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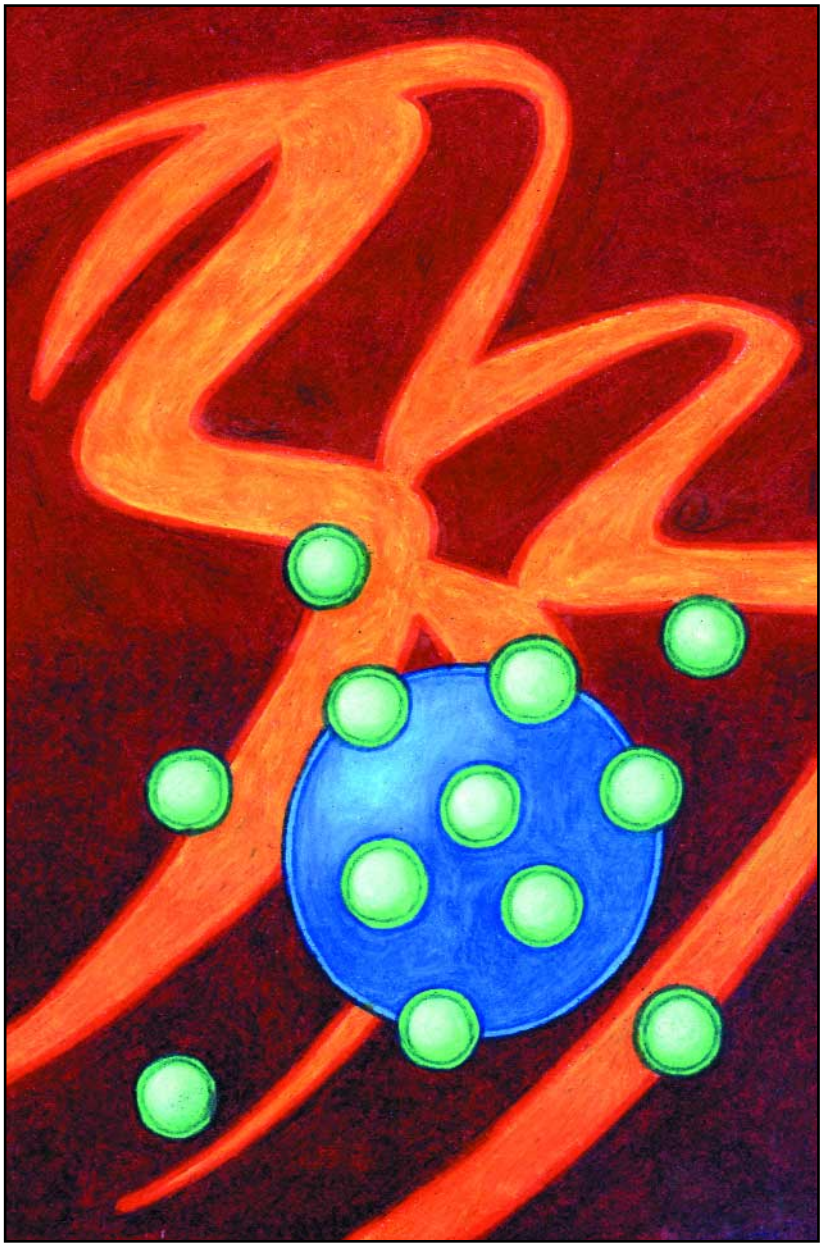
Hepatitis C:
Canadian Perspectives



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Gerald H. Dafoe
Chief Executive Officer

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Hepatitis C: Medical Information Update

Canadian Liver Foundation
National Hepatitis C Education Program

The World Health Organization estimates that up to 3% of the world's population is infected with hepatitis C virus (HCV) and that there are more than 170 million chronic carriers.[1] Many infected people have no symptoms and are unaware of their condition, unknowingly acting as sources of infection and running the risk of chronic liver disease, cirrhosis and liver cancer. Hepatitis C may account for 40% of chronic liver disease in the U.S.[2]

Hepatitis C infection becomes chronic in about 85% of adults, but the clinical progression is slow and signs of disease may not appear for 20 years or more. Because many HCV-infected people are aged 30-49 years,[3] the number of HCV-related deaths could increase substantially during the next 10 to 20 years as these people start to be affected by complications. In Canada over the next decade, important sequelae such as cirrhosis of the liver, liver failure, deaths due to liver disease, and demand for liver transplants may increase by two to three fold or more.

For many patients, hepatitis C is either self-limiting or benign. However, the common nature of this infection, affecting millions of people worldwide, means that even a low rate of disease-related complications translates into hundreds of thousands of cases of illness.

BACKGROUND

What is hepatitis C?

The hepatitis C virus was identified in 1989. Prior to that, it was known that some agent commonly caused hepatitis in people who had received blood transfusions or blood products. Until HCV was identified, this form of hepatitis was known as "non-A, non-B hepatitis."[4]

HCV is an enveloped RNA virus belonging to the *Flaviviridae* family. The virus seems to be constantly mutating, allowing the virus to evade the immune system.

Hepatitis C is most often spread through direct blood-to-blood contact with an infected individual.

Epidemiology

Estimates suggest that the current prevalence of HCV in Canada is 0.8% (240,000 persons) and there may be several thousand new cases acquired each year. The number of reported cases increased exponentially from 1992, when national reporting started, to 1998, primarily due to increased recognition of previously acquired infection.

According to surveillance data from the Laboratory Centre for Disease Control, the highest incidence rates of acute hepatitis C are found among persons aged 20-49 years with those in males higher than in females. Among chronic hepatitis C cases identified, most are in age groups 25-54 years and again the infection rates in males are higher than those in females.

There are at least six different HCV genotypes and some of these have subtypes. Types 1a and 1b account for more than 60% of all infections in North America, with types 2a, 2b, 3 and 4 accounting for the rest. Type 5 is rarely found in North America, except in Quebec.

TRANSMISSION

According to the Laboratory Centre for Disease Control, the main route of transmission of hepatitis C in Canada is injection drug use, accounting for approximately 70% of the identified cases, and blood or blood products may account for 10% of the identified cases.

According to U.S. data, the source of infection cannot be identified in 10% of cases of hepatitis C.[2]

Injection drug use

Injection drug use still is the major mode of transmission of HCV in Canada. As with other bloodborne pathogens, HCV is transmitted through transfer of infected blood via the sharing of syringes, needles or other drug paraphernalia.[5] The role of shared straws for intranasal inhalation of drugs in HCV transmission is not fully understood. However, partly due to the larger pool of infection, HCV infection is acquired by injection drug users more rapidly than other viral infections. A single episode of drug use may be enough to become infected. Rates of HCV infection among young injection-drug users are four times higher than rates of HIV infection. After 5 years of injecting, as many as 90% of users are infected with HCV.[2]

All injection drug users should be counselled according to current guidelines regarding prevention of HIV, hepatitis B and hepatitis C transmission. Education about the use of clean needles should be expanded to include all related equipment.[6]

Transmission from blood, blood components and blood products

The risk of infection through blood exposure in Canada has been markedly reduced, but not eliminated, through the introduction of universal testing of blood donors in May 1990. The current risk of infection is estimated to be approximately

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1 in 100,000. The risk of infection through blood components or blood products such as platelets, cryoprecipitate, albumin, factor VIII, and Rhogam has also been markedly reduced since the introduction of universal testing of blood donors.

Sexual transmission

The risk of sexual transmission of HCV is low. Heterosexual partners of HCV-infected people have an HCV prevalence of 0 to 10%.[7,8] Having multiple sexual partners may increase the risk of infection.[9] The average prevalence of HCV infection among long-term spouses of patients with chronic hepatitis C and no other risk factors is 1.5% (range 0% to 4.4%).[2]

Based on limited data, prevalence of HCV among homosexual males seems to be similar to that among heterosexual men, at least in the setting of STD clinics.[2] Again, having multiple partners increases the risk of infection.[10]

Due to the low risk of sexual transmission, partner notification/contact tracing is not justified, but HCV-infected people should be counselled to inform potential sexual partners of the risk of infection and to practise safer sex using barrier methods. Long-term partners should be informed of the risks and allowed to make the decision on condom use themselves. Screening can be offered to long-term partners.

Open genital lesions or sexual activity during menstruation may increase the risk of transmission.

Vertical transmission (mother to baby)

Perinatal infection of infants from an infected mother occurs in 5 to 10% of cases. This rises to between 14 and 17% if the mother also has HIV.[2] Method of delivery does not seem to affect the chances of infection.[2]

Counselling HCV-infected women against becoming pregnant is not recommended, however a woman should be informed of the risk of transmission to her baby. The infant should be tested for infection after 12 months.

HCV transmission through breastmilk has never been documented, despite a number of studies.[2] If the nipples are bleeding or cracked, it is recommended that breastfeeding be suspended until they are healed.

TABLE I
Classification of HCV Infection

Group	Anti- HCV	ALT	HCV-RNA	Clinical Implications
I	Positive	Normal	Negative	False positive anti-HCV; chronic hepatitis with complete response to therapy; remote HCV infection with recovery; transient absence of HCV-RNA in chronic infection
II	Positive	Normal	Positive	Subgroup of chronic hepatitis C with good prognosis; "tolerant" state of hepatitis C; rarely inactive cirrhosis
III	Positive	Elevated	Positive	Chronic hepatitis C, mild, moderate or severe without cirrhosis; chronic hepatitis C with cirrhosis, compensated or decompensated; hepatocellular carcinoma; acute hepatitis
IV	Negative	Elevated	Positive	Early acute hepatitis C; chronic hepatitis C in immunocompromised patients

Transmission risks and health care providers

Theoretically, any personnel who are exposed to blood in the workplace are at risk for HCV infection. However, prevalence of HCV infection among health care workers, including surgeons, is no greater than among the general population, averaging 1 to 2%, and is 10 times lower than that for hepatitis B virus (HBV) infection.[2] In one study a history of needlestick injury was the only occupational risk factor independently associated with HCV infection,[11] although transmission of HCV from blood splashes to the conjunctiva have been described.[2] The average incidence of HCV infection after a needlestick injury from an HCV-positive source is 1.8%.[2]

Percutaneous exposures

There are reports of HCV and other bloodborne infections being transmitted through unsterile personal services, such as tattooing, body piercing and electrolysis.

Household contact

There are insufficient data for specific guidelines at present, but because of the theoretical risk, household contacts of people with HCV infection should not share their personal hygiene items such as razors or toothbrushes. Since there is no disclosure of HCV status required by authorities, it makes common sense to practise universal precautions in a day care or other setting. Routine screening of household contacts is not required.

DIAGNOSIS

Screening and diagnosis

Routine Testing

Widespread screening for HCV is not currently recommended.[12] Family physicians should offer routine testing to anyone with one or more risk factors, especially a history of injection drug use, blood or blood component exposure before 1992 or children of HCV-infected mothers.

Laboratory Tests

Chronic hepatitis C is diagnosed primarily by serology. For initial testing, the test of choice is enzyme immunoassay (EIA) for the detection of antibodies to HCV (anti-HCV). Because of false positive reactions, supplemental tests are needed, such as recombinant immunoblot assay (RIBA). Qualitative detection of viral RNA (HCV-RNA) is also available using gene amplification techniques (e.g., PCR) and is considered the "gold standard." (See Table I). There are two types of assay for hepatitis C viral RNA. Qualitative tests give a positive or negative result; quantitative tests give the viral concentration or viral load. Qualitative HCV-RNA testing is not essential to make the diagnosis of hepatitis C in typical patients who are anti-HCV positive.

In general, HCV-RNA assays should be considered in the following cases:

- immunocompromised patients with negative anti-HCV who have active hepatitis
- indeterminate HCV serology
- infant of an anti-HCV positive mother

TABLE II
Factors Affecting Outcome of Chronic HCV Infection

Factors	Influence on Outcome
Alcohol	Increased progression, dose-related
Duration of infection	Progression more likely the longer the duration
HBV coinfection	Does not increase progression to cirrhosis, but does increase chance of HCC
HIV coinfection	Faster progression to cirrhosis, higher rate of cirrhosis
Age at infection	Older patients at time of infection have poorer prognosis
Route of infection	It is not known whether transfusion-related infections may have poorer prognosis than IVDU
Human leukocyte antigen (HLA) type	Some HLA types clear HCV more readily than others
Hemophilia	Insufficient, inconclusive data re: progression to cirrhosis
Diabetes	May increase risk of disease
Iron overload	May increase progression
Smoking	May increase risk of HCC (tenuous)

Of these, alcohol is probably the most important factor. Even moderate amounts of alcohol might increase disease progression.[2]

- normal alanine aminotransferase (ALT) levels and positive anti-HCV
- determination of the response to treatment.

Blood Donor Positive on HCV Screening

Blood donors who test anti-HCV positive are notified by Canadian Blood Services/Héma-Québec and referred to their physicians. All patients RIBA-positive or RIBA-indeterminate should be considered to have ongoing hepatitis C. In healthy blood donors with no risk factors for hepatitis C, there may be a false positive EIA test, but in this case the confirmatory RIBA will be negative. Those who are RIBA-negative likely do not have hepatitis C, but rather a false positive EIA test. HCV-RNA detection indicates the patient has ongoing hepatitis C infection. A negative HCV-RNA test does not guarantee that the EIA was a false positive, however a negative HCV-RNA in untreated patients with a positive anti-HCV by EIA does suggest absence of infection in the vast majority of cases.

Liver Biopsy

The most accurate tool for assessment of prognosis in chronic hepatitis C is a liver biopsy but it does carry measurable risks. The decision to use biopsy should be made by the clinician after informed discussion with the patient.

Acute hepatitis C – Clinical features and natural history

People with acute HCV infection typically are either asymptomatic or have a mild clinical illness: 60 to 70% have no discernible symptoms, 20 to 30% might have jaundice, and 10 to 20% might have non-specific symptoms such as anorexia, malaise or abdominal pain. Average time from exposure to symptom onset is 6 to 7 weeks, and 8 to 9 weeks for seroconversion.[2]

Fifteen to 25% of patients will completely resolve their infections after the acute stage,[2] but most will go on to chronic infection. It is impossible to predict who will clear the acute infection.

Chronic hepatitis C – Clinical features and natural history

Most experts now agree that 75 to 85% of cases of acute hepatitis C progress to chronic disease.[2] The course is usually insidious, progressing at a slow rate without symptoms or physical signs in the majority of patients for two or more decades after infection. Frequently, hepatitis C is not recognized until asymptomatic people are identified as HCV-positive during blood-donor screening, or elevated ALT levels are detected during routine physical examinations.

The long-term natural history of chronic hepatitis C infection is impossible to predict for an individual patient, although patients with no apparent active disease at diagnosis (anti-HCV positive, viral RNA positive, normal ALT levels, absent or scant fibrosis on liver biopsy) generally have the most favourable prognosis over the medium term (approximately 20 years). The wide range of factors that can affect outcome are shown in Table II.

A good response to antiviral therapy, with 6-12 months or longer clearance of HCV-RNA, favourably affects the natural history. The progression to cirrhosis may be decreased and the development of hepatocellular carcinoma (HCC) appears to be lessened.

After 20 years of infection, 3 to 20% of patients will show cirrhosis on liver biopsy, although most will be asymptomatic (compensated disease). When cirrhosis has been diagnosed, the probability of decompensation is 25% after 10 years. Once a patient develops decompensated cirrhosis, the death rate (without transplantation) is 50% after 5 years. In a recent retrospective study of patients with compensated cirrhosis, each year 3.9% of patients decompensated, 1.4% developed hepatocellular carcinoma, and 1.9% died.[13]

Fatigue

Fatigue is often considered to be a common problem in chronic hepatitis C infection, but studies show that the prevalence of severe fatigue (interference in daily activities, for at least 6 months) is roughly 10%. However, 5 to 10% of the general population also report severe fatigue, so it is unclear whether fatigue is caused by chronic hepatitis C infection. Degree of fatigue does not correlate with presence or level of viremia, nor with ALT levels or degree of inflammation or fibrosis on histology. The difficulty of studying fatigue is compounded by the lack of an objective measurement; fatigue can be quantified only with subjective rating scales.

CLINICAL MANAGEMENT

Follow-up

Table III summarizes the recommended follow-up for patients with chronic HCV.

Referral to a specialist

Among HCV-infected patients, any symptomatic patient or anyone with abnormal physical signs such as the presence of hepatosplenomegaly should be referred for an opinion, as should patients with persistently or intermittently abnormal liver chemistry (ALT > 1.5 times normal). Patients with combined hepatitis B virus (HBV) and HCV infection should always be treated by an expert.

HCV in infants/children

Studies of hepatitis C in children are extremely limited and most have been on post-transfusion patients. Preliminary data from the Hospital for Sick Children in Toronto suggest that children have a lower rate of progression to chronic hepatitis C following transfusion than adults. The disease appears to be mild in children.[12]

Recommendations from the Canadian Association for the Study of the Liver (CASL) state that children should not be given interferon outside clinical trials. Interferon is currently under review for use in children (younger than 18 years) as it can cause anorexia, weight loss and transient growth retardation.

HCV-infected teenagers should be counselled about the risk of alcohol consumption and the risk of sexual transmission to others. As well, vaccination against hepatitis A and B should be considered.

Health care workers and needlestick injuries

Health Canada has issued guidelines about the management of health care workers exposed to needlestick injuries or equivalent exposure. These workers should be monitored and treatment should be started at the first diagnosis of infection.[6]

Hepatocellular carcinoma (HCC)

This cancer is often associated with hepatitis C cirrhosis and appears to have become more prevalent recently in Canada. Demographic factors suggest a large increase in prevalence to come.

Patients with HCV and compensated cirrhosis have a 1 to 5% risk per year of developing hepatocellular carcinoma.[13] Screening for hepatocellular carcinoma has not been proven to reduce mortality.[12] The decision of whether to screen or not has to be made on an individual basis and depends on local resources.

The natural history of HCC is dependent on size: large, symptomatic tumours have a poor prognosis, with 1-year survival at 30 to 40% and 5-year survival at less than 10%. Small tumours have a mean doubling time of 5.7 months, although this is quite variable.

Optimal treatment of HCC requires a multidisciplinary team, including surgeons, oncologists, hepatologists and radiologists. Treatments such as resection or ethanol injection may cure the disease, although patients remain at risk for second cancers.

Successful treatment of HCV may reduce the risk of developing HCC, although it is too early to demonstrate this conclusively.

TABLE III
Recommended Follow-up for Patients with Chronic HCV

Patient Status	Recommended Follow-up
Normal aminotransferases (ALT), repeatedly negative HCV-RNA	Most of these patients have recovered from a remote HCV infection and simply require follow-up with ALT testing every 6-12 months.
Aminotransferases are persistently normal (i.e., on 3 to 4 serial tests within 1 year)	ALT tests every 6-12 months.[6]
Aminotransferases elevated and treatment not currently indicated	6-monthly bilirubin, albumin, international normalized ratio of prothrombin time (INR) and ALT tests.
Established cirrhosis	Specialist follow-up due to risk of liver failure.
Not currently immune to HBV/risk of hepatitis A	Discuss with patient the possibility of immunization for HBV/HAV.
Patients on treatment	ALT and HCV-RNA monitored early during treatment, since these tests will indicate who is unlikely to respond in the long term, in which case treatment should be stopped.[12]

Extrahepatic complications of HCV

The extrahepatic complications of hepatitis C are rare and seldom have an impact on outcome or prognosis. The associations, both proven and possible, are shown in Table IV.

