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The Reproductive Care of Women Living With Hepatitis C Infection

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I. ABSTRACT

Objective: hepatitis C virus (HCV) is an increasingly important public health problem worldwide. Health care workers providing care to women of childbearing age are uniquely placed in their practices to identify a significant proportion of at-risk patients and to provide appropriate screening and counselling. The primary objective of this guideline is to provide accurate, current information to those offering reproductive care to women living with HCV. This document is also intended to raise awareness of HCV in both the medical and general populations.

Options: the areas of clinical practice considered in formulating this guideline are disease prevention, targeted screening of individuals at risk of contracting HCV, management of identified patients in the context of reproductive care, and the appropriate referral of patients to those with particular expertise.

Outcomes: implementation of these guidelines should facilitate identification of infected individuals. It should also result in improved physical and mental well-being for patients and their families and reduction in transmission rates.

Evidence: the literature between 1966 and 2000, including non-English language publications, was extensively searched utilizing Medline. A multidisciplinary group consisting of experts within the fields of obstetrics and gynaecology, infectious diseases, hepatology, and public health convened in Montreal in February 2000. The working group also included a patient and a representative from the Hepatitis C Society of Canada. The level of evidence for the recommendations has been determined using the criteria described by the Canadian Task Force on Periodic Health Examination.

Benefits, harms and costs: the public health benefits of increased identification of at-risk individuals, diagnosis, treatment, implementation of risk reduction behaviours, and reduced transmission rates, both on an individual and at the community level, are significant. However, it must be remembered that the diagnosis of a chronic disease may have far reaching effects for the individual patient and her family.

Recommendations:

a) Screening

- Universal screening for HCV is not recommended, although targeted screening should be offered to all women falling into any at-risk category. Testing should take place following adequate counselling and informed consent of the patient. (III B)

b) Preconception and early pregnancy care

- Ideally, preconception or early pregnancy evaluation should include determination of risk of infection with hepatitis C, counselling, and testing as appropriate. (III B)
- Patients aware of their HCV positive diagnosis should be evaluated before embarking on pregnancy for complications that may compromise maternal health during pregnancy. (III B)
- Pregnancy is not generally contraindicated on grounds of HCV infection alone. (Although it is contraindicated in the context of ribavirin therapy.) (III B)

c) Care during pregnancy

- There is a risk of vertical transmission which is greater if the woman is also infected with human immunodeficiency virus (HIV). (II-2 A)
- Antenatal care will need to be tailored individually to meet the specific needs of the woman's medical and obstetrical condition, including the monitoring of liver function. (II-2 A)
- Alcohol should be avoided. (II-2 A)
- Immunization against hepatitis A and B should be provided as required. (II-2 A)
- Routine Caesarean section is not recommended as a specific intrapartum measure to reduce the risk of vertical transmission of hepatitis C. (II-2 D)
- Breastfeeding is not contraindicated. (II-3 B)

d) Care of infant

- All infants born to HCV positive mothers should be evaluated for evidence of hepatitis C infection. (III A)

e) Contraception and hormone replacement therapy

- Barrier methods should be recommended to those with multiple sexual partners. (II-3 B)
- The extent of liver disease should be carefully evaluated before considering the use of hormonal contraception or hormone replacement therapy. (III B)

f) Universal precautions

- Universal precautions/routine practices and additional precautions are recommended in dealing with all patients for the protection of both health care worker and patient. (II-2 A)

Validation: references were collected through Medline searches and comparison made to existing current guidelines for assessment of consistency. External reviewers expert in their field were also consulted.

