

Time for Action on Viral Hepatitis

Seng Gee Lim,¹ MBBS, FRACP, FRCP

Abstract

The recent outbreak of hepatitis C virus (HCV) at Singapore General Hospital (SGH) has highlighted the dangers of viral hepatitis. In this case, infection control and environmental contamination were the culprits, particularly, a drop of blood containing 5 million IU HCV. From a broader perspective, there has been a revolution in HCV therapy with the recent rapid evolution of short-term (12 weeks) safe, all oral directly-acting antiviral (DAA) therapy leading to cure rates of 90% to 100%, even in previously difficult to treat patients with liver cirrhosis, previous treatment failure and those on immunosuppression. Consequently, treating HCV in risk groups such as renal dialysis and haemophiliacs can eliminate a pool of infected patients to prevent future outbreaks. A seroprevalence study is needed to identify a possible “birth cohort” effect that could aid screening. For HBV, vaccination has reduced prevalence to 3.8%, but these patients are prone to complications such as HBV flares. Since 2014, 13 patients developed liver failure and were listed for liver transplantation at National University Hospital (NUH) but 6 died beforehand. This avoidable catastrophe is due to undiagnosed HBV infection or patients who did not return for follow-up. Good antiviral therapy is available, but the issues are similar to HCV, identification of patients and linkage to care. A cure seems likely in the future as pharmaceutical companies are developing new agents. Singapore has joined in this initiative with a recent award of a national research translational grant to better understand the pathophysiology and the processes needed for a cure of HBV.

Ann Acad Med Singapore 2016;45:27-30

Key words: Eradication, Hepatitis C, Linkage to care, Outbreaks, Screening, Treatment

The recent hepatitis C virus (HCV) outbreak in the renal ward at Singapore General Hospital (SGH) brought to public attention a little known virus. Little known to the public in Singapore largely due to the relatively low local prevalence, a revolution was occurring in hepatitis C therapy. Up to 2010, the standard treatment was a combination of injectable pegylated interferon and orally taken ribavirin. Although Asians responded to this very well with cure rates (defined as sustained virological response or SVR) of 70% to 90%,¹ the treatment usually took at least a year and was accompanied by significant side effects which led to the discontinuation of therapy in 9.6% to 13% of patients.² Outside Asia, response rates were even lower—around 40% due to the unfavourable polymorphisms of the *IL28B* interferon response gene,³ unlike Asians who have the good response genotype. All this changed in the last 5 years with the rapid evolution of all-oral therapy (called

direct-acting antivirals or DAAs) leading to SVR rates of >90%, even in previously difficult to treat patients such as those with cirrhosis, liver failure, immunosuppression and prior treatment failure.⁴ In the latest treatment regimens, SVR of 97% to 100% after only 12 weeks of therapy using a combination of sofosbuvir and velpatasvir across all genotypes, can be achieved.⁵ Noteworthy is the finding that most of the DAAs are relatively free of side effects and well tolerated, although drug interactions need to be monitored.⁶ While there are many possible combinations of antiviral therapy available that are highly efficacious, some confusion remains on the choice of therapy. A roadmap of HCV treatment in Asia provides a guide to clinicians on therapeutic choices.⁴

With this background in mind, it is timely to reflect back on the HCV outbreak at the SGH renal unit. HCV is a relatively asymptomatic infection testified by the millions

¹Division of Gastroenterology and Hepatology, National University Health System, Singapore

Address for Correspondence: Prof Seng Gee Lim, Division of Gastroenterology and Hepatology, National University Health System, 1E Kent Ridge Road, Singapore 119228.