Patient counselling

The family physician is often asked by the patient about lifestyle decisions. It is important to emphasize that HCV patients may stay well for many years and that hepatitis C should not be allowed to "take over" the person's life. Infected people should try to maintain their normal work, hobbies and activities for as long as possible. The virus is not easily transmitted and as long as the individual avoids blood-to-blood contact, there is little likelihood of transmission. Common-sense advice should be given about not sharing personal items with anybody and practising safer sex. Alcohol clearly potentiates liver damage in hepatitis C infection and patients should be counselled to abstain from alcohol.

TREATMENT

Treatment of acute hepatitis C

Acute hepatitis C is usually diagnosed only following transfusion or in a health care worker who suffers accidental exposure, since the initial infection is usually asymptomatic. Guidelines from the Canadian Association for the Study of the Liver suggest that treatment of acute hepatitis C should be with the combination therapy (interferon alfa-2b plus ribavirin). The duration of treatment should be determined by the viral genotype.

Treated patients are more likely to have normal ALT levels and negative HCV-RNA levels 6 months after treatment than untreated patients. The long-term outcome of treating acute hepatitis C is unknown.

Treatment of chronic hepatitis C

The major goal of treating hepatitis C is preventing progression.

The most effective treatment currently available is a combination therapy using synthetic interferon alfa-2b injections plus ribavirin capsules for 6 or 12 months, depending on genotype.

Therapy can be fine-tuned based on genotype: with genotype 1, response rate is better with 12 months' combination therapy than with 6 months' therapy, whereas with genotypes 2 and 3, treatment can be stopped after 6 months, as response rate is not improved after that.

Antiviral therapy, in those who show a sustained response, reduces progression to cirrhosis and reduces the incidence of HCC. A sustained response is defined as normalization of ALT and no detectable HCV-RNA in the blood 6 months or more after therapy is stopped. This response is usually sustained for years.

TABLE IV
Extrahepatic Complications of Hepatitis C

Proven Association[14]	Possible But Unproven Association
Cryoglobulinemia, with or without vasculitis	Autoimmune thyroid disease
	Diabetes mellitus
	Mooren's corneal ulcer
Membranoproliferative glomerulonephritis	Sialadenitis
	Idiopathic thrombocytopenia
	Lichen planus
Porphyria cutanea tarda	Non-Hodgkin's lymphoma

There are several indications that a patient will fail to respond in the long term, in which case therapy should be stopped:

- ALT fails to fall into the normal range after 6 months
- ALT normalizes but HCV-RNA is still present in the serum
- Breakthrough (re-appearance of HCV-RNA) occurs while on treatment.[12]

Increasing the dose in these cases is ineffective.

After 48 weeks of treatment with a combination of ribavirin and interferon alfa-2b, 38% (U.S. trial) and 43% (international trial) of patients had a sustained response. These results are compared to 13 and 19%, respectively, for patients receiving interferon alfa-2b plus placebo.

Interferon can cause flu-like symptoms in patients, but these often diminish with continued treatment. Side effects also include fatigue, joint pain, bone marrow suppression, and neuropsychiatric effects such as apathy and depression. These side-effects were also seen with combination therapy. Ribavirin is teratogenic and can induce hemolytic anemia. It is contraindicated for patients with pre-existing anemia, bone marrow suppression or renal failure.[2]

Therapy for HCV is rapidly changing. Treatment regimes currently in clinical trials include induction regimens, higher doses of interferon, PEGylated interferon, and helicase and protease inhibitors.

Vaccination against hepatitis A and B should be considered for all patients, since patients with chronic hepatitis C are at higher risk of decompensation if they acquire other viral hepatitis infections.

Selection of patients for antiviral therapy

Interferon therapy alone is effective in only a small proportion of patients, has severe side effects, and is expensive, so it is important to select those most likely to respond to treatment and to benefit in the long term. The combination of interferon alfa-2b plus ribavirin has been shown to be more effective than interferon alfa-2b alone at causing a sustained reduction of HCV-RNA in blood to undetectable levels.

Current guidelines suggest treatment only for those patients at greatest risk of progression: those with moderate degrees of necrosis, fibrosis and inflammation. The prime indication is ALT elevation to more than 1.5 times the upper limit of normal for more than 4 to 6 months.[12]

Patients with no apparent active disease (normal ALT levels, anti-HCV positive and viral RNA positive) generally have a favourable prognosis, so antiviral treatment is not routinely recommended for this group.[12,15]

Chronic hepatitis has a natural history that exceeds 20 years, so if the patient's life expectancy is reduced because of age or intercurrent diseases, interferon should not be used, especially if there is little evidence of chronic liver disease.[12] Conversely, treatment of an elderly patient with substantial liver disease, even if successful, may not affect longevity. Side effects are also more common in the older patient.

Interferon is an immunostimulant, so it should not be given to patients with autoimmune hepatitis or any other autoimmune disorder. Interferon is also ineffective in immunocompromised patients, such as HIV-positive individuals.

Response rates to antiviral therapy vary according to the hepatitis C genotype, so pre-treatment genotyping provides important information about the risks/benefits and duration of treatment and should be carried out where facilities are available.

Patients with cirrhosis respond less well to interferon therapy but treatment should not be denied on the basis of cirrhosis alone. Careful consideration should be given to the likelihood of benefit. Patients with hepatic decompensation should not be treated with interferon.[12]

Post-exposure prophylaxis and follow-up

Testing is recommended for those with needlestick, sharp object, or mucosal exposure to HCV-positive blood. There is no currently recognized post-exposure prophylactic intervention that will decrease the risk of infection.

Alternative therapies

Physicians should be aware that patients may be using herbal and other alternative remedies which may interfere with their treatment. Patients should not take any alternative therapy while on antiviral treatment. To date, herbal treatments have not been particularly useful for treatment of hepatitis C.

Liver transplantation

Liver transplantation gives excellent short-term survival in patients with end-stage liver disease due to HCV. Hepatitis C is the most common single cause for liver transplantation in Canada.

Reinfection of the transplanted liver with HCV after transplantation, which occurs in 100% of cases, is a major concern. Sixty to 70% of patients will go on to develop recurrent hepatitis, 20 to 30% will go on to cirrhosis. A small number will develop aggressive disease.

Treatment of recurrent hepatitis C in transplanted patients is still under debate. Interferon as a single agent is proven not to work, but combination of interferon and ribavirin looks promising from early studies.

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Current Status of Hepatitis C in Canada

Shimian Zou, Martin Tepper, Antonio Giulivi

Hepatitis C is a major public health concern around the world. It is estimated that approximately 3% of the world's population, or as many as 170 million persons worldwide, are infected with hepatitis C virus (HCV).[1] HCV was discovered by characterization of the viral genome in 1989,[2] without the actual isolation of the virus itself. The virus is a member of the flaviviridae family with a genome of single stranded RNA. Various genotypes exist in different regions of the world. So far, six major genotypes have been isolated with genotypes 1-3 described worldwide, genotypes 4 and 5 principally in Africa and genotype 6 primarily in Asia.[1] In Canada, the major genotypes are 1, 2, and 3.[3-5]

Hepatitis C is usually a subclinical infection with only 25% of patients with post-transfusion hepatitis developing jaundice.[6] In other prospective studies, only 20-30% of the patients had symptoms and approximately half of the symptomatic group developed jaundice.[7] Clinically and histopathologically, hepatitis C is similar to viral hepatitis caused by other pathogens.[8] The most important feature of hepatitis C is the high frequency (75-85%) with which acute disease progresses to chronic infection. Available studies of hepatitis C infection have shown that the disease has a protracted course and serious sequelae may not appear until decades after initial infection.[9] The pathogenesis of and the immune response to hepatitis C are poorly understood. Infection by HCV does not seem to induce a protective humoral response but it is becoming clear that some infected individuals do recover from their infection.

Hepatitis C is transmitted through blood or body fluids contaminated with the virus.[10,11] Important risk factors associated with transmission of HCV are the sharing of drug injection equipment and the receipt of unscreened blood or blood products. Vertical and sexual transmission can also occur. Inapparent parenteral exposure such as tattooing, body piercing and sharing of personal hygiene items, only if the instruments or items for such activities are contaminated with blood or body fluids, are also presumed to be risk factors. In different countries the relative importance of risk factors can vary both regionally and temporally. For example, until recently blood transfusion was an important route of transmission; however, with the development and implementation of sensitive (and specific) screening methods, the risk associated with blood transfusion and the use of blood products has been markedly reduced. In most developed countries such risk is minimal at the present time whereas in some developing countries the risk may still be at a relatively high level.[12]

As there are still many unanswered questions about HCV itself and the immune responses it induces, there is currently no vaccine developed for the disease. As a result, prevention and control rely primarily on the successful interruption of viral transmission and the management of cases. Treatment with interferon alone or combined with ribavirin has been shown to be effective in some cases, especially with the combination therapy for infections caused by certain genotypes of HCV.[13]

In Canada, surveillance and studies for HCV infection have been actively carried out to assess the risk of hepatitis C, to identify the major factors affecting the transmission of HCV, and to determine effective intervention measures for control of the disease.

Public health surveillance of hepatitis C in Canada

Public health surveillance for hepatitis C in Canada consists of the reporting of identified cases, enhanced surveillance and targeted research.

By January 1999, hepatitis C became reportable in all provinces and territories across the country. To determine the current status of surveillance activities for hepatitis C in different jurisdictions, a survey of the 12 provincial and territorial epidemiologists was conducted by Laboratory Centre for Disease Control (LCDC) in 1998. According to the survey, positive laboratory testing results were the criteria to stimulate reporting, with confirmed anti-HCV in all and HCV-RNA or seroconversion in some jurisdictions. Confirmatory testing was done either in central provincial laboratories, designated hospital laboratories or the federal laboratory. Health care sectors that must report HCV infections were laboratories (10 jurisdictions), physicians (11 jurisdictions), hospitals (8 jurisdictions) and the blood services (9 jurisdictions). A database had been set up for hepatitis C in 11 jurisdictions and duplicates had been checked in all 10 jurisdictions that answered this question.

While the nationwide reporting of hepatitis is important for the surveillance of hepatitis C, the data collected from such reporting are limited due to the nature of the infection, e.g., asymptomatic in most infections, the slow progression of the dis-

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ease, and the lack of a laboratory test to differentiate acute infection from remotely acquired infection. Likely, most of the reported hepatitis C cases have been remotely acquired infections.

To overcome the difficulties, at least in part, enhanced surveillance activities have been and are currently being carried out by LCDC in collaboration with certain regional health authorities to further define the risk of hepatitis C in Canada. Between 1993 and 1995, a sentinel health unit surveillance project was implemented involving eight health units across the country. In October 1998, an enhanced surveillance project was initiated in four health regions (Calgary Regional Health Authority, Capital Health of Edmonton, Winnipeg and the Ottawa-Carleton Health Department). In this enhanced surveillance, special effort was made to identify acute hepatitis C cases among all cases reported by laboratories, physicians, public health professionals and hospitals. Standardized case definitions (see footnote to Figure 4) and an investigational protocol including questionnaires were used to ensure consistency and comparability of data across regions or health units. In addition to clinical and laboratory information essential for the differentiation of acute versus chronic or remotely acquired cases, epidemiological data including risk factors potentially associated with the transmission for each case were also collected through case interview.

Furthermore, special research projects were carried out by public health agencies, physicians and university researchers in Canada to address specific research questions related to hepatitis C, including major transmission routes or risk behaviours, special population groups at higher risk, and long-term outcomes of HCV infection through follow-up of certain cohorts of the population.

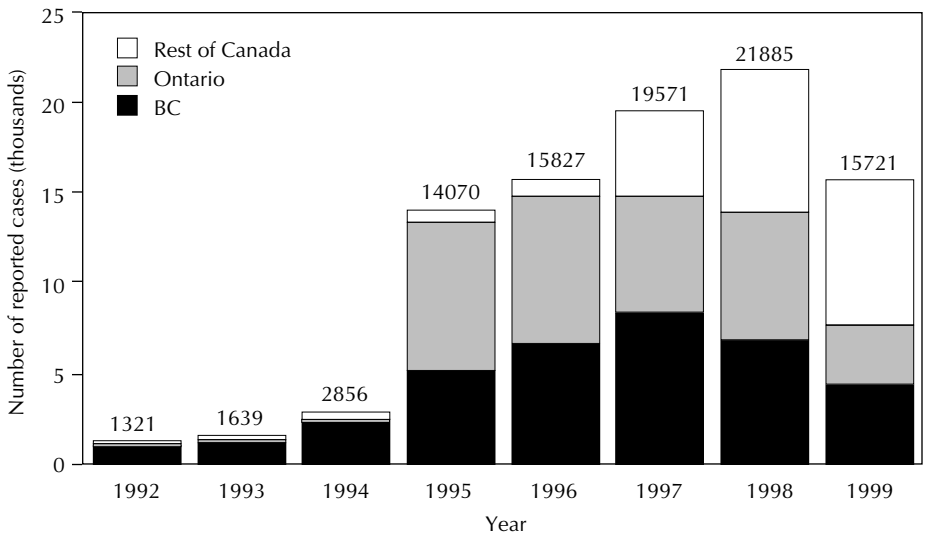

Figure 1. Annual nationally reported cases of hepatitis C infection in Canada by selected provinces, 1992-1999 (1999 incomplete).

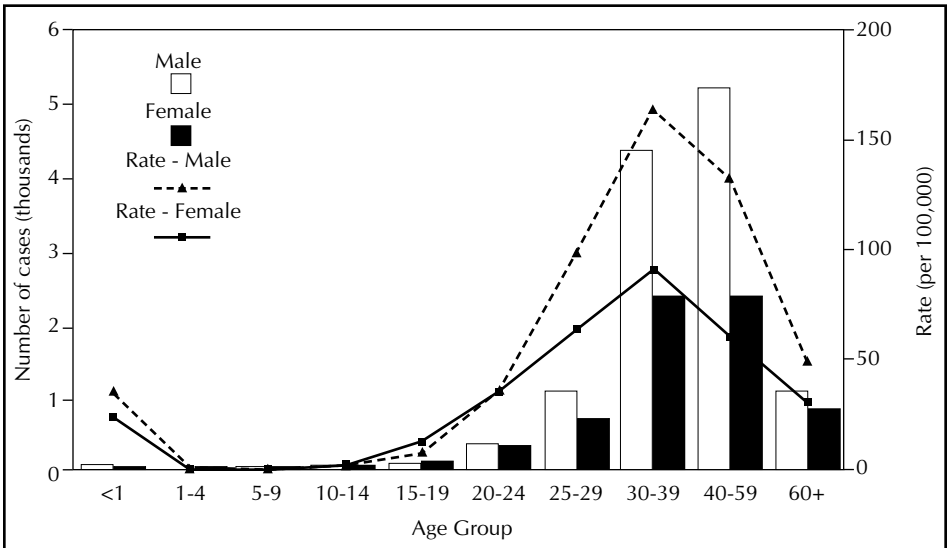

Figure 2. Number of nationally reported hepatitis C cases and rates in Canada by gender and age, 1997.

Prevalence and incidence of hepatitis C

Nationally Notified Cases of Hepatitis C

Reporting of hepatitis C started in British Columbia in 1992 and gradually more provinces began to report the disease. Figure 1 shows the number of reported cases each year in British Columbia, Ontario and the rest of the country (data source: Division of Surveillance, LCDC). The case definition employed was confirmed anti-HCV seropositivity. Data for 1999 are incomplete. While there has been an exponential increase in the number of reported cases over time, this is primarily a result of increasing recognition and reporting of remotely acquired cases as opposed to an epidemic of new infections.

Regional differences in reported hepatitis C cases exist across jurisdictions. Of the 19,571 cases reported in 1997, 42.3% (8,286) were from the province of British Columbia (BC) and 33.1% (6,472) were from Ontario. Due to variations in reporting practices, comparison of rates of reported cases among jurisdictions may not be reasonable.

The age distribution of the reported cases of hepatitis C showed that the age-specific rates were very low in infants and children, gradually climbing to a peak rate among those 30-39 years of age and declining thereafter (Figure 2, data source: Division of Surveillance, LCDC). As indicated above, these reported cases are largely prevalent cases and the bulge among those

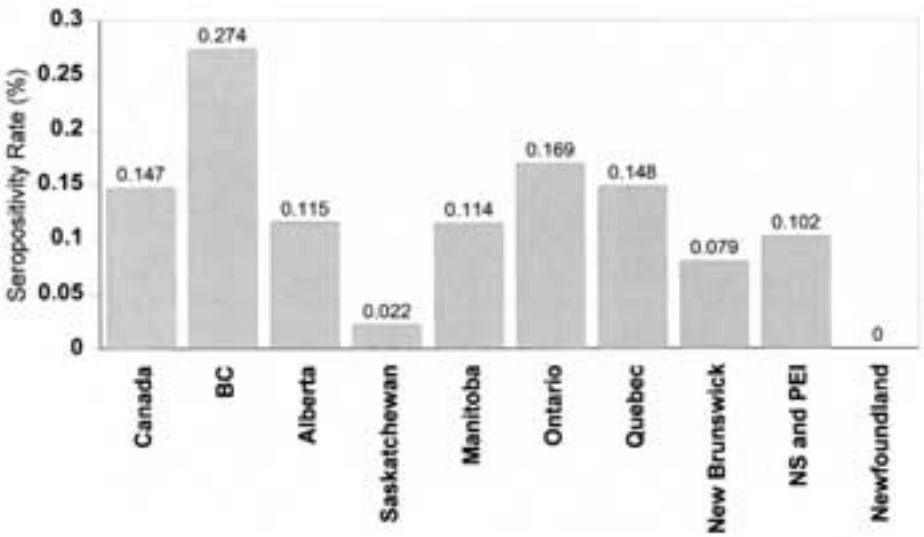

Figure 3. Hepatitis C seropositivity rate (%) among first-time blood donors in Canada and the provinces, 1997.

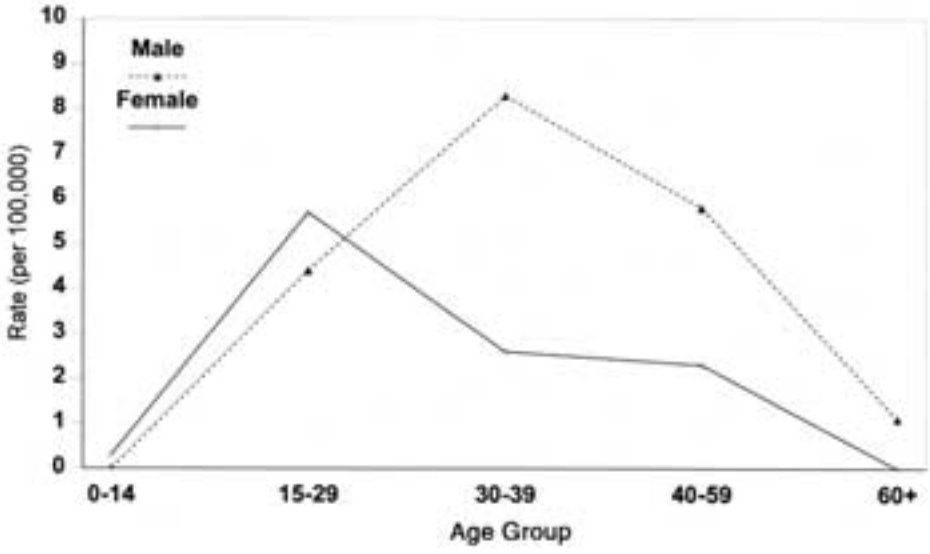

Figure 4. Incidence rates of acute hepatitis C in Canada by gender and age, 1998-1999, from enhanced surveillance in four health regions: Calgary, Edmonton, Winnipeg and Ottawa-Carleton

30-39 and 40-59 years old may represent infection acquired in the 1960s and 1970s. Males have close to twice the reported rate of females (83.3 vs 45.6 per 100,000); males have higher rates in all age groups beyond 20-24 years. Nevertheless, rates by age follow a similar pattern for males and females.

