

Hepatitis C Update

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New information has become available about the hepatitis C virus (HCV) and the disease it causes since the authors prepared the previous review¹ and the last annual report² on hepatitis C. This report provides an update on several important aspects of the virus, the disease it causes and the status of the disease in Canada.

Hepatitis C virus

The identification of the viral genome over 10 years ago rapidly led to the delineation of the genome organization and the structural and biochemical characterization of several viral proteins. However, studies of the viral life cycle, inhibition or inactivation of the virus as well as the development of vaccines or antiviral drugs have been difficult because of the lack of a robust and reliable cultivation system for the virus.³ The chimpanzee is still the only experimental animal susceptible to infection with HCV. Nevertheless, some new developments have been reported recently,^{4,5} which may eventually lead to a solution to this problem. The genome of HCV is heterogeneous and quasispecies with variations in the viral genome are being studied for their implication in persistent infection and immune response. A recent study showed that the distribution of hypervariable region 1 (HVR1) quasispecies in both immune and non-immune complexes conspicuously changed over time in most of the patients studied. These findings suggest that major HCV clones escape neutralization by anti-HVR1 antibodies by generating considerably divergent minor "decoy" clones which may be preferentially neutralized.⁶

Hepatitis C

More evidence has become available recently that indicates that in certain populations, the disease may be less severe than previously suspected. For example, a study of a cohort of Irish women infected with HCV genotype 1b via contaminated anti-D immunoglobulin in 1977 showed a benign course with lack of disease progression 22 years after inoculation. It was observed that acute icteric hepatitis and the HLA DRB1*01 allele were associated with viral clearance.⁷ Similarly, a study of children who had undergone cardiac surgery in Germany prior to the implementation of blood donor screening for hepatitis C showed a substantial risk of acquiring the infection. However, after about 20 years, the virus had spontaneously cleared in many patients. The clinical course in those still infected seems more benign than would be expected in people infected as adults.⁸ Thomas et al.⁹ conducted a community-based prospective cohort study with enrollment in 1988-1989 with a median follow-up of 8.8 years. Viral clearance was observed in 90 of 919 (9.8%) persons aged 17 years or older with a history of injection drug use and an anti-HCV positive test result during follow-up. Forty cases of end-stage liver disease (ESLD) were observed throughout follow-up for an incidence of 3.1 per 1000 person-years. The risk of ESLD was higher for persons aged 38 years or older at enrollment and who reported ingestion of more than 260g of alcohol per week. A study in asymptomatic chronic HCV carriers showed that HCV RNA levels in patients did not correlate with either the extent of inflammation of the liver or degree of fibrosis. In contrast, there was a strong association between ALT level and the histological severity of liver

disease.¹⁰ Nevertheless, a study in Italy indicated that serum HCV RNA levels correlate with histological liver damage and concur with steatosis in progression of chronic hepatitis C.¹¹ The prediction of hepatic fibrosis in HCV infection using historical features and published rates of fibrosis progression is poor in a Canadian clinical practice setting.¹²

Incidence, prevalence and disease burden

According to data available from the Division of Disease Surveillance, Health Canada,^{13,14} 14,287 and 12,544 male cases and 7,544 and 6,674 female cases of hepatitis C were reported in 1998 and 1999, respectively. Data from the reported cases need to be interpreted with caution as these cases include both acute and chronic infections and the reporting has been affected by increased awareness, access to sensitive tests and various initiatives aimed at hepatitis C such as the notification and look-back or trace-back programs. To better estimate the magnitude of transmission of hepatitis C and hepatitis B in Canada, an enhanced surveillance system for acute hepatitis C and acute hepatitis B was initially established in Edmonton, Ottawa, Calgary and Winnipeg and has since expanded to include Vancouver-Richmond and the province of New Brunswick.^{15,16} An acute hepatitis C case is defined as an acute illness with discrete onset of hepatitis symptoms, jaundice, aminotransferase levels 2.5 times above the upper limit of normal, and anti-HCV or HCV RNA positive but without a history of previous HCV infection. A case of HCV infection is also classified as an acute case if seroconversion can be determined. Due to the lack of a diagnostic assay to differentiate new from old infections, except as measured by seroconversion, and the asymptomatic nature of the disease in a large proportion of new infections, some of the acute hepatitis C cases identified by the system might still be misclassified old HCV infections that finally developed symptoms. Nevertheless, according to data from the enhanced surveillance in Edmonton, Calgary, Winnipeg and Ottawa in 1999, the incidence of clinically recognized acute hepatitis C was estimated at 3.6 per 100,000 person-years, with the rate in males (4.5 per 100,000) higher than in females (2.8 per 100,000). However, the rate among 10-19 year old females was higher than among males of the same age group,