Email: mdclimsg@nus.edu.sg

of chronically infected patients globally, many of whom are unaware they have HCV. The lack of symptoms also explains the difficulty of reporting and detecting acute infection, and consequently, the difficulties in recognising an outbreak. Looking forward, we should be aware that 2 or more cases of acute HCV in a healthcare setting is sufficient to be an outbreak, based on the United States (US) Centers for Disease Control and Prevention (CDC) definition.⁷ The salient points of the outbreak have been well documented in the Independent Review Committee (IRC) report⁸ and a subsequent editorial in the *Straits Times* including the write up by Professor Paul Tambyah.⁹ There are some important issues from a medical perspective. The first is that HCV virus seems to be highly resilient in the environment, being able to be detected in dried blood spots even after 1 year¹⁰ and may remain as infective virus on fomites for as long as 6 weeks,¹¹ in contrast to hepatitis B virus (HBV) which cannot be detected after 14 days¹² and human immunodeficiency virus (HIV) which lasts about 1 week.¹³ Secondly, the environmental contamination was by extremely high levels of virus, with as much as 5 million IU of virus per 50 µl drop of blood, likely increasing the risk of parenteral transmission. Secondly, we need to view this outbreak in the correct perspective. Unlike outbreaks like influenza, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV),¹⁴ which are primary infective agents transmitted by airborne means and close exposure, HCV is transmitted by parenteral means, hence transmission can only occur by contaminated syringes and needles, contaminated injection contents and now also by environmental contamination. Thirdly, is the issue of environmental contamination broadly applicable to all infectious agents? Patients infected by hepatitis B and C and HIV fall into this category and outbreaks have been reported with these agents, and when such patients are identified, higher infection safety precautions should be taken. The resilience of HCV in the environment and high levels of virus imply that added attention to this is important.

While infection control is one approach to preventing outbreaks, another approach gathering momentum is to try to eradicate the pool of patients that harbour chronic infection. In the USA, a notion that treating prisoners¹⁵ and intravenous drug user (IVDU) patients^{16,17} may be a good approach towards reducing the pool for potential transmission, and seems to have some success in HIV.¹⁸ While such risk groups may not be significant in Singapore, the pool of patients who are on renal dialysis is significant. Data from the National Registry of Diseases Office (NRDO) indicates that as of end 2014, HCV prevalence in renal dialysis patients in Singapore nationally is 3.8%. A report from SGH in 2000 indicated that the prevalence of HCV in haemophiliacs was as high as 46%.¹⁹ Such patients are

potential sources for future outbreaks. With such highly efficacious HCV therapy available today that is safe, it is no longer necessary to warehouse these patients, thus removing a potential source of transmission and outbreaks. Of course, it would be wise to still continue vigilance in infection control and monitoring. Eradicating HCV from risk groups is one strategy while in other countries, eg Georgia, where the prevalence of HCV is 6.7%, there is a commitment by the government to eradicate the virus completely in the entire country.²⁰ This is a matter that could be considered for Singapore since the burden of disease is relatively small.

The size of the HCV disease burden in Singapore is an issue that has not been well evaluated; the only study in 1991 showed 1.9% prevalence of anti-HCV using a first-generation assay²¹ and 0.54% in a blood donor population using a second-generation kit.²² Internal estimates from the Ministry of Health (MOH) put an approximate prevalence of 0.1% based on blood donor screening data and cumulative notifications of HCV cases to MOH. It may now be timely to conduct a community-based survey in the same manner as that of hepatitis B so we are better able to estimate the seroprevalence of hepatitis C in the community. This for instance will determine whether there is a “birth cohort” effect as was found in the USA, and is now the foundation of their screening strategy for HCV.²³ A “birth cohort effect” identifies higher seroprevalence in certain age groups that that would make that age group a risk factor for HCV screening. In the SGH outbreak, the phylogenetic analysis showed that the strain was unrelated to known strains from SGH patients, leading to the possibility of community acquisition, and potential danger of a community acquired infection getting into an at-risk population.

We should look at the recent HCV outbreak as a learning experience. Acute HCV often leads to chronicity in 70% to 80% but the outcomes of cirrhosis and liver cancer occur only after decades,²⁴ giving ample time to eradicate the virus thus preventing these serious complications. However, those who are immunosuppressed have a higher risk of developing fibrosing cholestatic hepatitis (FCH),²⁵ an atypical form of liver failure, because coagulopathy and encephalopathy tend to be late events, and the syndrome is characterised by severe cholestasis, with typical liver biopsy findings. Recognition and diagnosis is crucial as the prognosis is very poor but can now be rescued with appropriate therapy, at least in post-liver transplant patients,²⁶ provided it is given early.²⁷ In renal transplant patients, a recent report indicates that the DAAs are safe and efficacious²⁸ but there is little data on FCH.