Prevalence of Hepatitis C

Remis et al.[14] estimated from available data that the prevalence of anti-HCV positivity was approximately 0.8% (0.68-0.94%) in Canada, with 0.96% in males and 0.53% in females. Those in age groups <5 years, 6-14 years, 15-19 years, 20-39 years, 40-64 years, and 65+ were estimated to have a prevalence rate of 0.2%, 0.05%, 0.10%, 1.51%, 0.75% and 0.6%, respectively. Based on the positive rates of anti-HCV among first-time blood donors from different jurisdictions, it was further projected that the anti-HCV prevalence rate (%) in each province was 1.36, 0.91, 0.43, 0.54, 0.94, 0.49, 0.37, 0.51, 0.25, and 0.08 for British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland, respectively. Figure 3 shows the seropositivity rates for first-time blood donors in 1997 (Canadian Red Cross, unpublished data). While the rates are low, there are evident differences among the provinces with BC having the highest seropositive rate (0.27%) and Newfoundland having the lowest (0.0%).

The prevalence of HCV infection is much higher in certain at-risk population groups. For example, Strathdee et al.[15] showed that 88% of 1,006 injection drug users in Vancouver who had injected illicit drugs in the previous month were positive for anti-HCV. Inmates in prisons were found to have anti-HCV positive rates in the range of 28-40%.[16,17] A study of 437 street youth in Montreal indicated a prevalence of 12.6% (Roy et al., Hepatitis B and C among street youth in Montreal - final report, 1997) whereas another study of street youth in Ottawa showed a lower prevalence of 4%.[18] Finally, in a northern Alberta dialysis population, the prevalence of hepatitis C infection was 6.5%.[19]

Incidence of Hepatitis C

As indicated earlier, the rates of reported hepatitis C cases from the national reporting data over time were affected by increasing recognition and reporting of remotely acquired cases. To assess the occurrence of acute hepatitis C in Canada, an enhanced surveillance system was initiated in four health regions: Edmonton and Ottawa-Carleton in October 1998, and Calgary and Winnipeg in January 1999. The four regions cover a population of approximately 3 million, or 10% of the total population in this country. According to preliminary data collected up to October 1999, the incidence rate of recognized acute hepatitis C was 3.2 per 100,000 person years in these four regions. Males had higher incidence rates than females except in the 0-14 and 15-29 age groups (Figure 4). Incidence of acute hepatitis C peaked at 30-39 years of age for males and 15-29 years for females (Figure 4). There were substantial regional variations among the four regions with the highest incidence rate being in Edmonton at 6.7 per 100,000

person-years, followed by Winnipeg, Calgary and Ottawa-Carleton at 3.7, 2.2 and 0.5, respectively. Note that these were identified clinically recognized acute cases with symptoms, elevated liver enzyme and positive anti-HCV test results.

Based on the incidence data from this enhanced surveillance in the four health regions from October 1998 to October 1999, namely, 3.2 per 100,000 person-years for acute hepatitis C, an extrapolation to the entire population of Canada would suggest that an estimated 1,000 cases of clinically recognized acute hepatitis C could be identified annually in Canada. However, this is a conservative estimate as not all acute cases would have been recognized and not all clinically recognized acute cases would have been identified by this enhanced surveillance. Nevertheless, these data provide a consistent and comparable measure across these four jurisdictions.

Transmission patterns and risk factors

A few studies have looked at transmission patterns and risk factors for hepatitis C. In a report of a series of 63 consecutive patients by Scully et al.,[20] 43% of infections could be attributed to injection drug use and 33% to blood use. Among 54 cases reported in Prince Edward Island (PEI) from 1991 to 1995 and followed up by the Chief Medical Officer of Health, 46% were attributed to injection drug use, 39% to blood use, 6% to both and for 9% a risk factor was not identified.[21] In the Capital Regional District, British Columbia (BC), among 698 anti-HCV positive general population cases reported to the public health department in 1995 and 1996, 69.6% admitted to intravenous drug use and 16% to receipt of blood (LCDC, unpublished data).

Among the 720 community cases from eight health departments (Edmonton, Guelph, Kelowna, Kingston, Prince Edward Island, Saskatoon, Sherbrooke and Winnepeg) cooperating in the Sentinel Health Unit Surveillance Study from October 1993 to March 1995, 68% admitted to injection drug use and 30% to therapeutic blood receipt. For the 585 persons for whom full information was known, 67% had injection drug use (IDU) but not blood exposure, 17% had IDU and blood exposure, 6% had blood exposure but not IDU and 9% had neither (LCDC, unpublished data).

TABLE I
Distribution of Mutually Exclusive Risk Factors for Acute Hepatitis C*

Risk Factor	No. of Cases	% of All Cases	% of Cases with Known Risk Factors
Injection drug use	32	46.4	60.4
Drug snorting	3	4.3	5.7
Blood contact	1	1.4	1.9
Blood transfusion	1	1.4	1.9
Haemodialysis	1	1.4	1.9
Tattooing	2	2.9	3.8
Body piercing	2	2.9	3.8
Incarceration	2	2.9	3.8
Sex with hepatitis C	2	2.9	3.8
Hepatitis C in family	3	4.3	5.7
Hospitalization	2	2.9	3.8
History of dental visit	2	2.9	3.8
Unknown	16	23.2	
Total (w/o unknown)	53		100
Total (with unknown)	69	100	

* from enhanced surveillance, Oct. 1998 - Oct. 1999, in Calgary, Edmonton, Winnipeg and Ottawa-Carleton.

In addition to an assessment of the magnitude of acute hepatitis C cases, potential routes of transmission for each identified case were also investigated in the enhanced surveillance described previously by interviewing identified cases. For analysis of potential transmission routes, a ranking of risk factors was compiled according to available epidemiological information. From October 1998 to October 1999, 95 acute hepatitis C cases were identified, of whom 69 were interviewed (72.6%) for history of risk factors during the six months prior to the onset of the disease. Table I shows the distribution of risk factors reported by acute hepatitis C cases. Among the 53 acute hepatitis C cases who reported one or more risk factors, 60.4% (32) reported a history of IDU, among whom 78% (25) reported sharing needles. Higher frequency of IDU history was reported among those who were 15-39 years of age (67.7%), female (68.4%) and born in Canada (62.0%). One of the 69 cases reported a history of blood transfusion (see below in discussion). Finally, sex with HCV-infected individuals was identified as a risk factor for only 2.9% (2/69) of the acute hepatitis C cases.

Nine hundred and five (905) of the 2,505 identified chronic or likely chronic hepatitis C cases were also interviewed for risk factor information. Of 885 cases who reported one or more risk factors, 55.5% reported having ever injected drugs and 7.0% having ever snorted drugs without IDU. History of blood transfusion before 1990 was identified as a potential risk factor for 20.9% of these 885 cases. However, bias could have existed due to the fact that only 36.1% of chronic or likely chronic cases were interviewed and a disproportionately higher number of injection drug users might not have been interviewed. Nevertheless, a higher proportion of chronic cases reported a history of blood transfusion in comparison with acute hepatitis C cases.

Taken together, the data presented above indicate that injection drug use and blood exposure were the two most important routes of transmission for hepatitis C. However, injection drug use is the single most important route of HCV transmission currently in Canada, accounting for at least 60% of all HCV transmissions.

Prediction of hepatitis C burden in Canada

To assess the current risk of hepatitis C in Canada and to predict the burden this disease may pose to Canadian society in the near future, expected numbers of persons at different stages of the disease currently and in the next decade were estimated by simulation using a published hepatitis C natural history model with no treatment effect being applied (LCDC, unpublished analysis). Based on the estimate that 240,000 persons are currently infected

with hepatitis C virus in Canada,[14] the simulation analysis showed that the number of prevalent hepatitis C cirrhosis cases would likely double (increasing by 92%) from 1998 to the year 2008. It was also projected that the number of prevalent cases of liver failure and hepatocellular carcinoma related to hepatitis C would be expected to increase by 126% and 102%, respectively, for the same period. The number of liver deaths associated with hepatitis C would be expected to increase by 126% in 10 years. The medical and social care systems in Canada may not be ready to support these large increases.

It should be noted that these predictions are based on currently available data and the progression probabilities in the natural history model that were used in the simulation. Most recently, Seeff et al.[22] published their results of a 45-year follow-up of hepatitis C virus infection in healthy young adults. Their findings suggest that healthy HCV-positive persons may be at less risk for progressive liver disease than is currently thought. If the results are confirmed by other studies with representative HCV-infected populations and adequate sample sizes, the above predictions may need to be revisited.

In addition to patients with sequelae from existing hepatitis C cases, an estimated 1,000 clinically recognized acute hepatitis C cases will be identified annually in Canada, according to data from the enhanced surveillance system (see above). Based on the proportion of asymptomatic HCV infections (approximately 75% of all HCV infections), 4,000 new HCV infections may be expected each year in Canada; this does not take into account underreporting.

These results highlight the importance of both the control of disease progression of HCV-infected persons and the primary prevention of hepatitis C infections in this country.

Prevention and control of hepatitis C in the new era

Prevention and control of hepatitis C involves prevention of HCV infection, slowing disease progression, and reducing the likelihood of premature death. As indicated above, the transmission of hepatitis C has evolved from an illicit drug use and blood safety issue to an issue associated with illicit drug use and other likely routes of transmission. Accordingly, strategies for the prevention and control of hepatitis C have to change to effectively cope with the challenges in the new era. In October 1998, LCDC held a national consensus conference in Ottawa: *Hepatitis C - Prevention and Control: A Public Health Consensus* and a report was published.[23] The report provides a general guide for activities to be utilized across the country for the prevention and control of hepatitis C.

Prevention of Disease Transmission

This includes preventing transmission of HCV through high-risk behaviours such as the sharing of needles and other gear (injection drug use), preventing transmission through blood or blood components, organs, tissues, semen, unsafe medical or health care practices, as well as reducing the likelihood of blood and body fluid exposure in health care settings or through contaminated personal hygiene items.

For injection drug use, it is realized that effort should be made on different fronts to reduce the transmission of HCV and other bloodborne pathogens. These include prevention of initiation, harm reduction among illicit drug users, programs targeting special population groups at higher risk for injection drug use and for hepatitis C such as street youth, and research to explore new ways to contain the spread of HCV through illicit drug use. At the federal level, an interdepartmental committee has been working with different partners to collectively tackle the issue of drug abuse. This will not only benefit the prevention of HCV infection but will also help to reduce the transmission of other bloodborne pathogens such as human immunodeficiency virus (HIV) and hepatitis B virus (HBV).

Although the risk associated with blood, blood components and blood products is currently very low (less than 1/100,000), it is nevertheless essential to ensure the highest safety possible with these products because of their potentially disastrous impact should they be contaminated with HCV. In Canada, the Canadian Blood Services (CBS) and HemaQuebec (HQ) are responsible for blood donor screening, blood collection, and distribution. The Therapeutic Products Programme (TPP) of Health Canada is the regulatory body for the safety of blood and blood products, whereas LCDC is responsible for surveillance and risk assessment for blood and blood products. A Transfusion Transmitted Injuries Surveillance System is being piloted by LCDC in collaboration with certain provinces and the blood agencies (CBS and HQ). Once established, the system will be able to monitor transfusion-transmitted injuries including bloodborne infections among recipients to assess the risk of these injuries.

For nosocomial, occupational, and other inapparent parenteral transmission routes of HCV, LCDC has prepared several guidelines for the prevention and control of HCV transmission through these routes. These include *An Integrated Protocol to Manage Health Care Workers Exposed to Bloodborne Pathogens,*[24] *Proceedings of the Consensus Conference on Infected Health Care Workers: Risk for Transmission of Bloodborne Pathogens,*[25] and *Infection Prevention and Control Practices for Personal Services: Tattooing, Ear/Body Piercing, and Electrolysis.*[26]

Counselling of anti-HCV positive persons to prevent transmission is another component of primary prevention.[23] HCV-infected women of childbearing age should be informed that there is a risk of transmission to any infants born, that the risk increases if a woman is infected with both HIV and HCV, and that the infants should be tested for infection. Household contacts of HCV-infected people should not share their personal hygiene items. Household contacts should take "common sense measures" to protect themselves from exposure to the blood of an infected person. Although the risk may be low, HCV can be transmitted through sexual activities especially with risky sexual behaviours such as unprotected sex with multiple partners. The Canadian Liver Foundation is preparing a brochure for hepatitis C-infected individuals, with support from Health Canada and the Canadian Association for the Study of the Liver. The brochure should also serve as a source of general

information about the infection, the disease and the measures to prevent transmission of the virus.

Prevention of Disease Progression and Management of Hepatitis C Cases

This includes reduction of consumption of alcohol, consideration of vaccination against other hepatitis viruses such as hepatitis A virus, and treatment with interferon and ribavirin. The Canadian Association for the Study of the Liver (CASL) has prepared a guideline for the management of hepatitis C cases[13] which is available on the CASL website (http://www.lhsc.on.ca/casl/cont.htm).

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Hepatitis C in Canada's First Nations and Inuit Populations: An Unknown Burden

Peter Riben, Gillian Bailey, Shauna Hudson, Karen McCulloch, Tom Dignan, David Martin

Hepatitis C is recognized as an important cause of liver disease. The burden of disease in Canada, as evident from other reports in this supplement, is being described. The epidemiology and the disease burden of hepatitis C in the First Nations and the Inuit is not known. The assumption that it will mirror the epidemiology in the non-Aboriginal population – as evidenced by the experience with tuberculosis, HIV/AIDS and pneumococcal disease – may be false. The distribution of disease and risk factors may differ from the Canadian population and this may impact on the opportunities for interventions.

Currently the provision of public health services in Aboriginal communities is in the midst of change, as a result of the government's policy on transfer and self-government with the transfer of funds from Medical Services Branch (MSB) to the communities for the provision of those public health services. However, since there is currently no federal legislation governing public health *(more specifically communicable disease control)* on First Nation reserves or in Inuit communities, there is acknowledgment that public health practices in Aboriginal communities must conform to provincial/territorial legislation and regulations.

Though practices vary across the country and are, in part, dependent on transfer status of a community, communicable disease follow-up on reserves is an activity undertaken by First Nations health agencies and/or MSB. The process used for the reporting of diseases in Aboriginal communities is the same as the reporting process for non-Aboriginals.

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METHODS

The seven MSB regions were canvassed to determine how many cases of hepatitis C were identified in First Nations and Inuit in the past year (1999). Information about the age distribution, gender and risk factors were also obtained if available from either the MSB or provincial health reportable disease databases.

RESULTS

Four regions were able to provide varying levels of data on hepatitis C from the reportable diseases databases. A fifth region was able to provide information from an ongoing study of clients attending Alcohol and Drug Treatment Centres.[1]

The ability to identify the number of cases of hepatitis C in First Nations varied across the regions. Each province uses its own form to collect data on hepatitis C. Most provinces/territories do not ask for information on ethnicity/Aboriginal status and as a consequence cannot identify First Nations and Inuit in their data and are often unable to identify whether the residence is a First Nations community. Reported cases (incident and prevalent) of hepatitis C in First Nations in 1999 varied by province and ranged from 0.4% of all cases reported in a province to 29.3%. In some regions the cases in First Nations include individuals living both on and off reserve whereas others only include individuals living on reserve.

In two regions the age and sex distribution of cases in 1999 were reported. In one region, 12 of the 25 cases reported in First Nations on reserve were male. Most cases were reported in the 30 to 39 year age group; the 40 to 59 age group was the second most common. In the other region, 45.6% of the 228 reported cases were male and the average age was 31 with 50% of the cases occurring in individuals ranging from 24 to 38 years of age. Most cases were reported in the 30 to 39 year age group (35.1%) followed by 34.6% in the 20 to 29 age group.

Risk factor information was not consistently available for the cases. In one region, injection drug use and previous blood transfusions were the only two risk factors reported. In the other region that reported risk factor data, the most common risk factor reported was injection drug use (21%), followed by multiple sexual partners (10.5%). Receipt of a blood transfusion or blood product and a history of tattoos were the next most common risk factors reported.

Hepatitis C antibodies were determined in 412 individuals attending alcohol and drug rehabilitation programs in the Pacific Region.[1] Of these, 2 had indeterminate results and 75 or 18% (95% CL 14-22) had a positive result. Forty-nine of the 211 males and 26/200 females were found to be positive.

No information on hepatitis C in the Inuit could be obtained.

DISCUSSION

The current experience with tuberculosis[2] and HIV/AIDS[3] in Canada exemplifies the reason why it is necessary to collect ethnicity data and ensure that an accurate representation of the burden of disease in the Aboriginal community is

available. It is clear that the burden of tuberculosis and HIV/AIDS in First Nations and Inuit is considerably greater than the burden in Canadian-born non-Aboriginals, although it is uncertain which of the determinants (or combinations) of health is (are) responsible for this.

At this time, an accurate account of the burden of illness resulting from hepatitis C in the First Nations is not available. The range from less than 1% of cases to approximately 30% of cases within a province may be a reflection of true variation in incidence, the difference in reporting, or an ascertainment bias resulting from special studies and surveillance projects. A recent report generated from the Enhanced Surveillance of Canadian Street Youth found that 6% of self-identified Aboriginals were hepatitis C positive.[4]

The risk factors associated with transmission of hepatitis C identified in the Canadian blood donor study[5] are probably similar risk factors for First Nations. These include such factors as previous blood transfusions, tattooing, living in a closed institution and having sex with an injection drug user. Percutaneous exposure (injection drug use) to contaminated blood is probably the explanation for the high rate of seropositivity in the clients of the Alcohol and Drug rehabilitation programs as well as that found in street youth. The role of other risk factors is subject to conjecture. The role poverty plays, particularly in the absence of the other known risk factors, is unknown. Whether there are any other factors which are of importance such as genetic make-up cannot be answered.

To date, the MSB and provincial reportable disease databases have not provided the information required to determine the burden of disease in First Nations. A non-exhaustive list of reasons for this lack of information includes the relatively recent addition of hepatitis C to the list of reportable diseases, a lack of standardized ethnic identifiers on reports which make it difficult to analyze data by Aboriginal status, and a resistance to the exchange of information from one organization to another. Concerns over ownership of data and the confidentiality of patient information are reasons cited for not sharing data between the public health agencies responsible for follow-up and policy.

The lack of information regarding the incidence and prevalence of hepatitis C and associated risk factors in First Nations and the Inuit increases the difficulty of determining, and establishing, appropriate public health interventions which address the needs of First Nations and Inuit. Given the potential costs in terms of morbidity, quality of life, mortality, as well as the direct and indirect economic costs associated with hepatitis C, it is imperative that the burden of illness be accurately determined. This can be best accomplished through co-operative efforts which include the Aboriginal community and their leadership, First Nations and Inuit health agencies, all levels and branches of government, and academics.