II. INTRODUCTION

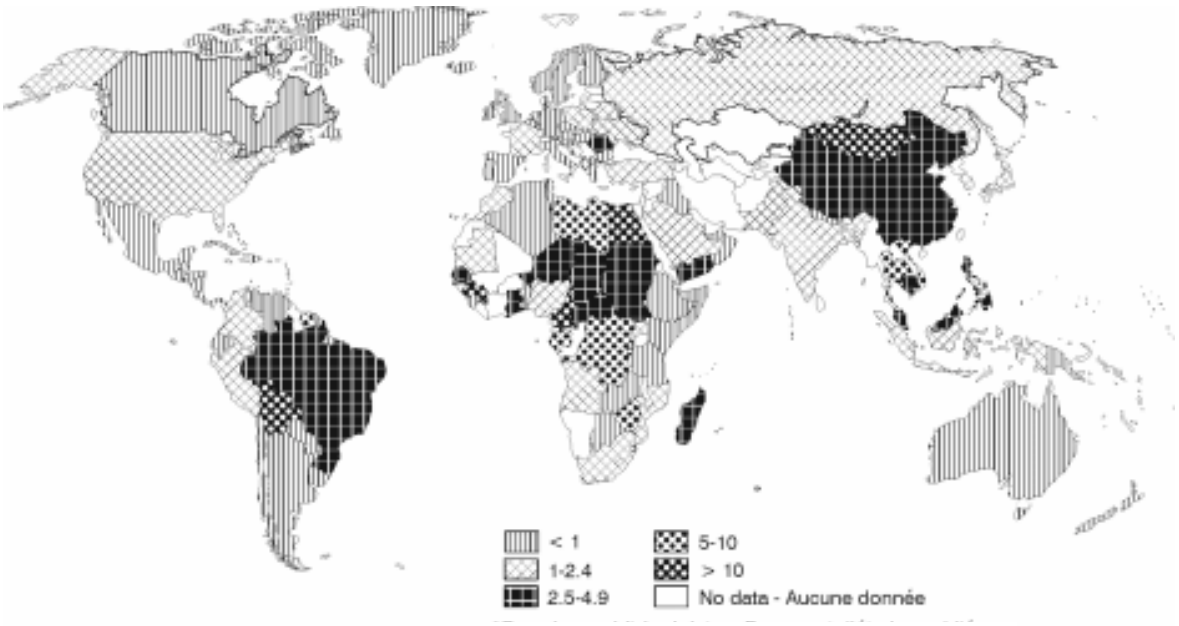
Hepatitis C virus (HCV), which was first discovered in 1989, is an important cause of chronic liver disease and is increasingly recognized as a major public health problem worldwide. It is a bloodborne pathogen and is the most frequent etiology necessitating liver transplantation, producing considerable costs to health care systems. It has been estimated that three percent of the world population is currently infected with HCV.[1] The estimated prevalence in Canada is 0.8 percent, suggesting a total number of 240,000 infected persons (Table I).[2] Only about 30 percent of those infected with HCV are thought to be aware of their infection. Extrapolation from the general population data in Canada would suggest that up to one in 120 deliveries might occur in an infected woman. The incidence is rising most rapidly in the 20 to 45 year age group, implying that HCV will be seen more and more commonly in women of childbearing years.

HCV is responsible for considerable morbidity and mortality, with the majority of acute infections becoming chronic.[3] It represents the most common cause of chronic viral and post-transfusion hepatitis, although in Canada the risk of this has fallen to almost nil since 1990 with the introduction of screening, and ranks only slightly below chronic alcohol use as a cause of cirrhosis, end-stage liver disease, and hepatocellular carcinoma.[3] Vertical transmission occurs with variable frequency dependent on the existence of co-factors and other medical conditions.[4,5,6,7] Nosocomial infection has been reported in both patients and health care workers. HCV has a huge impact on the family unit in psychological and social terms, but will also raise specific issues for women regarding contraceptive choices, pregnancy, assisted reproduction, and hormone replacement therapy.

The issues for those providing health care to women of childbearing age are several: identification of at-risk patients

FIGURE 1

PREVALENCE OF HCV IN DIFFERENT PARTS OF THE WORLD



Source: CCDR 2000;26(5).March 2000.

*Based on published data. - Provenant d'études publishées.

and provision of appropriate screening; evidence based counselling regarding the complex issues related to pregnancy, including vertical transmission and therapy; patient education; and psychological support of the identified patient and her family prior to, during, and after the pregnancy.

The following guideline has been developed to inform, educate, and prepare the health care community to identify and counsel women living with HCV.

III. EPIDEMIOLOGY

A. PREVALENCE AND INCIDENCE

1. General population

In a recent publication,[8] the World Health Organization (WHO) estimated that in 1999, 170 million persons were infected with HCV, representing approximately three percent of the world's population. Reported seroprevalence rates in the general population vary greatly throughout the world, although accurate and properly collected data are missing from numerous areas of the globe.

