel dedicated to provide health-related information including hepatitis.

A follow-up study of 272 Saga residents who were diagnosed as being HCV-positive in the free hepatitis screening provided by the prefecture since 2008 showed that 194 subsequently underwent comprehensive examination and only 32 of those were treated in antiviral therapy. This means that 78 and 41 HCV-positive residents dropped out of the system before undergoing comprehensive examination and the indicated interferon treatment, respectively. Therefore, factors that cause these dropouts at each step must be investigated to establish appropriate measures against dropouts.

1.2  |  Establishing a system to screen for hepatitis

With the causal factors of liver cancer in mind, the first step toward efficiently tracking down high-risk groups is to screen for residents
TABLE 2  Current status of hepatitis countermeasures implemented by local governments (documents on the 10th Council for the Promotion of Measures against Hepatitis held by the Ministry of Health, Labour and Welfare; http://www.mhlw.go.jp/stf/shingi/000013314.html)

Current status of hepatitis countermeasures implemented by local governments (as of April 1, 2013)

| Local governments | Public health center | Medical institutions |
|-------------------|----------------------|----------------------|
|                   | Free screening | To be performed | Paid screening | Performed | To be performed |
|                   | Performed | | | Performed | |
| Prefectures (47)  | 47 | 0 | 0 | 39 | 0 |
| Cities with a public health center (70) | 61 | 0 | 0 | 50 | 0 |
| Tokyo special wards (23) | 16 | 0 | 0 | 13 | 0 |
| Total (140)       | 124 | 0 | 0 | 102 | 0 |

Screening is provided free of charge in all prefectures, all cities with a public health center, and all special wards.

*Survey conducted in all prefectures, all cities with a public health center, and all special wards (140 total).

1-1. Implementation of hepatitis screening (as a part of the national project for the screening of specific infectious diseases)

* Major reasons for not providing screening free of charge.
(2) (when medical institutions provide no screening services).
Screening is free at public health centers (18).
Screening is free at medical institutions as a health promotion project [[at routine health check-ups?]] (17).
(3) (when public health centers provide no screening services).
Screening is free at medical institutions (13).
infected with hepatitis viruses. Because hepatitis screening is indeed part of health checkups offered by local governments and business owners, individuals undergoing health checkups need to be educated about the significance of hepatitis screening. In addition, because many health checkups are performed at medical institutions under agreement with local governments or business owners, public health nurses, attending and industrial physicians, and other healthcare professionals must explain the significance of hepatitis screening and provide easy-to-understand feedback on the screening results. The nationwide survey on the current status of hepatitis screening conducted by the Ministry of Health, Labour and Welfare between 2011 and 2012 revealed that 39.8% and 30.4% of individuals who were received hepatitis screening for HBV and HCV, respectively, did not recall having previously undergone hepatitis screening. Therefore, it is necessary to establish a new tool to provide screening results and related information as well as to record the results. However, in the case of the hepatitis screening offered by local governments, it may be necessary to instead investigate how to utilize the existing screening program more efficiently, if the program is under financial constraints due to priorities between administrative issues.

It is estimated that a considerably large number of hepatitis screenings are conducted in Japan in the form of a pregnancy checkup, and preadmission and preoperative screening. In 2010, 1.07 million women delivered one or more children, 0.6-0.7 million of whom were born before 1986, the year when the measures against mother-to-child transmission of HBV were put into place. Considering that the rate of HBV infection was approximately 0.3% prior to 1986, about 2000 HBV carriers are thought to give birth every year. HBV vaccination has been performed to prevent mother-to-child vertical transmission of HBV, but the current system to follow-up mothers infected with HBV does not appear to be adequate.

The 2010 survey on the current status of preadmission and preoperative screenings for hepatitis at our institution showed that 126 (1.9%) of 6648 individuals were positive for HBV antigens, while 487 (7.4%) of 6612 were positive for HCV antibodies. However, 80% of the suspected carriers of HBV or HCV did not have a consultation with the specialist in liver disease.

The majority of hepatitis screenings are performed in daily clinical practice without professional input from hepatologists. Therefore, it is necessary that healthcare professionals involved in hepatitis screenings have sufficient understanding and provide adequate support. Since 2008, the Hepatitis Information Center at the National Center for Global Health and Medicine has held workshops at primary hospitals in each prefecture on the screening and treatment of hepatitis 2-4 times a year, mainly conducted with healthcare professionals in leadership positions such as physicians, nurses, counselors specialized in liver diseases, and government personnel involved in hepatitis-related medical care.