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Public Health and Hepatitis C

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This paper reviews key public health aspects related to surveillance, transmission and primary prevention of hepatitis C. Hepatitis C is now a reportable disease in all Canadian provinces and territories. Although prevalence in Canada is estimated at under 1%, that associated with injection drug use (IDU) approaches 90%. The epidemiology of new HCV infections in Canada is now primarily defined by IDU behaviour, with annual incidence rates among new drug injectors exceeding 25%. HCV is less efficiently transmitted through other routes of exposure. An effective vaccine against HCV remains elusive. Some jurisdictions offer hepatitis A and hepatitis B vaccine to HCV-infected persons. An array of harm reduction strategies targeting IDU has been implemented but underdeployed across Canada, and has been ineffective to date in controlling the HCV epidemic. Public policy alternatives, such as legalization and regulation of injection drugs, are being debated. Improved HCV preventive strategies are urgently required and need careful evaluation.

Public health practitioners carry responsibility for the surveillance and primary prevention of Hepatitis C Virus (HCV) infection. This paper will review key aspects relevant to all disciplines concerned with public health in the areas of surveillance, transmission and primary prevention.

SURVEILLANCE

A co-ordinated surveillance approach is necessary to determine disease incidence, risk factors and transmission patterns for HCV infection. A well-tooled system will assist in evaluating existing programs and identifying issues where further action is needed.

The 1998 Health Canada HCV consensus conference recommended that three different surveillance approaches should be taken: case-by-case surveillance, enhanced surveillance in sentinel health units, and enhanced surveillance targeting specific locations or populations.[1] National reporting of HCV in Canada began in 1992, but the infection has only been reportable in all provinces and territories since January 1, 1999. In 1998 LCDC established a project of enhanced surveillance for newly identified HCV infections, collecting detailed information from physicians and patient interviews. The project is being expanded beyond the current 4 sites to include other urban and rural areas. Surveillance of acute symptomatic HCV infection can provide a means to evaluate the effectiveness of prevention efforts and to identify missed opportunities for prevention.[2]

The number of cases of HCV reported in Canada has dramatically increased from 1,321 in 1992 to 21,885 in 1998 (final number for 1999 is not yet available),[3] mainly due to an increased recognition of previously acquired HCV infection. Prevalence in the general Canadian population has been estimated at 0.8% (240,000 people currently infected).[4] A similar prevalence of 1% was found in pregnant women in British Columbia[2] and also at a community-based electroencephalogram clinic in Ontario.[5]

TRANSMISSION

Although HCV ribonucleic acid (RNA) has been detected in a wide range of body fluids and tissues (e.g., saliva, tears, breastmilk, vaginal secretions, seminal fluid), transmission is correlated primarily with exposure to blood.[6-8] Serum HCV-RNA titres of 10^6 copies per millilitre or more, measured by reverse transcriptase polymerase chain reaction, are more commonly associated with HCV transmission, but a specific threshold of viral load predicting infection cannot be defined.[9,10] Transmission is also driven by the high proportion of HCV-infected persons – approximately 85% – who develop chronic infection. Transmission risk for HCV following a single percutaneous exposure is intermediate (2.7-6%), compared to risk of HIV (0.3%) and hepatitis B virus (19-30% in HBeAg-positive source).[11]

Injection drug use

The majority of new HCV infections in Canada, as well as approximately 70% of prevalent infections, occur among injecting drug users (IDUs).[12] The high prevalence of chronic HCV in IDU populations, along with highly efficient transmission associated with the sharing of syringes and other paraphernalia, and a steady influx of new, susceptible injecting users have resulted in sustained high incidence rates among IDU populations, even with infrequent sharing of needles and syringes.[13] Among IDU cohorts in Vancouver and Montreal, the prevalence of HCV is reported as 87% and 70% respectively, and the annual incidence is reported as 26% and 27% respectively.[1,14,15] A dramatic increase in prevalence of HCV within the first 2 years of injecting drug use was found in the US-based ALIVE study. Thus prevention measures should target new injection drug users.[16] Recent disclosure of the world's largest known medically caused outbreak of HCV illustrates the remarkable efficiency by which used, non-disinfected needles and other injecting drug

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paraphernalia can transmit HCV. This outbreak involved an anti-schistosomiasis campaign conducted in Egypt from the 1950s to 1980s, in which thousands of persons were administered repeated injections of an antimony salt with re-used needles.[17]

Therapeutic blood and blood products

Blood transfusion, which accounted for a substantial proportion of HCV infections acquired over 10 years ago, now rarely accounts for recently acquired infections.[18] Transmission of HCV from therapeutic blood or blood products has plummeted since 1990, when donor screening was introduced in Canada. An estimated 10-15% of cumulative HCV infections in Canada may have been acquired in this manner.[1] Viral inactivation procedures introduced for clotting factor concentrates and human immune globulins prepared from pooled plasma, have eliminated transmission risk via these products. Third generation anti-HCV screening of all donor blood, introduced in Canada in 1996, has reduced the risk of HCV exposure from blood to approximately 1 in 120,000 donations.[19] Canadian Blood Services introduced nucleic acid testing for HCV for all blood donors in October 1999 as an investigational screening test (pers. commun. P. Doyle, 2000). Recommendations of Justice Krever are also being implemented in some provinces, such as British Columbia, with development of blood and blood product transfusion registries and tracking mechanisms to facilitate lookbacks (positive donor) and tracebacks (positive recipient).

Mother-to-child (vertical transmission)

Mother-to-child transmission of HCV has been found to occur in about 5% of HCV-infected, HIV-negative pregnant populations.[10,20] Co-infection with HCV and HIV is associated with HCV transmission rates about 3 times greater.[2,10,21-23] There is no definite epidemiologic evidence of mother-to-child HCV transmission from breastfeeding involving asymptomatic, HCV-seropositive, HIV-negative mothers with no detectable serum HCV-RNA.[21,23-25] More limited evidence suggests that asymptomatic, HIV-negative mothers with detectable serum HCV-RNA below 10^5 to 10^6 copies/ml but no detectable HCV-RNA in breastmilk are also at very low risk of transmitting HCV by breastfeeding.[26-28] There are conflicting data on the protective value of elective caesarean section.[22]

Sexual transmission

Despite some estimates that up to 20% of new HCV infections may be due to sexual exposure,[18] the literature reports a wide range of risk of interspousal HCV infection, which is inferred to be due to sexual transmission.[29-35] Alternative risk factors may account for many cases of apparent sexual transmission between sexual partners.[29,36,37] A Japanese study, which controlled for parenteral exposures, estimated the risk of spousal transmission to be less than 1%,[38] and no evidence was found of sexual transmission of HCV to husbands of women with hepatitis C who had received contaminated anti-D immunoglobulin.[39] The risk of infection through sexual intercourse with a carrier has been estimated at 2.5% over 20 years.[1] Some studies show increased prevalence of HCV infection in spouses of infected sexual partners compared to other household relatives or matched spouses of non-infected partners;[30,40] others show a correlation with duration of sexual relationship;[41,42] while still others indicate age to be predictive of interspousal and other interfamilial HCV infection.[29,31,32] The risk of transmission through anal intercourse is unknown, although it is biologically plausible that a higher rate of exchange of small amounts of blood could correlate with a higher risk of transmission.

Transmission to non-sexual close contacts

Transmission of HCV to non-sexual household contacts is very low, with most studies reporting approximately 2-3% prevalence of HCV infection among these contacts.[29-35] Transmission may occur through sharing articles that might be contaminated with blood, e.g., toothbrushes and razors.

Other exposures

There is documented transmission of HCV with tattooing,[43] but ear piercing, acupuncture and electrolysis pose little risk for infection.[44] Prevalence of HCV infection among health care workers is about 1 to 2% – the same as among the general population – and the most important risk factor associated with occupational HCV infection is unintentional needlestick injury.[2]

PREVENTION

Hepatitis A prevention

Patients with chronic hepatitis C, unlike those with chronic hepatitis B, were found to have a substantial risk of fulminant hepatitis and death associated with hepatitis A virus infection (HAV).[45] Hepatitis A vaccine is safe and effective[46] and should be made available free of charge to HCV-positive patients and IDUs. Some jurisdictions, such as British Columbia, also offer hepatitis B vaccination to this population. However the IDU population may not access medical care in the usual manner and targeted programs are necessary to reach this population. The Vancouver/Richmond Health Board initiated such a program in January 2000; teams of nurses immunized 3,000 at-risk persons, offering immunization in their residences, the needle exchange, drop-in centres, medical clinics and other locations in the Downtown Eastside of Vancouver.

Immunoprophylaxis

The obstacles to developing a vaccine for primary prevention seem daunting. HCV has a high rate of mutation during RNA polymerisation. A hyper-variable region of its genome codes for an exposed portion of envelope protein.[47-49] Few changes in the exposed area of envelope lead to functional constraints for the virus so that HCV pays a low cost for its ability to evolve swarms of closely related yet genetically distinct quasispecies in the same host. The net result is a moving immunologic target.[50]

While MHA class 2 alleles, CD4 T cell responses, helper cell phenotype and associated cytokine activity have shown an association with viral clearance,[51-56] most infected people show poor clearance of virus. There is no clearly defined protective response after natural infection. The lack of an *in vitro* or ideal animal model has also limited vaccine development. However in one study, a vaccine composed of envelope glycoprotein protected chimpanzees against low-level intravenous challenge by the homologous strain.[57]

Passive immunization has no proven efficacy for pre- or post-exposure prophylaxis.[58] The systematic exclusion of HCV-positive

people from donor pools will assure that even a theoretical benefit from human immunoglobulin cannot be easily evaluated.

Harm reduction measures

Harm reduction is a strategy that may reduce the transmission of many parenteral pathogens. Needle exchange as well as education on syringe cleaning and lower risk injection practices can reduce the risk of HCV transmission. But the majority of IDUs, even where these limited harm reduction measures are in place, still become infected with hepatitis C.[59-63]

Sexual HCV transmission is best prevented through limiting the number of sexual partners and using male or female condoms for each and every sexual encounter.[64] Condoms unequivocally reduce rates of transmission for other STIs that are more efficiently transmitted sexually, including HIV and genital herpes. These strategies are advisable for all casual relationships, especially if anal intercourse is entertained as there remains uncertainty about specific risk associated with that activity. Monogamous couples should be advised of the risk of transmission and of the above strategies, but it is reasonable to leave a decision about long-term barrier method use within the relationship.

Public policy

Public policy (including harm reduction strategies as currently deployed in Canada) has not been successful in controlling the HCV epidemic. For this infection, any scenario which allows even a slight probability of syringe sharing will provide ample opportunity for transmission.

The use of illegal substances is considered by some to be an alternate lifestyle and a matter of personal choice. The pharmacology and social reality of addiction provide other perspectives on that view. Cocaine, for example, stimulates an area of the brain normally responsible for rewarding an individual for actions that promote survival or self-propagation.[65] The result is a sincere desire to repeat the experience. Yet this drive may compromise rather than complement survival.

Many of the adverse health effects from drug misuse relate to their pharmacology as well as to the practice of injection per se. These include hypertensive and vascular events with stimulants, overdose with many classes of drug, the introduction of microorganisms into the circulation and the loss of an individual's ability to provide for herself or others. These sequelae burden the social welfare and health systems and may put children at risk of neglect or abuse.

Another set of harms relates to the legal prohibition of many of the substances of addiction in our society. Participation in the black market puts users at risk of violent death, contaminated supply and overdose from supplies of varying potency. Property and violent crime conducted by addicts to gain funds for costly drugs represent a drain on the fiscal and social welfare of our society.

Effective primary prevention strategies are needed that intervene where people are at risk of initiating addictive drug use or of moving from non-injecting to injecting use. While not an answer for every currently addicted patient, existing treatment strategies such as methadone maintenance, detoxification and abstinence-based treatment strategies are of proven value and must be more widely funded and deployed.

Solutions to the regulatory aspects of the problem are under-researched and controversial. Well-designed medical trials of alternative substitution and maintenance therapies are warranted to establish whether there can be further improvements over the existing benefits of methadone therapy for some patients. Decriminalizing simple possession could lessen the burden on the court system while allowing a greater focus on treatment. Independent of decriminalization, it may be of value to direct users convicted of minor property crimes through a drug court to treatment facilities rather than to jail.

Outright legalization and regulation (as with tobacco and alcohol) has been proposed as a solution by many health advocates. The proposal is to take currently illegal drugs out of the criminal code and place them under health regulation. Components of such a system might include sale/supply of injection drugs only through a licenced pharmacist, regulations to restrict points of sale similar to those for tobacco and alcohol, single-use needles and syringes with a known dose of sterile drug, prices consistent with a licenced supply (as opposed to a black market) and programs to assist addicts with obtaining and maintaining employment.

However, many practitioners retain misgivings about the scope and consequences of a legalization approach.[66-68] Legalization would indeed make safer drugs more available. But while this may help reduce harm to those currently addicted, it is plausible that the greater legitimacy of substance use could broaden the size of the addicted population. In our desire to change things for the better, we must remain connected to the principle of *primum non parum*.

So, where do we go next? Solutions to the hepatitis C epidemic and other problems resulting from addiction will be solved neither by uncritically espousing alternate solutions nor by accepting the status quo. We must assure that effective programs for which there is existing evidence are fully deployed and that imaginative new approaches are considered urgently, implemented thoughtfully and evaluated fully.

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Treatment Options in Patients with Chronic Hepatitis C

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Hepatitis C is a major health care problem plagued by the lack of a truly effective therapy. To date, the combination of interferon and ribavirin has provided the best chance of viral eradication. However, this therapy is expensive, has multiple side effects and works in less than half of patients. New strategies need to be developed to deal with the increasing burden of hepatitis C-related disease, and we anxiously await the arrival of new drugs such as helicase and protease inhibitors.

Hepatitis C (HCV) is a leading cause of chronic liver disease and a major public health problem. An estimated 170 million people are infected worldwide,[1] approximately 270,000 in Canada. The societal and health care burden of this epidemic looms large. Hepatitis C will lead to cirrhosis in up to 20% of people after 20 years of infection.[1] It is a major cause of hepatocellular carcinoma and HCV has surpassed alcoholic liver disease as the leading cause for liver transplantation in North America. In the United States, as many as 10,000-12,000 deaths occur annually as a direct result of HCV. As the cohort of persons infected with HCV by intravenous drug use in the 1960s and 70s ages, this number will certainly increase and some estimate it may triple over the next 10 to 20 years. As we have no effective vaccination strategy against the HCV epidemic, we are left with treating people with established chronic infection in hopes of altering the natural history of their disease. Unfortunately, therapeutic options to date have been disappointing. Interferon alpha (IFNα) was the first drug shown to induce a sustained virologic response and cause an improvement in liver histology. However, IFNα monotherapy is limited by expense, side-effects and poor efficacy. More promising is the combination of IFNα and ribavirin, which has recently become the standard of care for the treatment of chronic HCV. Despite improved response rates, over one half of patients will not respond to this combination. It is apparent that new therapeutic strategies are desperately needed in our battle against HCV. This article will review the currently available therapeutic options for HCV and will explore potential new therapies on the horizon.

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Interferon therapy

Interferons are naturally occurring substances that have antiviral and immune modulating effects. Interferon alpha (IFNα) was first shown to have activity against non-A, non-B and post-transfusion hepatitis, before it was discovered that HCV was the major cause of these entities. IFNα has been shown to induce improvement in serum biochemical tests (ALT) and liver histology and to result in the loss of HCV-RNA in some patients with HCV. In 1994, the first Canadian hepatitis consensus statement recommended that patients chronically infected with HCV who had an ALT twice the upper limit of normal (2X ULN) should be treated with a 6-month course of IFNα. Subsequently, it became apparent that the response rate for IFNα therapy depended on duration of treatment, and by 1997 consensus statements in Canada and the United States (National Institutes of Health) recommended treatment with IFNα 3 million units (MU) three times weekly (tiw) for 12 months.[2,3] If patients had not normalized their ALT or the HCV-RNA remained positive after 8-12 weeks, it was recommended that therapy be discontinued because such patients would be unlikely to respond to continued treatment.

Although different dosing regimens and duration of therapy have been investigated, the overall response rates to IFNα monotherapy have been disappointing. Only 10-20% of patients treated with standard IFNα therapy will have a sustained response (disappearance of virus by PCR testing 6 months after stopping therapy).[4] Most patients treated with interferon monotherapy will not clear the virus during treatment (nonresponders), or will only have temporary viral suppression while on treatment, only to show viral relapse after drug cessation (relapsers). In fact, a recent meta-analysis of IFN α2b trials found a sustained response in only 8% of patients.[5] The response to IFNα can be predicted by both viral and host factors.[6] Virological factors such as a low pretreatment serum HCV-RNA level and HCV genotypes other than type 1 result in improved response rates to IFN therapy.[7,8] Patients with established cirrhosis and those with coexisting immunosuppression, including HIV, have lower response rates to IFNα.[9] However, if patients do respond to IFNα therapy the response appears to be durable. In a study of 80 French patients followed for up to 7.6 years after successful IFNα monotherapy, 96% had a sustained virologic response and histologic improvement was noted in 94%.[10] Furthermore, HCV-RNA could not be identified in the liver tissue of any responders. Other studies have confirmed the durability of virologic remission,[11] and it appears that a "cure" of this chronic viral infection is possible.

Despite the overall poor response rates and expense of IFNα monotherapy, it has still been shown to be a cost-effective man-

agement. Decision analysis modelling has shown that a 6-month course of IFNα monotherapy for histologically mild chronic hepatitis C increases life expectancy with a marginal cost-effectiveness within the acceptable range for medical interventions.[12] Kim and colleagues compared the cost-effectiveness of 6 and 12 months of therapy with IFNα.[13] Although 12 months of therapy is more effective, the marginal cost-effectiveness is slightly more than for 6 months of therapy ($5,000 versus $4,000 US per quality-adjusted life-year gained). They concluded that the costs of IFN therapy are justified, especially in patients under the age of sixty. Interferon therapy also may improve health-related quality of life in hepatitis C patients,[14] and may have long-term benefits in reducing the risks of progression to cirrhosis and development of hepatocellular carcinoma.[15-17]

Other therapeutic trials

The disappointing response rates to IFNα monotherapy have led to the investigation of other agents alone or in combination with IFNα. Other interferons that have been investigated included IFN β and consensus interferon (CIFN), a bioengineered interferon.[18-20] Nonsteroidal anti-inflammatory drugs when given with IFNα do not improve the response rate compared to IFNα alone.[21-23] Small studies have shown some benefit to adding ofloxacin to IFNα.[24,25] The bile acids ursodeoxycholic acid and tauroursodeoxycholic acid improve liver enzymes in HCV patients without impacting on HCV viral levels.[26,27] Herbal and traditional Chinese medicines are being used by many patients, however randomized controlled trials of such agents are limited.[28,29]

Interferon has been combined with the immunomodulatory peptide thymosin with some increase in response rates.[30,31] Trials of the antiviral drugs amantidine and rimantidine have demonstrated limited value.[32-34] Ribavirin is a nucleoside analog with *in vitro* activity against many viruses. Ribavirin monotherapy only causes a transient response in liver biochemistry,[35] however the combination of ribavirin and interferon has proven superior to all other treatments tried to date.