Notification of hepatitis C in Canada began in 1992 and has been mandatory in all provinces since January 1999. The number of reported cases has increased dramatically since then, which may in part be due to reporting bias. However, there also appears to be an actual increase in incidence of identified cases, as suggested by numbers from British Columbia, where

TABLE I

DATA FOR THE GENERAL POPULATION IN CANADA[9,10]

	Number of patients	% population
Estimated prevalence	240,000 (range 210,000-275,000)	0.8%
Estimated annual incidence	1,000*	

* clinically recognized acute cases

TABLE II

PREVALENCE OF HCV IN HIGH RISK GROUPS IN CANADA

High Risk Groups in Canada	Prevalence of HCV (%)
Injection drug users after one year	70
Aboriginal populations (preliminary data)	15-20
Haemodialysis patients	*
Recipients of blood products, tissue, organs from 1960-92	1.5-2.7
Prisoners in correctional facilities[11] (women in Kingston: 86.9% tested) (men in western Canada: 23% tested)	 39.8 25

* No Canadian data available

TABLE III

POPULATION STUDIES SHOWING SEROPREVALENCE OF HEPATITIS C DURING PREGNANCY: GENERAL POPULATION AND POPULATION STRATIFIED ACCORDING TO HIV STATUS.

YEAR OF PUBLICATION	COUNTRY	TOTAL ANTI-HCV POSITIVE	HIV POSITIVE WOMEN	HIV NEGATIVE WOMEN
1992	USA (New York)[12]	29/648 (4.5%)	NR*	NR
1992	Haiti (rural setting)[13]	2/500 (0.4%)	NR	NR
1992	USA (Dallas)[14]	23/1,005 (2.3%)	NR	NR
1992	Italy (Rome)[15]	10/1,142 (0.9%)	NR	NR
1993	Japan (Kuruke)[16]	26/1,661 (1.6%)	NR	NR
1993	France (Paris)[17]	41/2,367 (1.7%)	NR	41/2,367 (1.7%)
1993	France (Clichy)[18]	13/670 (1.9%)	NR	13/670 (1.9%)
1993	USA (Philadelphia)[19]	26/599 (4.3%)	2/3 (66.7%)	24/596 (4.0%)
1994	Taiwan (Taipei)[20]	40/2,020 (2.0%)	NR	40/2,020 (2.0%)
1994	Japan (multicentre)[21]	53/7,698 (0.7%)	NR	NR
1994	Cameroon (Yaounde)[22]	26/384 (6.8%)	NR	NR
1994	Italy (Vicenza)[23]	24/5,672 (0.4%)	NR	NR
1995	USA (San Juan PR)[24]	19/997 (1.9%)	1/8 (12.5%)	18/989 (1.8%)
1995	Japan (Tsukuba)[25]	29/2,380 (1.2%)	NR	NR
1995	Italy (Milan)[26]	250/21,516 (1.2%)	NR	NR
1995	USA (Philadelphia)[27]	47/1,432 (3.2%)	NR	NR
1995	Japan (multicentre)[28]	163/16,714 (0.98%)	NR	NR
1995	Italy (Torino)[29]	35/5,000 (0.7%)	NR	35/5,000 (0.7%)
1996	Guinea (Conakry)[30]	8/302 (2.6%)	NR	NR
1996	Italy (Padova)[31]	29/1,700 (1.7%)	NR	NR
1996	Italy (Chieti)[32]	30/2,980 (1.0%)	NR	30/2,980 (1.0%)
1996	Italy (Udine)[33]	36/1,388 (2.5%)	NR	NR
1997	Spain (Seville)[34]	59/6,556 (0.9%)	NR	NR
1997	United Arab Emirates (Al-Ain)[35]	65/499 (13.0%)	NR	65/499 (13.0%)
1997	Japan (Kurume)[36]	23/1,661 (1.4%)	NR	NR
1997	Australia (Adelaide)[37]	17/1,488 (1.1%)	NR	NR
1998	Italy (Genoa)[38]	NR	NR	82/7,023 (1.2%)
1998	USA (multicentre)[39]	NR	169/511 (33.1%)	NR
1998	Malawi (rural setting)[40]	NR	6/50 (12%)	18/100 (18.0%)
1998	Italy (Florence)[41]	NR	NR	442/25,654 (1.7%)
1998	Japan (Tochigi)[42]	NR	NR	72/1,941 (3.7%)
1998	Egypt (Mansoura)[43]	105/767 (13.7%)	NR	105/767 (13.7%)
1998	Spain (Granada)[44]	16/3,003 (0.5%)	NR	NR
1998	Italy (Florence)[6]	NR	NR	80/5,000
1999	Tanzania (Ifakara)[45]	49/980 (5.0%)	1/66 (1.5%)	48/914 (5.3%)
1999	Italy (Monza)[46]	63/16,271 (0.4%)	NR	NR
1999	India (rural setting)[47]	0/46 (0.0%)	NR	NR
2000	Italy (Milan, Bergamo)[48]	370/15,250 (2.4%)	NR	NR