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4.9 versus 0.5 per 100,000. Age groups of 20-29 and 30-39 had the highest incidence rates, 6.0 and 6.7 per 100,000, respectively. For 2000, data from the above four regions plus Vancouver-Richmond showed a slightly lower incidence rate of clinically recognized acute hepatitis C cases at 3.0 per 100,000. Similarly, the rate among males was higher than females, 3.1 versus 2.9 per 100,000. Among the Canadian Aboriginals, the incidence of acute hepatitis C was on average 7 times higher than that among the non-Aboriginal Canadian-born population.¹⁷ Based on these data and other epidemiological information, it was further estimated that the total number of new HCV infections could be as high as 6 to 7 times that of acute cases of hepatitis C.¹⁸ In other words, the incidence of HCV infection in Canada could be in the range of 10-20 per 100,000. It should be noted, however, that these are only preliminary estimates due to limitations of existing data as mentioned above. As for prevalence, the estimate generated by Remis et al.¹⁹ – anti-HCV positivity at 240,000 or 0.8% – is still regarded as current since there is no evidence to suggest that any significant changes have occurred. Analysis of mortality data for the period 1979-1997 showed that the number of recorded deaths caused by non-A non-B hepatitis, most of which were caused by hepatitis C, has been increasing and that over 1,000 Canadians could have died from hepatitis C in 1997 alone.²⁰ The result supports the prediction that the burden of hepatitis C in Canada could double or even triple in the coming decade.²¹

Transmission patterns and related factors

Injection drug use is still the number one route of transmission in Canada. During 2000, 110 acute hepatitis C cases were identified through the enhanced surveillance and 62% of those cases were interviewed for risk factors potentially related to transmission of the infection. Approximately 80% of the cases reported a history of injection drug use or drug snorting. About one third of those cases also reported a history of sexual contact with a hepatitis C infected person. However, when those who had a history of injection drug use or drug snorting were excluded, only 1-2% reported such sexual contact as the potential transmission route.¹⁶ Compared with results from the earlier report,¹⁵ the percentage associated with drug

use increased slightly. However, this increase might have been the result of more comprehensive interviewing because the proportion of cases with unknown risk factors decreased from approximately 20% to only 7%. Thus, the 80% (70% or more with injection drug use) might more closely reflect the true transmission pattern in Canada.

Even the sharing of drug preparation paraphernalia has been reported to potentially transmit HCV.²² A study among street youth in Montreal showed that injecting drugs, being over 18 years of age and using crack cocaine were independent risk factors for HCV infection. Having more than one tattoo was marginally associated with HCV, though body piercing was not.²³ The exact role sexual transmission plays in spreading HCV is a subject under debate. Kok and Forrester recently conducted a literature review on the topic and found that sexual transmission of HCV does occur, although infection by this route appears to be infrequent. Populations identified as being at particular risk for hepatitis C through sexual transmission include men who have sex with men (MSM), female sex workers or sexually promiscuous groups, persons attending sexually transmitted diseases (STD) clinics, persons and their partners with HIV, sexual partners of HCV-infected hemophiliac men, and sexual partners of patients with chronic hepatitis C (Kok and Forrester, 2001, unpublished). Mother-to-infant transmission of HCV is another area under extensive study. Yeung et al.²⁴ conducted a literature review and reported that the overall weighted rate of such transmission is in the range of 1-5%. Maternal risk factors for increased mother-to-infant transmission include co-infection with HIV, history of injection drug use, and maternal viremia greater than 10⁶ copies/ml. By contrast, mode of delivery and breastfeeding do not influence rates of mother-to-infant transmission significantly. In addition to the above transmission routes, a study in Egypt suggested that parenteral antischistosomal therapy (PAT) had a major role in the spread of HCV throughout the country. Egypt's mass campaigns of PAT may represent the world's largest iatrogenic transmission of blood-borne pathogens.²⁵ A recent report from Australia documented exposure to med-

ical/surgical procedures among HCV patients with no previously recognized mode of transmission.²⁶ In resource-limited countries, nosocomial transmission of bloodborne pathogens is a major public health concern.²⁷ Even in Taiwan, medical injections were found to be the main mode to sustain the persistent endemic state of HCV infection within a community.²⁸