The good news is that we are now much more aware of the serious dangers posed by HCV in immunosuppressed patients, of infection control measures in such patients,

and in ensuring that we have coordinated recognition and outbreak response measures. The Ministry of Health is now examining the formation of such a “SWAT” team.²⁹ More importantly, treatments today lead to such good cure rates that eventually HCV will be significantly less of a threat than today.

For hepatitis B, it is a different story. Singapore has an admirable record in the control of chronic hepatitis B, bringing the seroprevalence down from 5% to 6% in the 1980s³⁰ to 3.6% in 2010, the most recent seroprevalence study.³¹ This was largely due to the rapid adoption of universal vaccination,³¹ initially with a plasma-derived vaccine before the current yeast-derived vaccine. This programme has been tremendously successful and we owe much to this early initiative. With the development of antiviral drugs and the subsequent wide availability of top line antiviral agents such as tenofovir and entecavir,³² control of chronic hepatitis B seems more than adequate, and eventual eradication only a matter of time but this may take another 50 to 60 years as the oldest vaccinees are now only about 30 years old, and most complications of chronic hepatitis B occurs in 50 to 70 age groups. The World Health Organization (WHO) estimates that 20% to 40% of chronic hepatitis B patients over their lifetime may develop these complications.³³ With the higher prevalence of HBV in Singapore and the larger burden of disease, this will remain an important health problem for the immediate future, and already, some signals that all is not right have been emerging. Flares of chronic hepatitis B leading to liver failure and requiring liver transplantation have featured recently, with 13 cases evaluated for liver transplantation at National University Hospital (NUH), but only 4 were transplanted, and 6 deaths since 2014. These patients were not on therapy and not on follow-up, making them an unrecognised risk for complications. A study performed a few years ago from NUH showed that 67% of patients with chronic hepatitis B were not on follow-up.³⁴ Multiple reasons for this include lack of knowledge, lack of reminders and lack of time.^{35,36} Although sentiments from patients are for a cure of chronic hepatitis B,³⁷ we are still some way from this event. However, recently, experts are increasingly believing that this is an achievable goal.³⁸ In concurrence, the National Medical Research Council-National Research Foundation (NMRC-NRF) awarded a Translational Clinical Research Grant for \$25 million for the eradication of hepatitis B in 2015. This consortium of 29 investigators across major research and healthcare institutions in Singapore, is one of the first major international grants awarded that is focused on HBV eradication. The current treatments with nucleoside analogues or immunomodulators are not able to achieve HBsAg seroclearance in most patients, the marker of a cure of chronic hepatitis B. Consequently, the grant

focuses on understanding the immunology and virology of the disease, examining new treatment targets and evaluating new classes of agents. Already new classes of agents such as a core inhibitor, TLR7 agonist, HBV receptor blocker, and siRNA are being evaluated in clinical trials³⁹ by multiple pharmaceutical companies that are pouring resources into this disease such that a cure for hepatitis B could be achieved in the near future. Consequently, for chronic hepatitis B, treatments today can control the disease and prevent complications, and although a cure is desirable, this will need to wait for new classes of therapies. The same issues arise as with HCV i.e. in identifying, testing and treating the vast pool of yet unrecognised patients.

In conclusion, although HCV can be cured much more easily today, and HBV can be controlled with oral therapy, there is no time for complacency as the warning bells show they can still cause problems. Singapore potentially has the resources, infrastructure, and capability to lead the way to eradicate and control these dangerous diseases. In order to be successful, we need to convene a working group to complement the “SWAT team” focussed on outbreaks, bringing together medical professionals, epidemiologists and the MOH to create a multipronged strategy that involves screening, testing and linkage to care,⁵ and monitoring outcomes. However, we have to be cognisant of the costs of intervention and explore innovative methods to address these. Globally, the WHO resolution on viral hepatitis⁴⁰ provides the framework for action to be taken on eradication of viral hepatitis.

