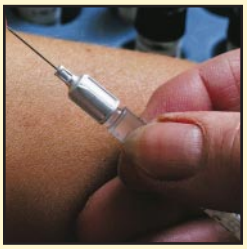
Canadian Liver Foundation
National Hepatitis C Education Program

hepatitis C

MEDICAL INFORMATION UPDATE

A Canadian Liver Foundation Initiative in cooperation with Health Canada

transmission
diagnosis
clinical management
treatment



CANADIAN LIVER FOUNDATION
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INTRODUCTION

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 may have no symptoms and are unaware of their condition, and unknowingly act as sources of infection and run 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. There are six known genotypes of HCV and many more subtypes. 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.

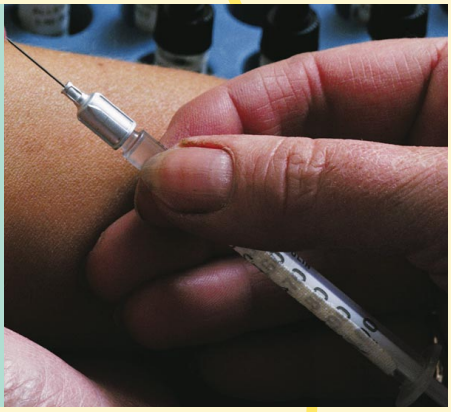
There are at least six different HCV genotypes and some of these have subtypes. Types 1a and 1b account for more than 60% of all infections in North America, with types 2a, 2b, 3 and 4 accounting for the rest. Type 5 is rarely found in North America, except in Quebec.

transmission

1.0 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.

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



1.1 Injection Drug Use

Injection drug use still is the major mode of transmission of HCV in Canada. As with other blood borne pathogens, HCV is transmitted through transfer of infected blood by sharing 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]

1.2 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 is estimated to be approximately 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.

1.3 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 those of 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 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.

1.4 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 alter 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 breast milk 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.

1.5 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 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]

1.6 Percutaneous Exposures

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

1.7 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

2.0 DIAGNOSIS

2.1 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 1). 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
- 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, 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 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.

Table 1 — 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

2.2 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.

2.3 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 2.

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]

Table 2. — 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 enhance disease progression.[2]

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, does not correlate 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.

3.0 CLINICAL MANAGEMENT

3.1 Follow-up

Table 3 summarizes the recommended follow-up for patients with chronic HCV.

3.2 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.

3.3 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, given that the disease is mild in children. Interferon is currently under review for use in children (younger than 18 years) and in children 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.

3.4 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]

Table 3 — 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]

3.5 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 - 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 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.

3.6 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 4.

Table 4 — Extrahepatic Complications of Hepatitis C

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

3.7 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

4.0 TREATMENT

4.1 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.

4.2 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.

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) or 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.

4.3 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 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]

4.4 Post-exposure Prophylaxis and Follow-up

Testing is recommended for those with needle stick, 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.

4.5 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.

4.6 Liver Transplantation

Liver transplantation gives excellent short-term survival in patients with end-stage liver disease due to HCV. Hepatitis C is the commonest 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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Canadian Liver Foundation

The Canadian Liver Foundation (CLF), established in 1969, was the first organization in the world devoted to providing support for research and education into the causes, diagnosis, prevention and treatment of all liver diseases. CLF is dedicated to providing education to physicians, patients, families and the general public through more than 30 volunteer chapters across Canada. Because hepatitis C is a serious liver disease, the Canadian Liver Foundation is committed to providing information and education about this increasingly prevalent infection. This is a rapidly changing field of medicine; information in this publication is current for October 1999.

For further information about hepatitis C, please contact the Canadian Liver Foundation at 1-800-563-5483 or your local or provincial public health department.

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