* not recorded

reliable reporting has existed since the early 1990's: numbers are still showing an annual rise. This is perhaps not surprising, given that the progression of this chronic disease is usually slow. Indeed it may not manifest in the first two decades of infection, and many cases in Canada may have been acquired in the remote past. The rise may also be related to factors such as increased availability of testing, improved sensitivity of tests, and a greater public awareness of the disease, leading to an alteration in test seeking behaviours. The total number of notifications across Canada has risen from 1,321 in 1992 to 19,571 in 1997. For women of all ages the notifications have risen from 482 in 1992 to 6,977 in 1997.[2]

Certain population subgroups are at much higher risk of being infected with HCV. In 1994, 71 percent of individuals with HCV had a history of using injection drugs and 28 percent a history of blood transfusion.[49] Interim data from a recent LCDC study of Canadian street youth showed 4.4 percent (range 0-9.2%) of individuals tested to be positive for HCV[50] and a similar study in Montreal, a prevalence of 12.6 percent (95% CI: 9.7-15.9%).[51] Preliminary data suggests that aboriginal populations, both urban and rural, have a 15 to 20 percent positivity rate for anti-HCV antibodies.[52]

2. Pregnant population

Many series of anti-HCV antibody seroprevalence in pregnant women have been published around the world, some of which have also taken into account the co-existence of human immunodeficiency virus (HIV) (Table III).

However, there is very little published data for seroprevalence and incidence of hepatitis C infection during pregnancy in Canadian women. The only serosurvey of a general population of pregnant women in Canada was done on 15,000 prenatal sera in British Columbia in 1994 and reported a seroprevalence rate of 0.9 percent (95% CI: 0.76-1.1%[53]). Unpublished data from Vancouver suggests that up to 54 percent of women with HIV are also infected with HCV.[54] The majority (63%) of these HIV positive women are injection drug users.[54] In Montreal, however, the percentage of injection drug users is smaller (18.5%) with the majority of HIV positive women coming from endemic countries (57.4%). In this last cohort, the prevalence of positive hepatitis C serology is 21 percent.[55]

A study of non-pregnant women of childbearing age in Canada reported a prevalence of 0.58 percent. An extrapolation from data obtained from the current population of new blood donors in Canada would suggest a seroprevalence of 0.2 percent.[56] However, it is doubtful that this figure could be applied directly to a population of pregnant women.

There is some data to suggest that women from aboriginal populations and inner city groups are over-represented in infected cases. The prevalence of HCV infection is highest in the 20 to 24 year age group and 50 percent more prevalent in urban areas compared with rural. However, as yet, this data is incomplete.

B. MODE OF TRANSMISSION

Table IV lists sources of acquisition of HCV identified by the World Health Organization.[8] It is important to remember that immigrants may have encountered either unusual or exposure-prone procedures with a higher risk prior to arriving in Canada. A proportion of patients with HCV do not fall into any currently recognized risk group.

Tests for HCV became commercially available for use in 1990, facilitating the demonstration of hepatitis C transmission routes.[57] These routes are similar to those for other bloodborne pathogens such as hepatitis B virus (HBV) and HIV, although the frequencies differ. However, the individual risks for some of these routes still need to be accurately defined. The risk of a person becoming infected with HCV will depend on the type of exposure.