Interferon and ribavirin combination therapy

Three small trials of IFNα and ribavirin therapy from Europe in the mid 1990s showed encouraging results with sustained response rates of approximately 40%.[36-38] Therefore, two large multicenter randomized double-blind placebo-controlled trials of combination therapy were undertaken, one in the USA and one international (including patients from Canada).[39,40] The design of the two trials was similar with patients receiving IFNα + ribavirin or IFNα + placebo for either 24 or 48 weeks (the international trial did not have a 24-week IFNα + placebo arm because 48 weeks of IFNα alone was considered standard of care). Pooling the results of the two trials represents data from 1,744 treatment-naive patients (had not previously received IFNα monotherapy). These results are summarized in Figure 1. The sustained response rate was significantly higher with IFNα and ribavirin being 44% (48 weeks) and 36% (24 weeks) for combination therapy versus 24% (48 weeks) and 11% (24 weeks) for IFNα alone. The response to therapy was influenced by the genotype of the virus. The sustained response to combination therapy was 17% (24 weeks) and 29% (48 weeks) for genotype 1, compared to 67% (24 weeks) and 65% (48 weeks) for genotype 2 (Figure 1). Sustained response was also associated with low viral load, limited fibrosis, female sex and age younger than 40. Combination therapy improves health-related quality of life,[41] and although combination therapy is more expensive it has been shown to be cost-effective.[42]

Other studies have demonstrated that interferon and ribavirin combination therapy is a treatment option for patients who were nonresponders or relapsers following IFNα monotherapy. In a trial of 345 relapsers, 24 weeks of combination therapy resulted in a 49% sustained response compared to 5% in the IFNα monotherapy group.[43] Histologic improvement was also more common in the combination therapy group. Similar results have been found in treating relapsers with consensus interferon (CIFN), with a sustained response rate of 58% after 48 weeks of CIFN.[44]

Based on these results, in 1999 the third Canadian consensus conference on the management of viral hepatitis concluded that the new standard treatment for HCV patients should be interferon 3 million units sc tiw in combination with ribavirin (1000mg if <75kg body weight and 1200mg if >75kg) po daily. The therapy is to be offered to HCV-infected persons with abnormal ALT level (1.5 X ULN) on three occasions over more than three months. A liver biopsy is recommended for grading and staging of disease before initiating therapy. Duration of therapy is determined by the genotype of the virus, with patients carrying type 2 or 3 being treated for 24 weeks and those with type 1 being treated for 48 weeks. In the era of combination therapy, the rule of stopping therapy if the HCV-RNA remains positive at 12 weeks has been questioned, and some recommend checking the PCR at 24 weeks.[45] In a review of 1,010 patients on combination therapy, 7.3% of patients with positive HCV-RNA at 12 weeks ultimately became sustained responders, compared to 2.7% of those PCR positive at 24 weeks.[45] This means stopping treatment at 12 weeks in PCR-positive patients would have missed a sustained response in only 24 of 1,010 patients (2.4%). Although a formal cost-effectiveness analysis has not been done, it is the practice of the authors to treat patients for 16 to 20 weeks and then stop treatment if the HCV-RNA is positive by PCR. If the PCR is negative, we genotype the virus (from a pretreatment stored sample) to determine if therapy is to be stopped at 24 weeks (genotype 2 or 3) or at 48 weeks (genotype 1).

The addition of ribavirin to IFNα increases the side-effect profile and ribavirin predictably causes hemolysis. Monitoring includes a weekly CBC for the first month and then monthly thereafter. The dose of ribavirin should be reduced if the hemoglobin falls below 100 g/L. The TSH should be monitored every 3 months, as there is a risk of thyroiditis with interferon therapy. It is essential to consider the risks and benefits in each patient before initiating combination therapy. Absolute contraindications to combination therapy include decompensated liver disease, active alcohol or substance abuse, and pregnancy or inability to practice adequate contraception, as ribavirin is teratogenic.

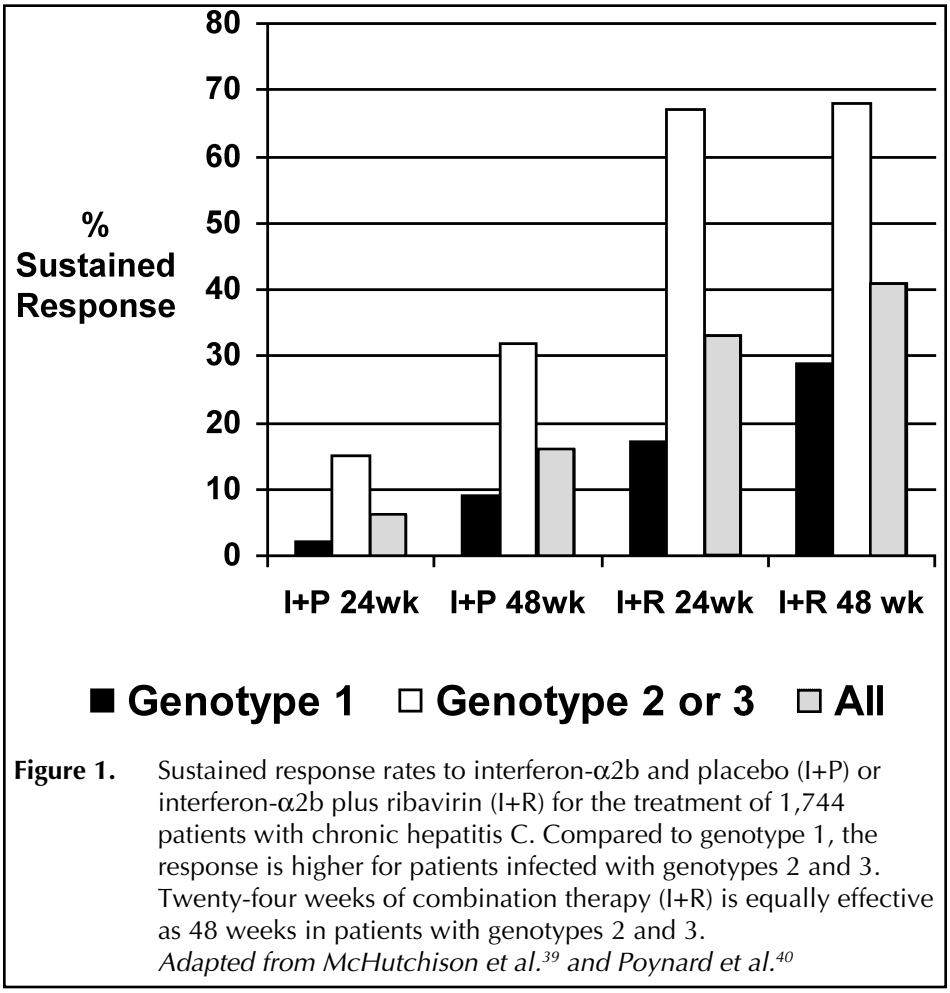

Figure 1. Sustained response rates to interferon-α2b and placebo (I+P) or interferon-α2b plus ribavirin (I+R) for the treatment of 1,744 patients with chronic hepatitis C. Compared to genotype 1, the response is higher for patients infected with genotypes 2 and 3. Twenty-four weeks of combination therapy (I+R) is equally effective as 48 weeks in patients with genotypes 2 and 3.
Adapted from McHutchison et al.[39] and Poynard et al.[40]

Future directions

Future treatment options can be conveniently divided into "near-future" and "needs development" categories. In the former, we can discuss drugs and treatment options that have already been developed and in some cases, subjected to phase III clinical trials, but have not yet become licensed or accepted for routine clinical use. In this category are the newer α-interferons that have a polyethylene glycol moiety attached ("pegylated"). Currently there are 2 forms under study: a 40 kDa branched PEG-α2a interferon (Pegasys®), and a 12 kDa linear PEG-α2b interferon (Peg-Intron®). It is clear that pegylation dramatically increases the circulating half-life of interferons from a mean of 9 hours with α2a-IFN to 77 hours with PEG-IFN α2a.[46] Such an increase would lead to a more stable and consistently high level of IFN, and would therefore be expected to improve the antiviral response rates. Indeed, preliminary studies with PEG-α2a suggest that a dose of 180μg sc once weekly induces approximately the same sustained response rates (36%) as combination IFN-ribavirin treatment.[47] Larger randomized trials are underway with both pegylated interferons combined with ribavirin to determine if the PEG-IFN and ribavirin combinations can increase the sustained response rates to 50% or greater.

Other methods of administering standard IFN continue to draw interest and show promising results, but are not yet widely accepted for routine use. In Japan, physicians routinely use high-dose daily induction IFN regimens, typically consisting of 5-6 million units of α-IFN daily for the first month of therapy.[48] In the west, we had always assumed that the higher sustained response rates reported by our Japanese colleagues were due to differences in genotype distributions, however response rates in Japan appear higher in each genotype. The emergence of pegylated interferons will soon make high-dose daily induction obsolete since pegylation produces a similar or higher consistent IFN blood level.

Despite the failure of amantidine monotherapy in HCV patients, a pilot study of Italian patients has recently reported promising results using triple therapy with IFN, ribavirin and amantadine in a small number of nonresponder patients.[49] In this study, triple therapy was associated with a sustained response in 3 of 10 nonresponders to IFN monotherapy. Previous studies in IFN nonresponders treated with other modalities such as CIFN or combination IFN-ribavirin showed discouraging results, with sustained responses of approximately 10%.[44,50] Consequently the exciting results of this pilot study need to be confirmed with a larger controlled trial.

How best to manage this population of nonresponders continues to be a difficult, unresolved issue. The recommendations from the 1999 Canadian consensus conference suggest that nonresponders to IFNα monotherapy be tried on combination IFNα-ribavirin or CIFN. However, virological response rates tend to be discouragingly low. Another way of approaching this problem, however, was recently suggested by Shiffman and colleagues who treated nonresponders with prolonged maintenance IFN monotherapy (3 MU tiw) for 30 months.[51] The rationale for this study is that IFN has anti-inflammatory effects that may be independent of its antiviral effect. In this study, histological improvement was noted in those patients maintained on IFN, despite ongoing viremia.[51] While we await the arrival of new drugs in the "needs development" category, maintenance treatment may be considered in those nonresponders whose liver histology shows marked necroinflammatory activity, with some fibrosis, who may develop cirrhosis within the next few years if left untreated.

"Needs development"

Because the genomic and x-ray cystallographic structures of several critical enzymes in HCV replication and assembly have recently been clarified, chemists and drug manufacturers have been fervently trying to synthesize compounds that might block such enzymes.[52] These enzymes include the HCV-RNA helicase, which is responsible for unwinding or unfolding the

RNA helix to allow replication to start, and several serine proteases which are responsible for cleaving larger viral proteins into smaller ones that will then complex with other viral proteins to eventually assemble into the complete virion.

Unfortunately work on such enzymatic inhibitors is hampered by lack of a suitable cell culture or small-animal model of HCV replication. Moreover, although several candidate helicase and protease inhibitors have been developed and tested in animals, concerns about drug toxicity and lack of efficacy continue to be problems. After all, many essential functions in humans such as blood coagulation depend on the action of serine proteases, and any antagonist drugs would have to be highly specific for viral proteases. However, because of the large number of labs and resources being used to study this issue, our opinion is that an effective and nontoxic helicase or protease inhibitor will be developed within the next 3 to 6 years.

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The Hepatitis C Prevention, Support and Research Program: Health Canada Initiatives on Hepatitis C

Health Canada

In September 1998, Health Minister Allan Rock announced new federal hepatitis C funding of $50 million over five years for initiatives relating to community-based support, research, and disease prevention. Since then, broad cross-country consultations have taken place with individuals and their caregivers who are infected, or affected, by this disease; non-governmental organizations; provinces and territories; and health care professionals. The result is a relevant, compassionate and targeted new Health Canada Hepatitis C Program with a four-point action agenda, that encompasses five components – prevention; community-based support; care and treatment support; research; and ongoing management, evaluation and public involvement.

Federal Health Minister Allan Rock introduced a comprehensive set of initiatives in September 1998 to build a pan-Canadian capacity to prevent the further spread of hepatitis C, to build a research capacity and to provide care and treatment support for those with the disease.[1] These new initiatives included the Hepatitis C Prevention, Support and Research Program. This Program was developed in consultation with those who had contracted hepatitis C through the blood system and their representatives, and those who had contracted hepatitis C outside the blood system, as well as other non-governmental organizations and professional groups with an interest in this disease. The Program is a five-year initiative with funding totalling up to $50 million.

Through an extensive consultation process, the new Program has developed a **4-Point Action Agenda**.[2] Its goals are to:

- contribute to the prevention of hepatitis C infection;
- support persons infected with, and affected by or at risk of contracting hepatitis C through the development and availability of tools and mechanisms;
- provide a stronger evidence base for hepatitis C policy and programming decisions and advance prevention, treatment and cure options by expanding the body of available research and research capacity; and,
- strengthen the response of the Canadian population to hepatitis C through increased awareness and capacity.

Hepatitis C (or Hep C as it is commonly known) has not traditionally received much public attention. The hepatitis C virus (HCV) was not identified until 1989 and prior to that, had been characterized as non-A, non-B hepatitis. In 1990, a specific test to detect the presence of HCV in blood became available, but at present scientists are still unable to culture the virus *in vitro* – a requirement which would facilitate the development of a vaccine and new treatments.

In Canada, it has been estimated that approximately 240,000 Canadians, or 0.8% of the population, are infected with hepatitis C and, of those, only about 30% are aware of their infection. Research indicates that individuals infected with HCV may not experience symptoms for up to 30 years.

Worldwide, hepatitis C is a significant health problem with an estimated 170 million people infected.[3] Studies have shown an anti-hepatitis C positivity rate in the US of about 1%; in the Middle East 1-2%; and in Western Europe 1-1.5%. Certain countries have a much higher prevalence (as high as 18%) mainly due to past mass immunization programs that did not use sterile equipment.

Some populations also have a much higher prevalence. In Canada, these include past recipients of blood, blood products or organs; injection drug users; prisoners and immigrants from areas in the world with higher hepatitis C prevalence. Hepatitis C has also been identified as the most common cause of post-transfusion hepatitis worldwide, accounting for approximately 90% of this disease in Japan, the US and Western Europe.[4]

Hepatitis C has not attracted significant research funding in Canada. This has been due, in large part, to a need for a critical mass of research which, in the past, has been difficult to attain because of the highly competitive nature of research and the scarcity of hepatologists doing research. There are only about 25 trained liver specialists practicing in Canada, a number of whom are internationally renowned in their field and are only located in major cities. This lack of specialists and experienced physicians gives rise to significant treatment challenges including long waiting lists for patients to be seen.

Following Minister Rock's September 1998 announcement, Health Canada staff were assigned the task of designing, implementing and delivering the new Hepatitis C Program. A new organization was soon formed within the department. The staff recognized the need to consult with a wide variety of stakeholders to ensure that many varied and sometimes contradictory views and opinions could be expressed and discussed in open fora. They also understood the need to address both research and

research capacity around hepatitis C as a matter of urgency in Canada.

In the fall and winter of 1998, the staff from the new Program undertook a broad set of consultations across the country on the potential design of the new Program.[5] What they heard from numerous stakeholders was not always complimentary about the past role and leadership of governments. It did, however, offer a promise that partnerships could be undertaken in the future and that strides could be made over the next five years in the areas of:[5] prevention; community-based support; care and treatment support; research; and ongoing management, evaluation and public involvement in the Program.

FIVE COMPONENTS

Prevention *is targeted programming aimed at preventing the transmission of hepatitis C among those who are currently uninfected, particularly those who are at high risk, such as injection drug users. Some programming will also be targeted, in the form of information and education, to those who face a marginal risk of infection, such as partners of hepatitis C individuals and health care workers.*

Increasing public awareness and knowledge about an issue as complex and sensitive as hepatitis C can only be done in partnership and collaboration with many other agencies, organizations, community groups and dedicated individuals. In developing and stimulating efforts in this area, the Program is encouraging and funding the development of tools and information materials to support activities at the national and local levels. For those at greatest risk of contracting this disease, risk reduction behaviour will be profiled. Finally, pilot projects will be funded and evaluated to assess their effectiveness.

Community-Based Support *includes programming to support both a strong community-based response to the needs of individuals and their families who are infected with or affected by hepatitis C, and emphasizing a strong role for community organizations in the Hepatitis C Program.*

The activities of this component contribute to gaining a better understanding of the nature and effects of hepatitis C infection and how communities can provide support to those who are infected with, affected by or at increased risk of hepatitis C infection. As of March 2000, over 40 community-based projects have been funded that are wide-ranging in scope and impact and include the following: an educational conference and roundtables on hepatitis C for front-line workers (New Brunswick); the production of a bilingual information newsletter on hepatitis C (Québec); the development and distribution of a brochure for pregnant women who are infected with hepatitis C (Ontario); the development of harm reduction tools and mechanisms to reach injection drug users and their families (Saskatchewan); the development and distribution of a comprehensive, user-friendly booklet that assists people to make decisions regarding treatment, housing, employment and related issues (Manitoba); the development of a *Safe Body Art* pamphlet to provide young people with information about the increased risks of hepatitis C associated with body piercing and tattooing (Alberta); and support for hepatitis C and HIV co-infection education and outreach activities, including the development of targeted educational material (British Columbia).

Care and Treatment Support *emphasizes national-level initiatives aimed at supporting those already infected with or affected by hepatitis C. Activities focus on increasing the health and well-being of individuals who are infected by delaying the progress of the disease and improving their access to the care and treatment support they require.*

Activities under this component include professional education and training; treatment guidelines; information dissemination and network development. In developing programming in this critical area, the Program is merging existing tools with new approaches. For example, the University of Manitoba has been funded to assess an existing CD ROM-based medical software program to determine if this application would be useful to rural physicians in identifying, diagnosing and counselling patients with hepatitis C infections. The results of this pilot project will be shared across regions and communities. As well, the Dietitians of Canada was funded to develop and conduct a needs assessment on nutritional guidelines for patients infected with hepatitis C. Other notable examples include funding to the Canadian Liver Foundation to develop two information documents, one targeted to patients, the other to doctors. The Society of Obstetricians and Gynaecologists of Canada has also been funded to produce clinical guidelines for the treatment of pregnant women who are infected with hepatitis C.

Research *will encourage and support the research, development and dissemination of knowledge about hepatitis C, as well as build the commitment and capacity of the Canadian research community to conduct research which will contribute to a better understanding of the hepatitis C virus and its epidemiology, treatment and prevention, to decrease its burden on infected and affected populations.*

In July 1999, the Program and the Medical Research Council of Canada announced the allocation of $18.4 million to further hepatitis C research. In announcing this program, Minister Rock indicated clearly his hopes and expectations. "This initiative," he stated, "targeted to Hepatitis C and its potentially devastating effects on people, will build much needed knowledge. Ultimately, this crucial work will benefit all Canadians, particularly those living with the virus." Dr. Henry Friesen, the President of the Medical Research Council, also added, "This program will help train more scientists and enable the scientific community to fill the numerous gaps in Hepatitis C-related knowledge, such as prevention, clinical research and treatment."[6]

This collaborative five-year research partnership will fund scientifically meritorious projects in the following areas: the biology, pathogenesis and epidemiology of the virus; screening and diagnostic technologies; the natural history of the disease; treatment strategies; quality of life issues and preventive measures. In February 2000, the first 13 projects under this initiative were funded.