1.3 Establishing a system to provide medical care for hepatitis

Four factors have been identified as adversely affecting the seamless operation of the management system for viral hepatitis: positive viral hepatitis in screening with no subsequent comprehensive examination, definitive diagnosis of viral hepatitis in comprehensive examination but no subsequent antiviral therapy, lack of proper treatment, dropout of follow-up, and termination of treatment (Figure 1). Local primary care physicians treat patients who are in stable condition or who are receiving ongoing, individualized treatment. In addition, close cooperation between medical institutions is essential, as the involvement of hepatologists and medical institutions specialized in liver diseases is necessary to accurately determining pathological conditions and the appropriate treatment approach in each cases. To this end, the establishment of the Committee for the Clinical Management of Hepatitis in each prefecture began in 2006 and in line with hepatitis-related issues in each prefecture. Furthermore, a network for the clinical management of hepatitis is currently being constructed as a cooperative system between the organizations that provide hepatitis screening for local governments, primary care physicians, medical institutions specialized in liver disease, and primary hospitals for cooperative medical care of liver diseases (Figure 2).

The Guidelines for the Establishment of a Post-screening Management System for Hepatitis C at the Prefecture Level, published in 2007, urges public health centers and municipalities to take into account the current situation in each prefecture and more specifically to perform the following when recommending comprehensive examination to individuals who are positive for hepatitis viruses:

1. To recommend that each patient with a positive screening result visit a medical institution specialized in liver diseases at least once, if possible, for the accurate diagnosis of disease pathology and the determination of appropriate treatment strategies.

2. To continuously educate patients who are positive for hepatitis viruses about the importance of involving specialized medical institutions in the determination of appropriate treatment strategies even if they visited their primary care physicians first.

3. To educate patients who are positive for hepatitis viruses about returning to their primary care physicians once their conditions are stabilized by treatment designed and provided at specialized medical institutions.

4. To educate patients about periodically visiting specialized medical institutions for the early detection of liver cancer even when patients have been treated by their primary care physicians.

In addition, prefectoral and municipal governments will actively gather information on medical care for liver diseases provided at individual medical institutions, and the information on the treatments and the names of institutions will be released using media such as the Internet, public relations magazines, and posters. In addition, the governments create leaflets about the local clinical treatment system for liver diseases and develop hepatitis patient notebooks, as it is essential to make the hepatitis management network common knowledge among local residents.

The roles and requirements that primary care physicians, specialized medical institutions, and primary hospitals for the cooperative medical care of liver diseases should play and fulfill are as follows:
1. Because of their close relationships with patients, primary care physicians are responsible for not only the treatment of liver diseases, but also general care, thereby functioning as foundations in community health care. Primary care physicians are also responsible for drug prescription, injections, and routine screenings, and for providing referrals to specialized medical institutions.

2. Specialized medical institutions are required to (i) make an accurate diagnosis and establish appropriate treatment strategies, (ii) provide optimal antiviral therapy such as DAAs, and (iii) determine high-risk groups and perform ideal follow-up and early treatment. It is desirable for each secondary medical district to have more than one specialized medical institution. However, these institutions are selected by the Committee for the Clinical Management of Hepatitis in each prefecture based on the number of full-time specialists certified with the Japan Society of Hepatology, on the situation of medical care provided and the number of treated cases at each institution, and on local circumstances such as population distribution, disease prevalence, and convenience of transportation.

3. Primary hospitals for cooperative medical care on liver diseases, designated by the Committee for the Clinical Management of Hepatitis in each prefecture, are medical institutions that can (i) provide general information on the treatment of liver diseases, (ii) collect and provide information on medical institutions specialized in liver diseases in each prefecture, (iii) hold workshops and lectures targeting healthcare professionals and local residents and provide counseling on liver diseases, and (iv) establish a forum on liver diseases with specialized medical institutions. The primary hospitals are required to establish a hepatitis information center where patients and their families and local residents can directly obtain counseling in person or by phone. The centers are expected to enhance the support and counseling system and strengthen the support system for mental health, enabling patients with hepatitis and their families to improve quality of life while undergoing treatment for hepatitis.

Because of the low number of hepatologists in Saga Prefecture, the local government constructed a system to provide treatments for liver diseases in collaboration with the Saga Prefecture Medical Association on Liver Cancer (currently the Saga Prefecture Medical Association on Measures against Liver Cancer). In this system, meetings are held to offer certain lectures in an attempt to build collaborative relationships between primary care physicians and specialized medical institutions. In 2011, the institutions were further divided into primary hospitals for cooperative medical care on liver diseases, medical institutions specialized in liver diseases, and cooperating medical institutions, and their roles in antivirus therapy, comprehensive examination, and the public subsidy system for medical expenses on the treatment of hepatitis were clarified. It is necessary to not only maintain this framework, but also construct an organic and human network to realize an ideal system of cooperative medical care between primary care physicians, who introduce medical institutions specialized in liver diseases at least once, and specialized medical institutions, which introduce primary care physicians after comprehensive examination.
1.4 | Education and provision of information about hepatitis and the development of human resources for the prevention and treatment of hepatitis, and for education about the human rights of patients with hepatitis