Acknowledgement

The author would like to thank Dr Derrick Heng, Group Director, Public Health Group, and Dr Jeffery Cutter, Director, Communicable Diseases Division, Ministry of Health, Singapore, for providing updated information on HCV prevalence. The author would like to thank Associate Professor Benjamin Ong, Director of Medical Services, Ministry of Health; Professor Paul Tambyah, Senior Consultant, National University Health; and Professor Leo Yee Sin, Director, Institute of Infectious Diseases and Epidemiology, Tan Tock Seng Hospital, for their valuable inputs and critical review of the manuscript.

REFERENCES

1. Lim SG. Chronic hepatitis C genotype 1 treatment roadmap for resource constrained settings. *World J Gastroenterol* 2015;21:1972-81.
2. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361:580-93.
3. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009;461:399-401.

4. Lim SG, Dan YY. A 2015 roadmap for the management of hepatitis C virus infections in Asia. *Korean J Intern Med* 2015;30:423-33.
5. Ward JW, Mermin JH. Simple, effective, but out of reach? public health implications of hcv drugs. *N Engl J Med* 2015;373:2678-80.
6. Honer Zu Siederdisen C, Maasoumy B, Marra F, Deterding K, Port K, Manns MP, et al. Drug-drug interactions with novel all oral interferon-free antiviral agents in a large real-world cohort. *Clin Infect Dis* 2015;Epub ahead of print.
7. Centers for Disease Control and Prevention. Healthcare-associated hepatitis B and C outbreaks reported to the centers for disease control and prevention (CDC) 2008-2014. Available at: <http://www.cdc.gov/hepatitis/outbreaks/pdfs/healthcareinvestigationtable.pdf>. Accessed on 27 December 2015.
8. Ministry of Health, Singapore. Hepatitis C cluster in the renal ward of Singapore General Hospital Ministry of Health. Available at: https://www.moh.gov.sg/content/dam/moh_web/PressRoom/Current_Issues/2015/IRCReport.pdf. Accessed on 27 December 2015.
9. Tambyah P. Unusual factors in SGH hepatitis C outbreak. The Straits Times. 12 December 2015. Available at: <http://www.straitstimes.com/opinion/unusual-factors-in-sgh-hepatitis-c-outbreak>. Accessed on 27 December 2015.
10. Bennett S, Gunson RN, McAllister GE, Hutchinson SJ, Goldberg DJ, Cameron SO, et al. Detection of hepatitis C virus RNA in dried blood spots. *J Clin Virol* 2012;54:106-9.
11. Paintsil E, Binka M, Patel A, Lindenbach BD, Heimer R. Hepatitis C virus maintains infectivity for weeks after drying on inanimate surfaces at room temperature: implications for risks of transmission. *J Infect Dis* 2014;209:1205-11.
12. McAllister G, Shepherd S, Templeton K, Aitken C, Gunson R. Long term stability of HBsAg, anti-HBc and anti-HCV in dried blood spot samples and eluates. *J Clin Virol* 2015;71:10-7.
13. Tjotta E, Hungnes O, Grinde B. Survival of HIV-1 activity after disinfection, temperature and pH changes, or drying. *J Med Virol* 1991;35:223-7.
14. Gautret P, Gray GC, Charrel RN, Odezulu NG, Al-Tawfiq JA, Zumla A, et al. Emerging viral respiratory tract infections--environmental risk factors and transmission. *Lancet Infect Dis* 2014;14:1113-22.
15. Hagan LM, Schinazi RF. Best strategies for global HCV eradication. *Liver Int* 2013;33 Suppl 1:68-79.
16. Negro F. Epidemiology of hepatitis C in Europe. *Dig Liver Dis* 2014;46 Suppl 5:S158-64.
17. Bennett H, McEwan P, Sugrue D, Kalsekar A, Yuan Y. Assessing the long-term impact of treating hepatitis c virus (hcv)-infected people who inject drugs in the UK and the relationship between treatment uptake and efficacy on future infections. *PLoS One* 2015;10:e0125846.
18. Cairns G. HIV treatment as prevention. Available at: <http://www.aidsmap.com/page/1270646/>. Accessed on 27 December 2015.