A Joint Advisory Committee, composed of scientists, physicians and stakeholders, has been established to advise Health Canada and the Medical Research Council

on research priorities and the management of the partnership, and to ensure transparency and accountability to all stakeholders and the general public. This initiative has been grandfathered into the new Canadian Institutes of Health Research (CIHR).[7]

Management, Evaluation and Public Involvement *is the component in which several activities will be undertaken to ensure that the Program is well-managed, transparent to the Canadian public and is accountable for the effective use of the resources dedicated to it.*

Although not as visible as the other components, these elements are critical in developing and maintaining the strategic partnerships that will advance and support the goals of the Program. A Program Advisory Group (PAG) has been established with representatives from stakeholders and the Program to assist with setting directions; responding to emerging issues; ensuring coordination of key sectors and organizations involved in Program initiatives; and fostering citizen engagement in ongoing implementation. Current membership of the PAG includes the Canadian Hemophilia Society, the Canadian Liver Foundation, the Hepatitis C Society of Canada, the Canadian Centre on Substance Abuse, the Canadian Association for the Study of the Liver and the Canadian Public Health Association.

THE WAY FORWARD – ONGOING COMMITMENT AND CONSULTATION

The success of any national program aimed at preventing hepatitis C infection, stimulating research and caring for those already infected, relies heavily on involving all partners throughout its design, development and delivery.

The five components of the Hepatitis C Program outlined above provide a unique combination of research, community-based support, education and outreach activities. This multi-faceted approach has been developed in consultation with a wide range of stakeholders, including researchers, provincial governments, health care professionals, non-governmental organizations working in this area and, of course, individuals and their families who have been infected with and affected by this disease.

How to Contact Us: The Hepatitis C Prevention, Support and Research Program at Health Canada looks forward to updating you periodically on the progress and outcomes of these initiatives. We are currently working on developing our own website. In the meantime, if you require further information on any of the five program components or the Four-Point Action Agenda, please visit us on the Health Canada website at www.hc-sc.gc.ca, where you can search under the topic of hepatitis C.

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Living with Hepatitis C

Neil Van Dusen

Greetings from Halifax, Nova Scotia. My name is Neil Van Dusen. I am a 41-year-old hemophiliac, Factor IX deficient. I've been married for 19 years and have 4 children – 2 boys and 2 girls, ages from 7 to 16. At some point in my life, I acquired the hepatitis C virus and have since been growing progressively sicker.

At first things weren't too bad. The weariness and feelings of constantly being tired I put down to working a full-time job and helping to raise 4 children. I coached hockey and spent weekends at the local rinks. I was active in the community and pitched in at home when needed. Life was busy – with the 4 kids there rarely was a dull moment. I began falling asleep on the couch while watching movies with my wife. It became too frequent and staying awake was more work than it was worth. I lost concentration easily and would forget things that normally I wouldn't (losing the car in a parking lot was a scary experience – I thought someone had stolen it!).

In 1995 during my yearly visit to the Haemotology Clinic, I was informed that I had tested positive for the hepatitis C virus. My wife and I felt that the best way to deal with this news was to learn all that we possibly could about it. We asked questions and surfed the Internet for any and all information. I was examined by a gastroenterologist, who recommended a liver biopsy to determine what damage had already occurred. The results were not promising. I had scarring of the liver and the only recommended treatment was "interferon". I was told that this treatment could help or, in some cases, make things worse and that 1 in 4 patients did get good results. I figured that 1 in 4 was better than 1 in 0 and proceeded with the treatment. Unfortunately, I was unable to finish the treatments as my platelet count dropped to very low levels and I was forced to stop. Since that time, my platelet counts have not risen and my immune system is somewhat compromised.

I now find myself with less energy and my future on hold as I await the outcome of my battle with this virus. As time passes, I find symptoms becoming increasingly worse. Fatigue is the major problem, with napping, resting and generally taking it easy the order of the day. Getting out of bed some days is a major chore in itself. Most nights, sleep is restless and I find I will awaken at odd hours and not be able to return to sleep. The physical symptoms are redness of the palms and fingertips and "spidering" on the body. Most people would say, "Hey, you look pretty good." But looking good and feeling good are two very different things. I can truly say that I can't remember what it feels like to "feel good". I suffer from itchiness, body aches, headaches and feel tired most of the time. Depression is also very common, as is eye strain and lack of interest in particular activities for extended periods of time. I have suffered spontaneous bleeds, which I never had before. Another bothersome symptom is lack of libido. My spleen is enlarged and I go for the usual battery of tests and ultrasound check-ups.

So, as time passes and I grow weaker and feel worse with the inevitability of a liver transplant somewhere in the future, I have lost hair, weight and teeth. Stress plays an important role in how things go as well. Just the other day I received notice that even when the day comes that I can return to work, my position will not be there for me. I fear that I will lose disability insurance, life insurance and medical and drug plans.

When people ask what I want, I tell them I would like to have my health back, be able to play with my kids, walk the dog and go to work. Maybe I'll even get lucky and get a new liver, survive the operation and not have my body reject the organ, and live a long and happy life. I've had a lot of things taken away from me but the one thing that remains is hope. I hope to beat this thing. I hope the medical community finds effective treatment and a cure. I hope that we have learned from the mistakes of the past. I hope that by putting some of my thoughts on paper I will help others understand how devastating hepatitis C and living with it can be.

Thank you for this opportunity to express my feelings.

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Through the Eyes of a Mother

Leslie Gibbenhuck

My name is Leslie. I am 43 years old and the mother of the three greatest children in the world – Tyler (16), Ashley (13) and Jarad (11). I am married to an RCMP constable and we live in the Sunny Okanagan of British Columbia. I would be kidding if I told you our life is rosy, but we do try to make the most of it!

Our life as a family was what I frequently look back on as "normal". Husband and wife save for a family. Wife gets pregnant, delivers a healthy baby boy. Family not complete, so they have a baby girl 18 months later. Husband works full time. Mom cares for children. A house, two vehicles, nice furniture, a savings account, RRSPs, annual vacations, all the toys and trinkets! Parents deal with common colds, ear infections and vaccination complications but, in general, health, finances and life are all pretty good!

In July 1988, our third child was born. Jarad was sick from the moment of birth but no one could find a reason for his ill health. It became apparent, two months later, that something was desperately wrong. Jarad required immediate open heart surgery. What we didn't know was that Jarad got infected with hepatitis C from one of the 23 units of blood and blood products he received during open heart surgery. He was just eight weeks of age.

On June 1st, 1995, we received the good news/bad news telephone call. Jarad does not have HIV, he has hepatitis C. Our GP informed us that he did not know much about hepatitis C, except that it used to be called non-A, non-B hepatitis. It was actually a relief to finally get a diagnosis but I quickly learned that life with a relatively new disease was anything but smooth.

Myriad emotions have touched our lives since – confusion, guilt, frustration and anger, just to name a few. But more importantly there have been questions. Why did it take doctors almost 7 years and over 400 medical appointments, treatments, and procedures to diagnose Jarad's hepatitis C infection? Why had we not been told, when BC Children's Hospital had tested Jarad the year before and knew he was positive? Why were we being treated, by previously supportive hospital staff, with fear and reservation? Why did this happen? What will his future hold? What will ours be like?

I have been told that when you go through a life-shattering experience such as this, normal is what is happening at the time, so I embarked on a voyage of discovery. I could not find much written about hepatitis C. I was steered to organizations for help but was told by them they have nothing written on children with the disease. I realized I was about to become a pioneer. I was also forced to be doctor, nurse, lawyer, accountant, politician, detective, activist and mother. I have had to learn about what took place and why, and have had to fight very hard for Jarad's care and his rights. Every day brings something new. A call, a question, a court date, an obstacle. I live in my office, spend hours on the Internet and hours on the telephone. My days are long, there is no time off, not even on weekends.

The lack of information about hepatitis C has been the biggest hurdle we have had to overcome. The quality of information is also a problem, with some of the recognized credible sources contradicting each other. Hepatitis C was only named in 1990, although it has been around for many years. The various issues involved with hepatitis C and the speed with which the disease is emerging, all combine to create a full-time job for anyone wishing to stay on top of it. This, as I see it, is my job!!

Unfortunately, there is no vaccination to prevent getting infected with hepatitis C, no medication for afflicted children to take, and no cure for it. It is a chronic degenerative disease that strikes and causes debilitating fatigue, nausea and headaches, at least in our son. All children should attend school, yet mine cannot. He does not have the physical strength nor the stamina to make it through a day.

I am most unhappy with the health care available for a child infected with hepatitis C. Health care causes more frustration for us, and other families, as we seek out someone who can stop the pain, take away the symptoms and restore a child's life to normal. After all, doctors are supposed to make the sick well. But no one is tracking the children. No one is testing for viral load or genotype. We have been told that biopsy, done routinely in adults to determine the degree of liver damage, would be a waste of taxpayer money in children. I am even more saddened by doctors who pull away citing the "complexity of his condition and the high level of technical expertise his care will require in the future." Jarad has hepatitis C – he may require a transplant.

Jarad is somewhat of a 'celebrity', so acquaintances are plentiful. Unfortunately for him, real friends do not stick around. Children cannot fathom chronic illness. Their parents are afraid. Children get

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impatient when Jarad cannot play right now because he is feeling sick. They question why he takes many rest breaks and cannot keep up with their energy levels. Children do not understand why there is not simply a pill he can take that will make him all better.

I have become a 'teacher' – a childhood dream of mine, except that I do not do it in the classroom and do not collect a wage for what I do. I teach about hepatitis C in children, share our experiences and my knowledge all over North America. Thanks to hepatitis C, I have got to travel to places I never dreamed I would go. I have been asked to speak in Toronto, Regina, Calgary, Vancouver, Victoria, New York, Washington, DC, Houston, Texas and San Francisco, California. This summer, Jarad has been invited to meet Paul Newman and attend the Hepatitis C camp Newman is sponsoring in upstate New York.

This virus, despite how much I hate it, has brought with it good as well as bad. I have been fortunate to meet many fabulous people who are as committed to education, awareness and prevention as I am. I have been forced to learn about politics and am bitterly disappointed with most of the knowledge that I have gained. I have viewed giving and greed. I have seen much pain and sorrow.

There is no way money can ever begin to make up for my son's life, for his suffering to date, nor his suffering in the future. There is no way compensation will begin to cover what this disease has already cost us financially, let alone what it has or will cost us emotionally, in the future. Money will never give Jarad a fair crack at life, restore his childhood or give him a normal adulthood. It will not prevent nor make up for the comments and discrimination that Jarad will face in the future.

As a family, we have already been forced to declare personal bankruptcy. We now have only one vehicle, our accommodation is now rental, our furniture is 19 years old and in need of serious repair, savings have been used up, the RRSPs are cashed and taxes paid on them, it has been 15 years since we last went on vacation, the toys are broken and the trinkets gone. Health is not great – parents are stressed and tired, Dad suffers from depression, we live from paycheck to paycheck and we are all learning to live with what we have!

In order to assist families with liver disease going through similar situations, I recently incorporated the Children's Liver Alliance Canada Inc. This allows me and others to share our knowledge and experience. Our board expertise covers three vital areas: pediatric liver disease that children are born with; pediatric liver disease that is acquired; and bereavement. We are an international grassroots organization that offers the one-on-one peer support and guidance that families need most.

If there is a lesson that hepatitis C has taught me, it is that children are a gift to be cherished, loved, held, stroked and cuddled. And not just as babies – I take time out for all three, every day. And I never take life for granted – you never know when it will be gone.

Living with Hepatitis C as a Nurse

Debi Ripley

My name is Debi Ripley. I am a 46-year-old mother of two teenaged children and I am a non-practising nurse although I am taking my nursing refresher course. I have hepatitis C and probably became infected in the late 1970s or early 80s. I wasn't diagnosed until 1995.

I have a few risk factors for hepatitis C: I was an operating room registered nurse for 15 years (health care workers have a 10% risk of contracting hepatitis C, and the emergency and operating rooms have an even higher risk due to the constant presence of blood), and I received a blood transfusion after a caesarean section for my son in 1983.

I worked as a scrub and circulating nurse in operating rooms in my hometown of Moncton, New Brunswick, as well as Edmonton and Calgary, Alberta, and four different trauma hospitals in Riverside and Los Angeles, California. Many times I had been cut with dirty scalpels and suture needles. Universal precautions only help to take care of surface blood.

Due to the progression of my disease, my specialist feels that I was first infected in the O.R., then re-infected by a tainted blood transfusion. All I know is that I became progressively sicker since 1985 when I became pregnant with my second child.

Through the years my illness remained undiagnosed although I ran the gamut of symptoms – irritable bowel syndrome, pain in my right upper abdomen, constant aches in my joints, muscles and bones with an unexplained rheumatoid factor, headaches, decreased resistance to infections (in California I had meningitis, encephalitis, and several bouts of pneumonia back at home), depression, insomnia, extreme fatigue, and weight loss.

By the time I became too sick to work, I had lost my job in California and consequently lost my house, furniture, my husband and car, and sold my personal possessions to come home. All the doctors I had seen for these vague but real symptoms came to the same conclusion: I was overly stressed and, as a woman, these symptoms were "all in my head" – psychosomatic.

In desperation I was forced to accept social assistance and finally I consulted the family doctor in one last call for help. In the many blood tests he discovered that my liver enzymes were more than double the high normal. A subsequent hepatitis C test proved positive.

I was relieved, devastated and puzzled all at the same time. Relieved to know that there was a name to this illness, yet devastated to think that I had a "terminal" disease and that there was a real possibility of losing my career. I was puzzled because, even being a nurse, I was not sure what hepatitis C was. I also had to face the probability that I unknowingly accidentally infected patients.

But knowing that I had a physical disease with a name helped to put everything else into perspective. I knew that I could research hepatitis C and learn how to cope with this potentially debilitating disease. And that is what I did.

My nursing training and instincts kicked in and before long, even through two treatments (the average treatment is one year in length) plagued with many side effects, I formed a hepatitis C support/self-help group to help others infected/affected with hepatitis C, regardless of the source and to raise awareness in the Atlantic provinces.

What I have gone through goes a long way towards understanding others with any chronic illness. The emotions of the grieving process are the same as when one loses a loved one, but we are in the continual process of losing our health. Helping others gets our minds off ourselves and brings a personal satisfaction that we have made a difference in someone's life.

Yes, I have lost everything to this disease, but I also gained so much more. Material possessions do not mean the world to me anymore – they are things that can come and go. I have learned the hard way to appreciate the so-called little things in life – a sunny day, laughing with my kids, my parents' love, the peace and joy in my heart from my God, and knowing that I am making at least a small difference in this world.

My passion and perfectionism for the challenges of the operating room has been replaced by my genuine devotion to helping people in all aspects of hepatitis C. The old adage still applies – once a nurse, always a nurse. I'm just in a different field.

"One thing that I do, forgetting those things that are behind and reaching forward to those things which are ahead…"

Philippians 3:13

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Hepatitis C Virus Diagnosis and Testing

Mel Krajden, MD, FRCPC

Development of serological and nucleic acid testing (NAT) has revolutionized hepatitis C virus (HCV) diagnosis. Although third generation anti-HCV enzyme immunoassays (EIAs) are very effective for testing high prevalence populations, confirmatory testing is still necessary when these tests are applied to populations with a low HCV prevalence to exclude false positive results. Limitations of third generation anti-HCV EIAs include: the relatively prolonged time between acute infection and detection of seroconversion (which typically requires at least 5-6 weeks); delayed seroconversions in immunocompromised hosts (requiring months to years); and the inability of serological tests to confirm active HCV infection. In contrast, nucleic acid testing (NAT) can directly detect HCV RNA in serum, plasma or tissue and thereby confirm active infection as well as narrow the window between infection and HCV detection to as little as 1-2 weeks. Commercial NAT assays are now highly sensitive, specific, and reproducible and have largely replaced unreliable home brew nucleic acid amplification assays. Qualitative commercial NAT are typically more sensitive than quantitative assays and therefore the method of choice to confirm active infection. Given the efficacy of combination therapy with interferon/ribavirin and newer antiviral agents under development, HCV infection may become curable, which will likely impact future disease transmission. As the therapeutic costs are currently very high, there is clearly a need to assess the utility of quantitative NAT and to further evaluate the role of HCV genotyping to optimize antiviral therapy. Thus for the foreseeable future, a combination of both serological tests and NAT will be required for cost-effective HCV diagnosis and monitoring.

Public health and clinical care management of hepatitis C virus (HCV) infection depends on accurate laboratory diagnosis. Unfortunately clinicians and public health officials are faced with a confusing array of serological and nucleic acid detection tests. This manuscript will explain the strengths and weaknesses of the available diagnostic tests and illustrate how a combination of serological and nucleic acid testing (NAT) is now required for accurate HCV diagnosis and antiviral monitoring.

HCV antibody detection by enzyme immunoassay (EIA)

HCV is typically diagnosed by measuring an immune response to infection by detecting anti-HCV antibody in serum or plasma by enzyme immunoassay (EIA). Modern EIAs use recombinant or synthetic viral antigens to capture circulating anti-HCV antibodies to microtitre plate wells or microparticle beads. These antibodies are then detected by anti-IgG labelled with enzymes which catalyze the transformation of substrates to generate colour or light. The generated signals are compared with controls and the signal intensity is usually proportional to the amount of anti-HCV in the specimen.[1]

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HCV EIA sensitivity and specificity

Current third generation EIAs are substantially more sensitive and specific than the older first and second generation assays.[2,3] However, their overall sensitivity is still highly dependent on the clinical status of the population tested. In chronically infected non-immunocompromised persons, EIA sensitivity approaches 97-99%.[3,4] In contrast, in acutely infected non-immunocompromised individuals, EIA sensitivity is much lower. For example, only 50-70% of acutely infected individuals will be antibody positive at the onset of symptoms,[5] since after acute HCV infection it takes approximately 5-6 weeks to generate a detectable amount of anti-HCV. Figure 1 illustrates the approximate time interval between acute infection and detection by various generation EIAs and NAT in non-immunosuppressed individuals. As can be seen in Figure 1, both NAT and a new HCV antigen test which is under development, can narrow the time between infection and detection to 1-2 weeks. In immunosuppressed individuals, however, the time between infection and detection of an antibody response may be many months to years, or may never occur.[6-8] For these individuals, NAT (or HCV antigen testing if it becomes commercially available) may be required to diagnose infection prior to seroconversion (Table I).[6-8]

The specificity of third generation EIAs is also affected by the population prevalence. For individuals with clinical evidence of HCV infection, i.e., abnormal liver function tests in the absence of other causes of liver disease, third generation assays are 95-98% specific.[3,4] However, in low prevalence populations such as blood donors, the

specificity is 50-60%.[2-4,9] Thus for low prevalence populations, supplemental EIA, immunoblot or NAT is required to correctly identify infected individuals.