To prevent new cases of infection with hepatitis virus and to improve treatment standards, it is important to develop human resources for the prevention and treatment of hepatitis. In addition, it is necessary to establish job positions that serve as a bridge to facilitate cooperation between hepatitis testing facilities and primary care physicians as well as specialized medical institutions. To achieve this, in 2009, Yamanashi Prefecture became the first prefecture in Japan to foster clinical coordinators for patients with liver diseases. In 2011, a national project was launched to promote the fostering and placement of hepatitis care coordinators (the exact title of this position varies regionally; these coordinators may be called “liver disease clinical coordinators,” “liver disease care coordinators,” or “hepatitis care coordinators”) in each prefecture, and as of June 2015, 33 prefectures have established the fostering and placement system. The role of the coordinators includes (i) the prevention of hepatitis virus infections through the provision of information and screening for hepatitis as well as the recommendation and explanation of the significance of comprehensive examination to individuals with positive screening results, (ii) the recommendation and explanation by primary care physicians of the significance of comprehensive examination and specialized treatment, and (iii) the provision of smooth, safe antiviral therapy at specialized medical institutions. The coordinators also assist patients in taking advantage of public subsidy systems and returning to work after treatment. Coordinators are also expected to take a leadership position to improve the regional treatment system for liver diseases and to promote public awareness of the importance of developing a social climate where patients with hepatitis can live peacefully without unfair discrimination. New clinical coordinators are enter the field every year across Japan and are expected to create opportunities to play active roles in the cooperative medical care system for liver diseases. In the future, medical institutions should design additional approaches, such as the improvement of clinical environments, the development of tools for guiding patients, and the continuous provision of follow-up courses.

2 | CONCLUSION

In Japan, the hepatitis management system is being constructed organically owing to the specification of the roles of the national government, local governments, citizens, and primary care physicians and other healthcare professionals, including specialists, in the Basic Act on Hepatitis Countermeasures. The establishment of a proper clinical treatment system, especially a cooperative medical care system, is underway for various diseases other than liver diseases, but the hepatitis management system is innovative because it was designed and is currently operated to manage the disease nationwide. However, many Japanese citizens have not yet undergone hepatitis screening, or even are unaware of the disease. In addition, some individuals do not take any action even though they are aware that they carry the hepatitis virus. Consequently, in daily clinical practice, we encounter many cases of hepatitis with no ideal treatment approach due to the lack of early treatment. As the aging of patients with viral hepatitis progresses, it is important for all the players in the treatment of hepatitis to cooperate more closely to address challenges.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

REFERENCES

1. Suzuki Y, et al. Actual situation of non-B, non-C liver cirrhosis in Japan. In: Kogo Y, et al., editors. Survey of non-B, non-C liver cirrhosis in Japan. 1st ed. Sapporo: Kyobunsha, 2012; p. 6–16.
2. Kumada H, Chayama K, Rodrigues L Jr, et al. Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir for hepatitis C virus genotype 1b-infected Japanese patients with or without cirrhosis. Hepatology. 2015;62:1037–46.

3. Omata M, Nishiguchi S, Ueno Y, et al. Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. J Viral Hepatitis. 2014;21:762–8.

4. Kumada H, Suzuki F, Suzuki Y, et al. Randomized comparison of daclatasvir + asunaprevir versus telaprevir + peginterferon/ribavirin in Japanese hepatitis C virus patients. J Gastroenterol Hepatol. 2016;31:14–22.

5. National hepatitis C roundtable. The Guidelines for the Establishment of a Post-screening Management System for Hepatitis C at the Prefecture Level. Tokyo: Japanese Ministry of Health, Labour and Welfare; 2006, in Japanese.

6. Iwane S, Eguchi Y, Yoshihara D, et al. Aiming to improve the screening and examination rate of viral hepatitis patients - efforts to viral liver disease in Saga Prefecture. Kanzo. 2015;56(suppl 3):901, in Japanese.

7. Japanese Ministry of Health, Labour and Welfare. Survey of the current status of hepatitis screening in 2011. Tokyo: Survey Research Center Co; 2012, in Japanese.

8. Ministry of Health, Labour and Welfare. Vital Statistics in Japan, 2011.

9. Furukawa NE, Kawaguchi Y, Oeda S, et al. Current management practices for HBs antigen or anti-HCV antibody positive individuals in non-hepatology departments. Kanzo. 2013;54:307–16, in Japanese.

10. The Hepatitis Information Center. The documents used in the workshop. Available from http://www.kanen.ncgm.go.jp/study.html. Accessed January 2, 2016.

11. Eguchi Y. Treatment status in Japan. KAN·TAN·SUI. Vol. 71, No. 6. Tokyo: Arcmedium; 2015; p. 1175–83, in Japanese.

---

How to cite this article: Iwane S, Oeda S, Eguchi Y. Reducing the mortality rate of hepatitis and liver cancer in Japan. J Gen Fam Med. 2017;18:205–211. https://doi.org/10.1002/jgf2.42