Intervention

Following the hepatitis C consensus conference in 1998 and the publication of the conference report²⁹ (Hepatitis C - Prevention and Control: A Public Health Consensus) in 1999, the first national hepatitis C conference was held in Montreal in May 2001. The former conference brought hepatitis C to the forefront of the public health agenda nationwide whereas the latter conference raised the awareness of hepatitis C among the general public, academics as well as the health care community in this country. Various national programs including surveillance, prevention and control guidelines and recommendations as well as health promotion activities have been or are being developed. New guidelines prepared for hepatitis C include Management of Viral Hepatitis: Recommended Guidelines for Physicians, Management Guidelines for HCV-HIV Co-Infected Adults, and Reproductive Care of Women Living with Hepatitis C Infection (Health Canada website at http://www.hc-sc.gc.ca/hppb/hepatitis_c/careguide.html). Provinces and territories have also developed policies or strategies to combat the disease. For example, British Columbia recently established a Viral Hepatitis Strategy which integrates surveillance, prevention and care of hepatitis into a coordinated effort. Measures to prevent initiation of injection drug use and to reduce the transmission of hepatitis C and other blood-borne pathogens through injection drug use is still a priority in the prevention and control of hepatitis C. In addition, other routes of transmission are also being investigated such as sexual and vertical transmission, nosocomial transmission and other inapparent parenteral transmission. To further reduce the risk of HCV transmission through blood or blood products, Canadian Blood Services implemented nucleic acid amplification testing (NAT) for screening of blood donations in 2000 on an investigational basis (CBS website at www.bloodservices.ca). It was esti-

mated that such testing could prevent up to 13 HCV infections contracted through the blood supply annually. Manual cleaning and disinfection of gastroscopes with 3% glutaraldehyde has been shown to decrease the risk of transmission of HCV.³⁰ Further, vaccines against HCV infection are being extensively studied. However, immune correlates of protection remain poorly defined although increasingly evidence suggests that both humoral and cellular immune responses are likely to contribute to protection or neutralization of the virus. Different forms of vaccines are currently explored including DNA-based vaccines. While capable of generating a cellular response, such DNA-based vaccines appear to be limited in their capacity to induce a strong and long-lasting antibody response.³¹ For the treatment of hepatitis C, following the introduction of the combination therapy with interferon and ribavirin, new antiviral drugs are being investigated through clinical trials, such as pegylated interferon. The search for more effective treatment also includes novel drugs designed to inhibit the function of three major viral proteins: protease, helicase and polymerase, and antisense molecules or catalytic enzymes that target critical elements of the viral RNA genome itself.

Future challenges

From a public health perspective, interruption of transmission of HCV through injection drug use is the biggest challenge in the control of this disease in Canada and in the world. The virus is effectively transmitted through this route. Shortly after initiation of injection drug use, a large proportion become infected with the virus. This may in part explain the relative ineffectiveness of certain existing harm reduction measures in the prevention of HCV transmission compared with prevention of HIV transmission.³² More effort is needed to find effective ways to prevent initiation of injection drug use and transmission of HCV among users. Determinants of drug use initiation and transmission of HCV through injection drug use need to be studied and identified so that novel intervention strategies and measures could be designed and effectively implemented. Further, spread of the virus from injection drug users to others through other means such as sexual or other exposure to HCV-contaminated blood or body fluids is an

area that has drawn more and more public health attention. Targeted research is required to examine the social and behavioural factors that put certain population groups, such as Aboriginals, at greater risk of infection. In addition, transmission of HCV in health care environments needs to be closely monitored and assessed. Various intervention measures or strategies need to be evaluated to assess their effectiveness so that these measures or strategies can be improved and new options can be explored to better prevent and control HCV transmission in Canada.