Despite the relatively low specificity of anti-HCV EIAs in blood donors who are at low risk of infection, serological screening is very effective and has virtually eliminated post-transfusion HCV infection.[10] This is because the presence of anti-HCV is strongly correlated with active viral replication/infectivity and the fact that most infections (50-85%) will become chronic in the absence of therapeutic intervention.[11-16]

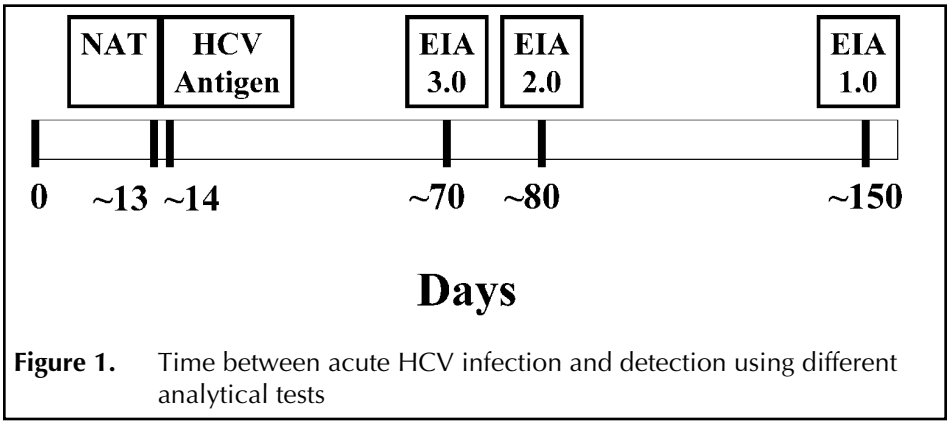

Figure 1. Time between acute HCV infection and detection using different analytical tests

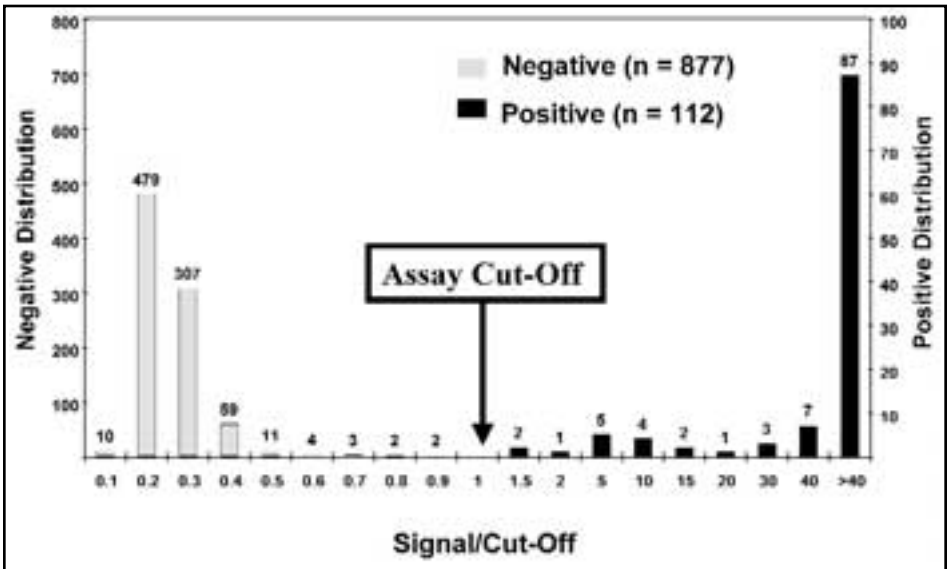

Figure 2. Abbot AxSYM™ third generation anti-HCV EIA signal to cut-off results

HCV immunoblot assays

Immunoblots were developed as supplemental or confirmatory tests to enhance HCV EIA specificity. They consist of recombinant or synthetic HCV proteins coated onto plastic strips that are then exposed to the patient's serum. True anti-HCV positives specifically bind to HCV antigens on the strip and generate a colour reaction. These strips may also contain non-viral antigens that may be co-expressed during the synthetic process used to make the antigens to capture the anti-HCV in the EIA. Including these non-viral antigens on the immunoblot can control for false positive EIA results due to antibody reactivity to these non-viral antigens. Based on the number of specific HCV antigens to which antibody in the specimen reacts on the immunoblot, EIA specimens are confirmed as HCV antibody positive, negative or indeterminate.[3,17-20]

Although immunoblot assays are still available – e.g., Third-Generation Recombinant Immunoblot Assay or Strip Immunoblot Assay (SIA), (RIBA™-3, Chiron), INNO™-LIA Ab III (Innogenetics, NV), DECISCAN™ HCV (Sanofi Pasteur), and LiaTek® HCV (Organon) – given the advances in modern EIAs and NAT discussed below, their value for clinical diagnosis is limited.

Figure 2 illustrates EIA signals generated from HCV antibody negative and positive individuals (n=989) tested at the British Columbia Centre for Disease Control (BCCDC) by third generation Abbott AxSYM™ HCV EIA (Abbott). While most specimens are strongly antibody positive or clearly negative based on their signal intensity, a substantial number of specimens display weak signals above the assay cut-off. Of the approximately 70,000 clinical specimens tested each year at the BCCDC, 8-10% will have some degree of antibody reactivity by AxSYM™ third generation EIA on initial testing. The majority, 82-85%, yield strong antibody positive signals (typically 2-3 times or more of the assay cut-off) and 15-18% will yield weak signals.

Strongly positive third generation EIA specimens are typically immunoblot positive. When initial strong HCV EIA reactive specimens are confirmed as anti-HCV positive by a second manufacturer's EIA that uses different recombinant or synthetic proteins, approximately 99% are immunoblot positive.[20-23] Thus immunoblot testing of strongly EIA positive specimens is generally not necessary for confirmation of reactivity.

For individuals with very high levels of anti-HCV, the major clinical question is whether they remain actively infected or have resolved their HCV infection but remain antibody positive. Approximately 95-99% of individuals with abnormal serum transaminases and no other cause of the liver disease who are third generation anti-HCV EIA positive are confirmed as being actively infected by NAT.[3,4] Unfortunately, 25-40% of HCV-infected individuals will have consistently elevated serum transaminases. In these individuals, detection of HCV RNA by NAT or HCV antigen (if available) is the only way to confirm active infection other than performing a liver biopsy (see NAT section).

While immunoblots clearly enhance EIA test specificity by confirming the presence of specific anti-HCV reactivity, their most important limitation is that they are typi-

TABLE I

Test	Comments
Third Generation Anti-HCV Enzyme Immunoassay	➤ Very effective screening test. ➤ In high prevalence populations, sensitivity >97% and specificity >95%. ➤ In low prevalence populations (e.g., blood donors), sensitivity >97%, specificity 50-60%; therefore confirmatory testing is required. ➤ During acute infection, sensitivity is about 50-70%, as detection of seroconversion requires at least 5-6 weeks. Early antibody levels may be insufficient for immunoblot confirmation. NAT should be used to confirm acute infection where appropriate. ➤ The time to seroconversion may be prolonged in immunocompromised individuals (months to years). ➤ The presence of antibody does not confirm active infection, however, 85-95% of individuals who have strongly positive EIA reactivity are NAT positive.
Immunoblot Assay	➤ Can confirm specific HCV antibody. ➤ Are typically less sensitive than EIAs and are therefore poor at confirming acute infection or infection in immunocompromised individuals. ➤ Cannot determine if infection is active and therefore provides limited diagnostic information. NAT should be performed to confirm active infection where appropriate.
Qualitative HCV NAT	➤ Most sensitive NAT, provides a yes or no answer. ➤ Sensitivity 95-99%, specificity 98-99% but requires meticulous laboratory procedures. ➤ Confirms active infection and end of treatment response. ➤ NAT is positive within 1-2 weeks after HCV infection. ➤ Can be used to detect mother-infant transmission as passively transferred maternal antibody can be detected in infants for at least 12-18 months.
Quantitative HCV NAT	➤ May be useful to predict interferon/ribavirin therapeutic outcome, but the predictive value needs to be validated using standardized commercial assays. ➤ May be used to monitor therapy by early assessment of non-responders. Further studies are necessary to document clinical utility of viral load testing. ➤ Typically less sensitive than qualitative assays.
Genotyping Assay	➤ Differentiates the major HCV genotypes based on sequence differences. ➤ HCV genotype I is typically more difficult to treat but it remains controversial whether it is correlated with more severe clinical illness. ➤ Most common commercial method of genotyping involves specific hybridization of the AMPLICOR PCR product to genotype-specific immobilized probes (reverse-hybridization line probe assay (LiPA) INNO-LIPA, INNOGENETICS).
HCV Antigen Test	➤ Under development. ➤ Can detect acute infection within approximately 2 weeks. ➤ May be helpful for serological confirmation or to monitor treatment response.

cally less sensitive than EIAs. This lack of sensitivity is important when trying to determine if a weakly reactive or indeterminate EIA result is due to small amounts of anti-HCV or non-specific cross-reacting antibody. For example, small amounts of anti-HCV can occur when testing during acute infection prior to complete seroconversion, testing immunocompromised hosts who may have blunted antibody responses[6-8] or they may reflect a resolved infection with waning anti-HCV.[4] Given that immunoblots are less sensitive than EIAs, weakly EIA reactive or indeterminate specimens are also typically immunoblot negative or indeterminate. Thus for the specimens where it is most important to distinguish true anti-HCV from non-specific reactions, neither EIA nor immunoblot testing provide a definitive diagnosis of active infection. Diagnosis in weakly reactive individuals typically requires NAT or follow-up testing to confirm seroconversion.[3,4,24,25]

NAT principles

NAT allows direct detection of specific HCV RNA in serum, plasma or tissues independent of the host's immune response. Viral nucleic acid detected in the plasma or serum reflects active HCV replication in the liver[26] which can generate as many as 10^{10-13} virions per day in chronically infected individuals.[13] NAT-based detection of HCV RNA is performed in two major ways. The most familiar to the reader is target amplification. This technique involves *in vitro* synthesis of HCV-specific nucleic acid followed by detection of the amplified product. Examples of target amplification assays include the polymerase chain reaction (COBAS AMPLICOR HCV PCR Test (qualitative), COBAS AMPLICOR HCV Monitor PCR (quantitative) (Roche)),[27] Transcription-Mediated Amplification (TMA, Bayer)[2] and Nucleic Acid Sequence Based Amplification (NASBA, Organon).[28] The other major approach involves signal amplification. For signal amplification the HCV RNA is hybridized to a specific probe which undergoes extensive enzymatic amplification with the output signal corresponding to the amount of input HCV RNA target in the specimen. Branched chain DNA or bDNA (Quantiplex HCV RNA 2.0, and a newer version 3.0 under development, Bayer) are examples of this type of analytical technique.

NAT will play an increasingly important role in clinical diagnosis because direct detection of HCV RNA can (a) narrow the interval between acute infection and detection of anti-HCV from the current 5-6 weeks by third generation EIAs to 1-2 weeks (Figure 1);[29-31] (b) detect infection in immunocompromised individuals with blunted antibody responses; (c) differentiate active from resolved infection in seropositive individuals; (d) determine perinatal infection independent of the presence of passively transferred maternal antibody, and (e) be used to monitor treatment response.[14-16,32]

Although NAT tests have certain advantages over serological tests, high quality NAT is still not widely available, in part because of a number of technical issues that will be resolved in the coming years and the fact that the cost remains prohibitive (approximately six times that of EIA tests).

Technical factors affecting NAT accuracy

Widespread application of NAT for HCV diagnosis has been slow due to technical limitations. To get accurate and reproducible NAT results requires meticulous standardization of the entire analytic process. In the past only in-house or home-brew NATs were available. These tended to be poorly reproducible between centres and often yielded false positive test results.[33] These home-brew assays were largely replaced with commercial assays which were reproducible but varied in their sensi-

tivity. In addition, quantitative results from the same specimen tested by different manufacturers' assays varied by about 10 fold.[4,26,34] These early commercial assays also had difficulty accurately detecting and quantifying certain HCV genotypes.[27]

Within the last year commercial assays have been adjusted to detect and quantify all the known genotypes and/or HCV strains,[27] and have been standardized against a new International HCV standard.[35] One IU/ml corresponds to about 2-8 copies/ml of HCV.[36,37] This is expected to dramatically improve the inter- and intra-assay reproducibility and accuracy of detection. Assay standardization, availability of semi-automated high-throughput instrumentation and use of internal controls to monitor for inhibition of nucleic acid amplification, have increased test capacity, accuracy and reliability.[38,39] A list of various qualitative and quantitative HCV RNA detection assays are listed in Figure 3.

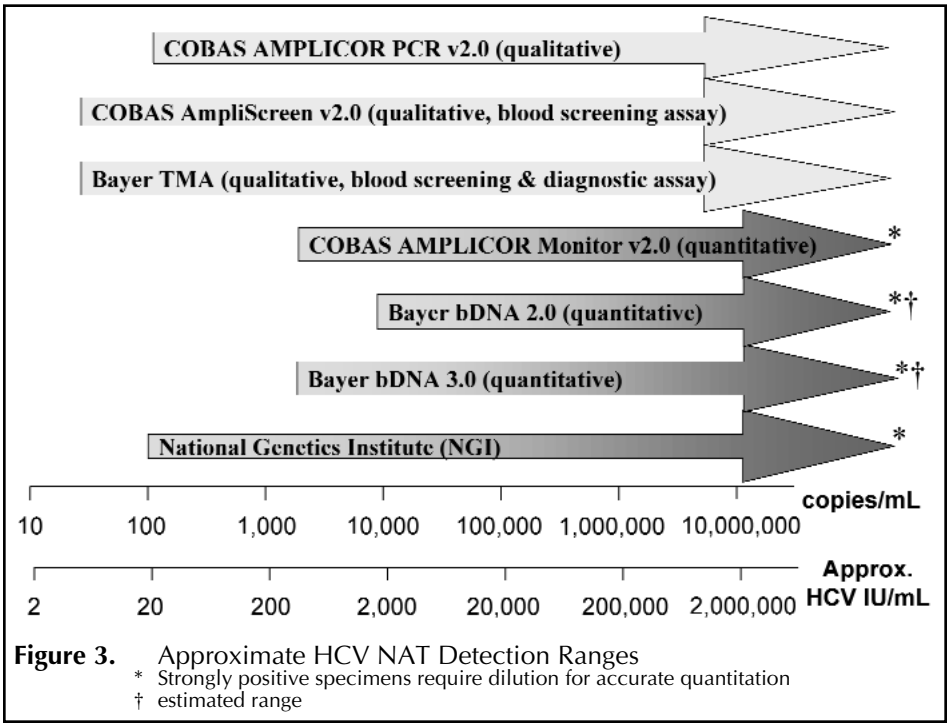

Figure 3. Approximate HCV NAT Detection Ranges
* Strongly positive specimens require dilution for accurate quantitation
† estimated range

Combining serology and NAT to document active HCV infection

As discussed above, at the present time serology alone cannot determine if an individual is actively infected with HCV. Individuals can be grouped into those who demonstrate (Figure 2): 1) strong anti-HCV antibody responses by third generation EIA (e.g., 2-3 times or more than the cut-off of the assay), the vast majority of whom are immunoblot positive and NAT positive; and, 2) weak serological responses, who are generally immunoblot negative or indeterminate and are usually NAT negative.

Of the approximately 70,000 specimens tested by third generation HCV EIA at the BCCDC in 1999, 7,700 (11%) demonstrated some degree of seroreactivity. Of these individuals, 82-85% demonstrated strong EIA signals confirmed by testing on a second manufacturers' third generation EIA. When individuals with strong third generation anti-HCV EIA seroreactivity are tested by NAT, e.g., AMPLICOR (qualitative), 85-95% are NAT positive (Figure 3).[3,18-20]

In contrast, for individuals with weak anti-HCV responses (which represent 15-18% of seroreactive specimens tested at the BCCDC in 1999), immunoblot testing was typically negative or indeterminate and therefore was of limited diagnostic value. When these individuals are tested by AMPLICOR (qualitative), using specimens collected and handled appropriately for NAT, approximately 5-10% are positive. Most of the NAT positive antibody weakly reactive or indeterminate specimens were either undergoing acute seroconversion or had a blunted antibody response from immunosuppression.

Which NAT assay should be used for clinical diagnosis?

As discussed previously, the literature regarding the sensitivity, specificity, reproducibility and standardization of the various commercial NAT is very confusing. Given the adoption of the International HCV Standard (IU), it is expected that manufacturers will soon be able to agree on the relative amount of HCV RNA in a given specimen and the relative sensitivity of their assays.[36,37] Figure 3 demonstrates the relative sensitivities and range of detection of available NATs as well as those under development.

As can be seen in Figure 3, qualitative NAT (AMPLICOR & TMA) are more sensitive than the quantitative assays. The AmpliScreen (Roche) and TMA (Bayer) assays that have been developed for blood donor screening are the most sensitive.[40] Qualitative tests are currently 10-100 fold more sensitive than quantitative assays and can reliably detect 5-50 IU/ml (approximately 10-100 copies/ml). Qualitative assays are able to provide a yes or no answer regarding the presence of HCV RNA in the specimen and, as outlined in Table I, should be used to: 1) detect acute infection prior to seroconversion, 2) resolve weakly reactive or indeterminate serological results and, 3) determine if an individual is actively infected and/or has responded to therapy.

It is difficult to assess the clinical sensitivity and specificity of qualitative NATs given the lack of a clinical "gold standard" of HCV infection. Based on well-characterized HCV-infected and control populations, the sensitivity and specificity of commercial qualitative NAT approach 95-99% and 98-99% respectively.[4] These figures are dependent, however, on meticulous laboratory procedures.

HCV genotyping

The term genotype refers to the sequence-based phylogenetic clustering of HCV types and subtypes found in patients. At present, there are at least 11 types and greater than 90 subtypes.[2,41]

HCV genotypes are typically differentiated by the commercially available reverse-hybridization line probe assay (INNO-LIPA HCV II, Innogenetics, Belgium). This involves specific hybridization of the AMPLICOR PCR product to genotype-specific immobilized probes on the line probe assay which generate a colour reaction (a nucleic acid equivalent of an immunoblot). Alternative techniques to determine the genotype include restriction fragment-length polymorphism of PCR products and direct sequencing.[42]

Although infection with certain genotypes (e.g., genotype I) appear to be more difficult to treat,[14,15,32] whether this represents an intrinsic feature of genotype I virulence remains controversial.[2,43]

Quantitative NAT for antiviral monitoring

Combination therapy with interferon and ribavirin has revolutionized the treatment of HCV infection. Treatment for 24-48 weeks can eliminate detectable HCV RNA from blood and improve hepatic histopathology in approximately 40% of HCV-infected individuals who have elevated serum transaminases.[14,15,32] Of particular importance is the fact that most virologic responders remain serum HCV RNA negative for at least two years after therapy is stopped.[16] Correlates of therapeutic response include: sex, age, degree of hepatic fibrosis, the amount of detectable HCV RNA in the serum (viral load) and the genotype of the virus. Approximately 30% of individuals infected with genotype I will respond to combination therapy after 48 weeks of treatment. In contrast, 60% of individuals with non-genotype I will respond with 24 weeks of combination therapy. Although response to combination therapy correlates with low pretreatment viral loads (< 2,000,000 copies/ml as measured by the National Genetics Institute assay) for genotype I-infected individuals, that correlation was based on viral load measurements using a non-commercially available assay which is not directly comparable to currently available commercial assays.[4] In addition, the predictive value of HCV load determinations was less important than the infecting viral genotype.[2,14,15,32,43]

Unlike HIV infection where HIV viral load predicts outcome and serves as a strong surrogate marker of treatment response, this is not the case for HCV viral load. In general, outcome for HCV infection is most strongly correlated with the degree of hepatic fibrosis.[2,43,44] A number of studies are currently underway to determine if monitoring HCV load during combination therapy can be used to rapidly identify non-responders early so that ineffective therapy can be stopped early to reduce the overall therapeutic costs. The results of these studies should be available within the next year. Because commercial quantitative assays are less sensitive than qualitative assays, they should only be used for therapeutic monitoring and not to confirm active infection or to determine if the therapy has been effective.