19. Chow WC, Tien SL, Tan CK, Lui HF, Vathsala A, Ng HS. Treatment of chronic hepatitis C in patients with end-stage renal disease and hemophilia--the Singapore experience. *Intervirology* 2006;49:107-11.
20. Mitruka K, Tsertsvadze T, Butsashvili M, Gamkrelidze A, Sabelashvili P, Adamia E, et al. Launch of a Nationwide Hepatitis C Elimination Program--Georgia, April 2015. *MMWR Morb Mortal Wkly Rep* 2015;64:753-7.
21. Yap I, Guan R, Kang JY, Tay HH, Lee E, Choong L, et al. Seroprevalence of antibodies to the hepatitis C virus in Singapore. *Southeast Asian J Trop Med Public Health* 1991;22:581-5.
22. Kuperan P, Choon AT, Ding SH, Lee G. Prevalence of antibodies to hepatitis C virus in relation to surrogate markers in a blood donor population of Singapore. *Southeast Asian J Trop Med Public Health* 1993;24 Suppl 1:127-9.
23. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep* 2012;61:1-32.
24. Westbrook RH, Dusheiko G. Natural history of hepatitis C. *J Hepatol* 2014;61:S58-68.
25. Delladetsima JK, Boletis JN, Makris F, Psychogiou M, Kostakis A, Hatzakis A. Fibrosing cholestatic hepatitis in renal transplant recipients with hepatitis C virus infection. *Liver Transpl Surg* 1999;5:294-300.
26. Leroy V, Dumortier J, Coilly A, Sebach M, Fougere-Leurent C, Radenne S, et al. Efficacy of sofosbuvir and daclatasvir in patients with fibrosing cholestatic hepatitis C after liver transplantation. *Clin Gastroenterol Hepatol* 2015;13:1993-2001.
27. Pellicelli AM, Montalbano M, Lionetti R, Durand C, Ferenci P, D'Offizi G, et al. Sofosbuvir plus daclatasvir for post-transplant recurrent hepatitis C: potent antiviral activity but no clinical benefit if treatment is given late. *Dig Liver Dis* 2014;46:923-7.
28. Saxena V, Terrault NA. Treatment of hepatitis C infection in renal transplant recipients: the long wait is over. *Am J Transplant* 2015. [Epub ahead of print].
29. The Straits Times. 'Swat team' may be set up to tackle disease outbreaks. 29 December 2015. Available at: <http://www.straitstimes.com/singapore/health/swat-team-may-be-set-up-to-tackle-disease-outbreaks>. Accessed on 29 December 2015.
30. Guan R. Hepatitis B virus infection in Singapore. *Gut* 1996;38 Suppl 2:S13-7.
31. Ang LW, Cutter J, James L, Goh KT. Seroepidemiology of hepatitis B virus infection among adults in Singapore: a 12-year review. *Vaccine* 2013;32:103-10.
32. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2015. [Epub ahead of print].
33. Lavanchy D. Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect* 2011;17:107-15.
34. Wai CT, Mak B, Chua W, Lim SG. The majority of hepatitis B carriers are not on regular surveillance in Singapore. *Singapore Med J* 2004;45:423-6.
35. Wai CT, Mak B, Chua W, Tan MH, Ng S, Cheok A, et al. Misperceptions among patients with chronic hepatitis B in Singapore. *World J Gastroenterol*. 2005;11:5002-5.
36. Wai CT, Wong ML, Ng S, Cheok A, Tan MH, Chua W, et al. Utility of the Health Belief Model in predicting compliance of screening in patients with chronic hepatitis B. *Aliment Pharmacol Ther* 2005;21:1255-62.
37. Lim SG, Aung MO, Chung SW, Soon CS, Mak BH, Lee KH. Patient preferences for hepatitis B therapy. *Antivir Ther* 2013;18:663-70.
38. Zeisel MB, Lucifora J, Mason WS, Sureau C, Beck J, Levrero M, et al. Towards an HBV cure: state-of-the-art and unresolved questions--report of the ANRS workshop on HBV cure. *Gut* 2015;64:1314-26.
39. Phyo WW, Soh AY, Lim SG, Lee GH. Search for a cure for chronic hepatitis B infection: How close are we? *World J Hepatol*. 2015;7:1272-81.
40. World Health Assembly. Viral hepatitis. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R18-en.pdf. Accessed on 27 December 2015.