REFERENCES

- Zou S, Tepper ML, Giulivi A. Current status of hepatitis C in Canada. *Can J Public Health* 2000;91(suppl 1):S10-S15.
- Zou S, Tepper ML, Giulivi A. Hepatitis C in Canada. *Can Commun Dis Rep* 2001;27S3:13-15.
- Sattar SA, Tetro J, Springthorne VS, Giulivi A. Preventing the spread of hepatitis B and C viruses: Where are germicides relevant? *Am J Infect Control* 2001;29:187-97.
- Mercer DF, Schiller DE, Elliott JF, Douglas DN, Hao C, Rinfret A, et al. Hepatitis C virus replication in mice with chimeric human livers. *Nat Med* 2001;7(8):927-33.
- Bartenschlager R, Lohmann V. Novel cell culture systems for the hepatitis C virus. *Antiviral Res* 2001;52(1):1-17.
- Korenaga M, Hino K, Katoh Y, Yamaguchi Y, Okuda M, Yoshioka K, Okita K. A possible role of hypervariable region 1 quasispecies in escape of hepatitis C virus particles from neutralization. *J Viral Hepat* 2001;8(5):331-40.
- Barrett S, Goh J, Coughlan B, Ryan E, Stewart S, Cockram A, et al. The natural course of hepatitis C virus infection after 22 years in a unique homogenous cohort: Spontaneous viral clearance and chronic HCV infection. *Gut* 2001;49:423-30.
- Vogt M, Lang T, Frosner G, Klingler C, Sendl AF, Zeller A, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. *N Engl J Med* 1999;341:866-70.
- Thomas DL, Asemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: Host, viral and environmental factors. *JAMA* 2000;26(4):450-56.
- Yeo AET, Ghany M, Conry-Cantilena C, Melpolder JC, Kleiner DE, Shih JWK, et al. Stability of HCV-RNA level and its lack of correlation with disease severity in asymptomatic chronic hepatitis C virus carriers. *J Viral Hepatitis* 2001;8:256-63.
- Adinolfi LE, Utili R, Andreana A, Tripodi MF, Marracino M, Gambardella M, et al. Serum HCV RNA levels correlate with histological liver damage and concur with steatosis in progression of chronic hepatitis C. *Dig Dis Sci* 2001;46(8):1677-83.
- Myers RP, Hilsden RJ, Lee SS. Historical features are poor indicators of liver fibrosis in Canadian patients with chronic hepatitis C. *J Viral Hepat* 2001;8(4):249-55.
- Health Canada. Notifiable Disease Annual Summary. *Can Commun Dis Rep* 2000;26S5:59.
- Health Canada. Notifiable Disease Annual Summary. *Can Commun Dis Rep* 2001;27S6:55.
- Zou S, Zhang J, Tepper M, Giulivi A, Baptiste B, Prey G, et al. Enhanced surveillance of acute hepatitis B and acute hepatitis C in four health regions in Canada. *Can J Infect Dis* 2001;12(6):357-63.
- Forrester L, Shi Y, Stoodley G, Zou S, Giulivi A, Poliquin D, et al. Enhanced surveillance of acute hepatitis B and acute hepatitis C in Canada. National Conference for Viral Hepatitis Coordinators 2001, Virginia, US.
- Forrester L, Shi Y, Stoodley G, Zou S, Giulivi A, Poliquin D, et al. Incidence of acute hepatitis C in the Canadian Aboriginal population, 1999-2000. National Conference for Viral Hepatitis Coordinators 2001, Virginia, US.
- Zou S, ElSaadany S, Forrester L, Giulivi A. Estimating the incidence of new hepatitis C virus infection in Canada. *Am J Epidemiol* 2001;153(11):S214.
- Remis R, Hogg R, Krahn MD, Preiksaitis JK, Sherman M. Estimating the number of blood transfusion recipients infected by hepatitis C virus in Canada, 1960-85 and 1990-92. Report to Health Canada. June 1998.
- Pohani G, Zou S, Tepper M. Trends of hepatitis B and hepatitis C mortality in Canada, 1979-1997. *Can J Public Health* 2001;92(4):250-54.
- Zou S, Tepper ML, ElSaadany S. Prediction of hepatitis C burden in Canada. *Can J Gastroenterol* 2000;14:575-80.
- Green ST, Mohsen AH, McKendrick MW, Dawes Y, Prakasam SF, Walberg R, Schmid ML. Potential for hepatitis C transmission among non-needle/syringe sharing Sheffield drug injectors through the sharing of drug preparation paraphernalia. *Commun Dis Public Health* 2001;4(1):38-41.
- Roy E, Haley N, Leclerc P, Boivin JF, Cedras L, Vincelette J. Risk factors for hepatitis C virus infection among street youths. *CMAJ* 2001;165(5):557-60.
- Yeung LTF, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology* 2001;34(2):223-29.
- Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet* 2000;355:887-91.
- Trasanco CC, Kainer MA, Desmond PV, Kelly H. Investigation of potential iatrogenic transmission of hepatitis C in Victoria, Australia. *Aust N Z J Public Health* 2001;25(3):241-44.
- Yerly S, Quadri R, Negro F, Barbe KP, Cheseaux JJ, Burgisser P, et al. Nosocomial outbreak of multiple bloodborne viral infections. *J Infect Dis* 2001;184(3):369-72.
- Sun CA, Chen HC, Lu SN, Chen CJ, Lu CF, You SL, Lin SH. Persistent hyperendemicity of hepatitis C virus infection in Taiwan: The important role of iatrogenic risk factors. *J Med Virol* 2001;65(1):30-34.
- Health Canada. Hepatitis C - Prevention and Control: A Public Health Consensus. *Can Commun Dis Rep* 1999;25S2:1-25.
- Sakai N, Tatsuta M, Iishi H, Yano H, Osaka S, Aoki A. Effectiveness of manual cleaning and disinfection of gastroendoscopes with 3% glutaraldehyde for decreasing risk of transmission of hepatitis C virus. *Am J Gastroenterol* 2001;96(6):1803-6.
- Brinster C, Inchauspe G. DNA vaccines for hepatitis C virus. *Intervirology* 2001;44(2-3):143-53.
- Leonard L, Navarro C, Pelude L, Forrester L. The effectiveness of harm reduction strategies in modifying hepatitis C infection among injection drug users in Canada. *Can Commun Dis Rep* 2001;27S3:52-55.

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