HCV antigen detection

Another method of HCV detection that is under commercial development, involves detection of HCV antigens in plasma or serum.[45] One version of this test detects free HCV antigen in the specimen. This may be of particular benefit in detecting acute seroconversions. Based on studies in blood donors, HCV antigen can be detected within the first 2 weeks of acute infection, which is quite similar to NAT (Figure 1).[29] However, given the greater sensitivity of NAT and its general availability, the role of HCV antigen testing for routine clinical diagnosis remains unclear. Other versions of the HCV antigen test are designed to detect HCV antigen in the presence of HCV antibody, which may be useful to confirm active infection in chronically infected individuals or to monitor response to antiviral therapy if the test performance proves satisfactory.

SUMMARY

HCV diagnosis and testing is clearly a rapidly evolving field. This paper outlines how anti-HCV serology and NAT can be combined to provide a definitive answer as to whether or not an individual has been or is actively infected. The strengths and weaknesses of the various tests are outlined in Table I. In the future, one can expect more accurate and reproducible NAT which will increase diagnostic accuracy and guide therapeutic intervention on an individual basis.

Although clinical therapeutics is not typically considered the domain of public health officials, it is important to understand that a number of new therapeutic agents are currently under development for the treatment of HCV. These include Pegylated and Consensus Interferon which are more potent than the current interferon alpha used in combination with ribavirin.[46] Given the promising data from the current interferon alpha and ribavirin combination and preliminary data from these new antiviral agents, HCV may well become a curable illness where both prevention and treatment are required to minimize the risk of transmission and reduce the burden of illness in the population.[47,48]

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Building a Better Blood System for Canadians

Lynda Cranston

Each year, donated blood saves or improves the lives of thousands of Canadians. Yet blood is also the potential carrier of both viral and bacterial infections. This possibility was fully realized in the 1980s when blood supplies around the globe were infected with Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV).

It is the mission of Canadian Blood Services (CBS) to provide the safest possible blood components to blood transfusion recipients in nine provinces and three territories across the country. Our mission statement commits us to provide a safe, secure, reliable, cost-effective, affordable and accessible supply of blood, blood products and their alternatives and to manage the blood supply system in a manner that nurtures the trust, commitment and confidence of Canadians.

Lines of defense

At CBS our operating assumption is that there will always be threats to the blood supply. As a result, we are instituting changes to enable the organization to remain at the height of vigilance to guard against any potential threat to the blood system and to respond quickly and effectively if and when a problem arises.

Our first line of defense against potential threats to the blood system involves recruiting only **volunteer** blood donors. This is perfectly within the Canadian tradition; but its most significant value may be that the safest blood donor is one whose only incentive is to save someone's life.

CBS screening procedures rely heavily on the honesty of prospective donors. Safety demands that they respond truthfully to pointed questions on their health and risk activities; a donor motivated by money, time off work or other incentives may be less likely to be completely honest. The exclusive use of volunteer donors, whose only motivation is altruism, remains a fitting safety feature of our system.

While CBS is in the process of becoming a totally new organization, we nevertheless have a unique opportunity to build on an existing tradition of community service as we design a new framework for Canada's blood supply. The fact is that, in Canada, blood donors are arguably the most important link in the blood system.

Our second line of defense is the **screening** of prospective blood donors. Strict screening ensures that each donor presents the least possible risk of transmitting diseases.

Potential donors whose tests or answers indicate that they are at higher risk for certain diseases or medical conditions are deferred from giving blood. Applicants may be deferred for their own safety, or to protect the safety of the blood supply.

The criteria CBS uses to determine the eligibility of blood donors are based on scientific knowledge of risk factors. All screening measures must meet stringent regulatory requirements and keep pace with the accepted standards of blood services worldwide.

Deferral periods range from as short as a few days for cold symptoms, to a few years for the risk of malaria. In some cases, applicants are permanently deferred, such as for individuals who have engaged in high-risk behaviours or have lived in certain higher risk areas of the world.

Our third line of defense involves the **testing** of each and every unit of donated blood. Every time someone makes a donation, CBS takes a sample of this blood for testing by trained laboratory technicians using sophisticated, reliable procedures.

For example, CBS routinely tests for the following transmissible diseases:

- Hepatitis B and Hepatitis C
- Human immunodeficiency viruses (HIV-1 and HIV-2)
- Human T-Cell lymphotropic virus HTLV-I and II
- Syphilis

As innovations to improve safety or efficiency are developed, CBS has a clear process for evaluating their potential benefits and risks, as well as their costs relative to other alternatives or technologies. With major advances being made in testing blood for transmissible diseases, new tests are being added to the roster of testing requirements as we continue to meet accepted and improved international standards.

Testing for HCV

As a case in point, in the fall of 1999, Canada joined Europe and the United States with the introduction of a new, more sensitive test for Hepatitis C (HCV), called Nucleic Acid Amplification Testing, or NAT.

CBS filed an Application for Investigational Testing with Health Canada to use the AmpliScreen 2.0 HCV PCR assay, manufactured by Roche Molecular Systems, to screen blood donations for HCV nucleic acid. NAT is being introduced on an investigational basis in order to demonstrate its efficacy in detecting HCV. The Canadian regulator, the Bureau of Biologics and Radiopharmaceuticals (BBR), does not require CBS to conduct NAT at this time. However, it does expect

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CBS to investigate NAT's efficacy. The data collected from the investigation will be used to support the manufacturer's application for licensing of the testing kit as a blood donor screening test in Canada.

NAT works by detecting low levels of viral genetic material present when an infection occurs but before the body begins producing antibodies in response to a virus. As a result, NAT significantly reduces the "window period" or the time between initial infection and when the virus is first detectable. Studies have shown that NAT can detect HCV within 14 to 28 days as compared to about 70 days using previous tests.

For purposes of organizational efficiency, NAT testing at CBS begins with a number of blood samples being "pooled" together in the laboratory. If the pool is positive, then the samples are tested in smaller pools and then individually until the actual positive sample is identified. CBS will then notify the donor, provide appropriate counselling to that individual, and discard all the products made from that donation.

The CBS NAT sites across Canada are located in Vancouver, Toronto, Ottawa and Halifax. The blood centres in these cities have undergone extensive renovations to accommodate the special requirements of NAT and 28 new technical positions have been created to conduct testing.

HCV is an often debilitating and sometimes fatal disease. With the addition of the HCV PCR assay to HCV antibody testing, it is anticipated that a greater number of HCV infectious units will be detected. The exact degree to which transfusion safety will be improved is not known at this time. It is thought that the risk factor, formerly estimated at 1 in 120,000 units, will be reduced to 1 in 500,000 units or less. Mathematical models indicate that NAT will detect an additional four to six cases of HCV each year in Canada and since each blood donation may result in two or more blood components for transfusion, NAT has the potential to prevent up to 13 HCV infections annually.

Managing risk

At CBS, risk management is integral to our business planning. Blood is a precious resource, and we take very seriously our responsibility for its efficient and safe use. NAT is becoming the standard of practice in the blood and plasma industry in Europe and the United States; since blood products cross international borders, it is important to have consistent standards.

Canada was not alone in facing a tragedy over tainted blood in the 1980s and 90s. It was in fact a global crisis and a direct reflection, albeit a negative one, of the overall globalization trend of our era. The business of blood banking is becoming truly global; we are increasingly interdependent and CBS must plan accordingly.

When it comes to risk, however, there can be no guarantees. There may never be a time when blood will be absolutely 100% safe. There must be vigilance and systems in place to minimize the risk. We are in the process of building a better blood system to be able to tackle the challenges that will inevitably come our way in the future.

Perhaps most importantly, a creed of safety now permeates the CBS organization. We ensure that CBS meets or exceeds all relevant national and international standards for safety in blood management and operations and we are fostering a corporate culture within CBS whereby employees understand their individual and collective responsibility for safety.

Bloodborne disease diagnosis and testing is a rapidly evolving field and CBS intends to remain at the forefront of change both through our responses to new challenges and changing technology as well as through instigating innovations via significant research and development activities. Today, innovation and change are necessary components of a viable blood system. That's why CBS is making a significant commitment to ongoing research and development as a key part of our role and our vision for the future blood system.

In fact, we are committed to setting aside up to 10% of our operating budget for research directed at improving blood safety and reducing our dependence on blood. This represents a significant pool of ongoing funding that can be used in the development of innovations in both products and systems for:

- Maintaining the safety of the blood supply;
- Enhancing our utilization of blood products;
- Developing alternatives to human blood.

Today, CBS is concentrating on shaping a very different future for the blood system than its recent past. We are building a better blood system for this country that is, and will be, much better prepared for the changed realities of our times.

Hepatitis C: Mental Health Issues

William Rowe, DSW, Jocelyn Rowe, MD, Leah Malowaniec, BSW

Hepatitis 'Non-A, Non-B'

When the hepatitis C virus (HCV) was identified in 1990, relatively little was known about the progression of the disease or the psychosocial implications of its diagnosis. If you were one of the Canadian blood donors who received a letter in 1990, informing you that hepatitis C had been identified in your blood and unfortunately no further donations could be accepted, there would have been a small note attached. The note would explain that the significance of this finding was unknown, but that you should see your doctor.

When your physicians contacted public health authorities and medical directors of blood collection agencies, they would have been advised that hepatitis C was not known to be the cause of any serious illness, so patients should be reassured.

But patients needed to know much more: What *was* hepatitis C? How did they get it? Should they start using condoms with their spouses of *12 years?* Would they become ill from this? What symptoms should they watch out for? Were there other tests they should have? Are there any treatments they should start? Were their children at risk?…

We did not *have*, and could not *obtain,* information regarding the medical implications of testing positive for the hepatitis C virus. We had little to guide us in our attempts to offer support. One woman commented, "Having hepatitis means that many things change, and a lot of them are invisible. Unlike having cancer or being hurt in an accident, most people do not understand even a little bit about HCV and its effects." Patients and health professionals had very little information to work with.

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Wake-up call

We now know, of course, that the thousands of Canadians who have been diagnosed with HCV do have substantial and specific social service and mental health needs. We are better informed about what some of these needs are, and the nature of the responses and interventions that are necessary. What we do not yet sufficiently understand is to what degree effective social and mental health services are in place. To what degree do Canadians diagnosed with hepatitis C have adequate access to care and support? Public awareness relating to hepatitis C and mental health is still in its infancy. To what degree is public health policy responsive to the medical and mental health needs of Canadians diagnosed with hepatitis C?

Difficult news

In the year 2000, we are well informed of the range of emotions experienced by persons diagnosed with HCV: shock, fear, denial, confusion, shame, regret, blame, suicidal ideation, and acute anxiety or anger.[1] These responses have been well described for persons coping with diagnoses of cancer, HIV, and other life-threatening illness. We know that with appropriate support, acute reactions can be anticipated and can evolve into adaptive coping strategies and support networks.[2,3] But persons isolated at and around the time of diagnosis of life-threatening illness can have much worse outcomes. The situation is intensified when there are pre-existing psychosocial stressors and health challenges. Persons faced with health and social service providers who are unprepared and unavailable, experience much greater emotional suffering, more rapid progression of their disease, and earlier death. Their families and friends suffer greater devastation, and are less able to recover functioning (jobs, relationships) or well-being (physical or emotional) in the future. One woman remarked, "Looking back, I don't know how I functioned on a day to day basis. Every aspect of my life suffered. I was frightened, confused, guilty, incapacitated, and completely useless, unable to hardly take care of myself, let alone my house, or family."

Clearly these crises require specific and consistent response from health and social service providers.

Acute responses

Persons receiving news of life-threatening illness will be overwhelmed. Typically, staggering quantities of information are offered, but people report "not hearing a word" after the doctor told them the diagnosis. People sometimes remember "nothing at all about what [they] did for the rest of the day." Ordinarily few of the details of complex explanation of medical implications and treatments are remembered the next day.

Ideally, physicians recognize the need for adequate preparation, background information and support, and engage the appropriate support personnel and services. Under the best circumstances, these services would be immediately accessible and available 24 hours per day. To what extent is this the case? Physicians have considerable experience in breaking bad news, but do not necessarily cope well with the task. We may not know how to make effective

use of limited time or have the additional training necessary to provide the intense specific support and intervention needed. Do social work professionals take the initiative to identify service and learning needs? Is there the will or the interest to develop and implement appropriate interventions and programs for patients and caregivers?

Dealing with uncertainty

Physicians report that 'counselling' patients with hepatitis B or C viral infections is often the most difficult aspect of patient management.[4] Specific challenges identified are: the uncertainty surrounding the progression of symptoms and the disease; misinformation among medical professionals and the general public about HCV; physicians' time constraints, and the patient's distress at the time of diagnosis. Physicians note that "the patient's level of anxiety often impairs or even precludes their ability to understand and retain much of what has been said" by the diagnosing physician. Physician distress in the face of uncertainty and inadequate support can also be high.

Inadequate knowledge or support will prevent nursing, housekeeping, lab or dietary staff (to mention a few) from being able to provide consistent and appropriate care for patients with unusual diagnoses (as witnessed in previous years with cancer and HIV). It is therefore crucial that a broad base of health and social service professionals working in the area of public health and counselling be educated about HCV, and available for consultation and ongoing support for patients and care providers.

Interferon: Mental health impact

Interferon is currently the only available treatment for HCV. As with many pharmacologic and immunologic manipulations, interferon can cause or exacerbate mental health problems.[4] There have been reports of severe depression, suicidal ideation, delirium, and manic depression induced by interferon.[5] Adverse psychiatric symptoms are the most common reason for discontinuing treatment and these side effects have been reported at both high and low doses.[6] One patient stated, "My constant companion was depression. The fog that I was in, caused by the medicine, kept me from seeing it clearly. I just thought that I was going insane!" People with a history of psychological instability or underlying psychiatric issues may be at greatest risk for problems associated with interferon.[6]

How consistently are patients/clients counselled about possibility of adverse psychiatric reactions? How closely are clients monitored? Physical, social and economic situations can deteriorate considerably before symptoms are recognized and treated. Self esteem and years of life can be lost in the process.

Other reported side effects of the medication include fever, chills, anorexia, nausea, weight loss, myalgia, fatigue, hair loss, and cognitive problems.[7] These add further distress to the lives of people affected by HCV, as with any chronic illness. Increased use of interferon therapy is anticipated, thus more people will potentially be at risk of experiencing adverse psychiatric side effects.[6] Are we sufficiently prepared, educated, and motivated to provide adequate monitoring and supportive care? Whose job is it?

Importance of support groups

The stigma attached to hepatitis C is similar to the early days of HIV. Support groups for people with HCV and their partners, friends and families are helpful in allaying fears and anxiety associated with the infection.[7] Some larger Canadian cities offer meetings, support groups, and telephone contacts, and there are several online chat groups accessible via the Internet. However, those who live in smaller cities or rural regions, or are without access to the Internet would benefit from contact with and support from others who are living with HCV. A person diagnosed with HCV who moved to a smaller city remarked, "When I came to this area, I found that services and support were virtually non-existent… there is a real need. After an article printed in our local paper on tainted blood came out with my phone number and intentions of starting a support group, I've had many people call me. Their stories all seem to be the same as mine… The information available is fairly outdated, confusing, and non-committal."

Issues relating to disclosure, the uncertainty of disease progression, and emotional factors may be best processed in a client-centered group format. "Having HCV has changed me. I fought this diagnosis initially – was angry and depressed. It took some time, but I no longer feel dirty, like I deserve this," commented one woman. Additionally, the opportunity to help and educate others about HCV may lead to a greater sense of well-being and improved mental health.

Families, partners and friends

Families, partners and friends of those diagnosed with HCV may also benefit from support groups. Issues related to contraction of the disease, expectations of the HCV-positive person, and sex/intimate relationships may cause distress for those who are in close relationships with people diagnosed with HCV. The revelation that a loved one may have contracted HCV by engaging in risky behaviour (intravenous drug use, unprotected sex, etc.) can cause significant family and interpersonal upheaval. Addressing these issues in the context of a support group with a psycho-educational element may reduce some of the stress, anxiety, and uncertainty related to HCV.

Socio-demographics

The socio-demographic characteristics of people infected with HCV differ from those who are not infected. A study detailing the health and socio-economic status of HCV-positive blood transfusion recipients in British Columbia revealed that those who were diagnosed with HCV were more likely to be male and unmarried than those not infected with HCV.[8] People who were HCV positive were also more likely to be unemployed, reported a lower household income, received more income from social assistance, and more frequently reported that they were unemployed due to illness or disability than the control group. One person noted, "When I learned that I had HCV, I had just graduated from college and I was too weak to look for work. All that hard work and now I was too sick to get a job."

Those diagnosed with HCV also made significantly more visits to their family physicians, other medical doctors, nurses, social workers, psychologists, and emer-

gency rooms. Further, they were more likely than those not infected with HCV to have spent money on alternative therapies, and were significantly more likely to have been refused insurance coverage. The implications of these demographic and socio-economic differences may be tremendous if they are not considered in treatment planning.

It is of great importance that services provided to those diagnosed with HCV be accessible, free of charge, and client-centered. Further research to determine the socio-economic profile of those infected with HCV nationally would be useful to expand our understanding of the treatment needs of Canadians.

Drugs and alcohol

Within the population of people diagnosed with HCV, specific groups may have unique needs. People who are habituated to drugs or alcohol may need distinct mental health services. Drug or alcohol users who are diagnosed with HCV may wish to make significant lifestyle changes to promote health. They may experience mental health concerns as a result of their altered lifestyle. Alternative coping strategies must be introduced, and support must be given to maintain new methods of coping. The stigma associated with a diagnosis of HCV is often greater for substance users, as people who have used injection drugs are assumed to be personally responsible for contracting the illness. One person commented that "When I sat in my first support meeting, everyone focused on how they got HCV. Most of the people in the room were victims of blood transfusions. When it was my turn, I didn't say how I got it. I was too embarrassed… but I am no less of a person because I contracted HCV through drug use." Injection drug use is associated with at least half of HCV infections in Canada,[9] and it is therefore important that health and social service providers are sensitive to the specific needs of this population.

HIV co-infection

Those who are infected with both HIV and hepatitis C may need more intensive mental health support, in order to cope with the implications of dual diagnosis. "The prevalence of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection ranges from nearly 30% to over 50%, depending on the population. HIV co-infection appears to worsen HCV infection, with studies showing more severe fibrosis, a higher frequency of cirrhosis, and increased deaths from liver disease."[10] This dual diagnosis may increase emotional stress for many people.

Professional education

To work effectively with individuals diagnosed with HCV, professionals must have access to education that addresses both the disease and its mental health implications. A model for practice does not currently exist that integrates the essential elements of HCV and mental health issues. Designing an approach that is based on the practice model for people living with HIV/AIDS may be beneficial. Elements of education, harm reduction, prevention information, and a client-centered approach must be present in the model.

Call for research

Further study is necessary to adequately assess the mental health needs of Canadians who have been diagnosed with HCV. Specifically, research must be conducted to determine the extent to which Canadians infected with HCV are experiencing mental health problems, the severity of their symptoms, and how effectively existing services are meeting their unique needs. The uncertainty surrounding the progression of the disease and its psychosocial implications may negatively impact the health of Canadians, and it is therefore essential that these issues are addressed on the levels of practice, policy, and research.

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