1. Injection drug use

The most significant mode of transmission of hepatitis C in Canada now is injection drug use. The rate of infection in those who have *ever* used injection drugs is at least 30 percent.[1,3,58] Up to two thirds of users seroconvert within the first year of use. HCV is not only associated with chronic use and may be contracted even by those who have injected only a few times. The evidence for transmission with the use of inhaled drugs, such as intranasal cocaine, is controversial. It is not clear whether this is an independent mode of transmission via shared use of contaminated straws or a marker for injection drug use.

TABLE IV

SOURCES OF ACQUISITION OF HEPATITIS C VIRUS

High Risk (over 20%)
- Injection drug users
- Recipients of unscreened blood products
- Transfusion of blood products that did not undergo viral inactivation

Moderate Risk (1-20%)
- Newborns of HCV positive mothers
- Persons undergoing chronic haemodialysis
- Recipients of blood from unscreened donors
- Recipients of organ transplants
- Parenteral exposure through the use of contaminated or inadequately sterilized instruments/needles in medical/dental procedures

Low risk (below 1%)
- Persons engaged in high risk sexual activity
- Sexual partners of HCV positive individuals
- Rituals (such as circumcision, scarification, excision), traditional medicine (such as blood letting), other skin breaking activities (such as ear and body piercing)
- Tattooing not carried out in properly regulated premises
- Household contact

2. Blood/blood product transfusion

In Canada the risk of infection through blood transfusion has been reduced, although not eliminated, by the testing of donors for HCV. In fact, even prior to 1990 and the introduction of screening, the risk had started to fall because of changes in donor screening practices. After testing for hepatitis B became available in the early 1970's, the virus that was later identified as hepatitis C became the most common cause of post-transfusion hepatitis. Currently the risk stands at one in 103,000 per unit of blood transfused, with the likelihood of further reduction as the more sensitive nucleic acid testing is introduced (Table V).[2] However, it must be remembered that in some countries with a higher prevalence in the donor population, the risk may be greater depending on the testing modalities used. The chance of becoming infected with HCV from an infected unit is over 90 percent.

3. Needle stick injury with an HCV contaminated sharp

The occurrence of infection after a needle stick accident with an HCV contaminated sharp has been reported as about four percent (see Section IX: Occupational Exposure).

4. Vertical transmission

For the risk of transmission from mother to child please refer to Table VI, although caution should be applied in interpreting some of the early data. The risk of vertical transmission ranges from zero to 80 percent. Merging the data from these studies gives a crude vertical transmission rate of 7.9 percent (179/2,264). If the mother is co-infected with HIV, the risk of HCV transmission has been observed to increase up to 60 percent. Vertical transmission seems to be directly related to the presence of circulating HCV RNA in the maternal blood during pregnancy.[7,32,59-61]

5. Breastfeeding

A few researchers have reported the presence of HCV RNA in breast milk. When present, it has been in much lower concentrations than in the blood. The importance of these findings is not yet clear and while there is a theoretical risk of transmission, no case has yet been reported (see Section V.B.7: Breastfeeding and VII. D: Principles of prescribing in HCV infected women).[36,62]

TABLE V

CHANGE IN INCIDENCE OF POST-TRANSFUSION HEPATITIS

	Incidence
Mid 1980's	3.1% per transfusion event*
Late 1980's	1.3% per transfusion event*
Early 1990's	0.6 per 1,000 blood units tranfused, 0.5%-0.8% HCV+**
Present	1 in 103,000 per blood unit transfused

* receipt of transfusion with mean of 3.5 units
** personal communication with Canadian Blood Services

6. Sexual transmission

The risk of sexual transmission is very low. HCV has been found infrequently in semen of men co-infected with HIV. The rate of transmission has been controversially estimated at about 2.5 percent for prolonged sexual exposure (>20 yrs) to infected individuals. There are many cohorts of haemophiliacs and their partners with supporting negative data. Another study found that having had intercourse with an injection drug user was independently predictive of HCV infection. Women with multiple sexual partners may be more likely to acquire HCV; a study looking at prostitutes not using condoms reported a higher incidence of HCV, even adjusting for IVD use.[63] There is no data for transmissibility during menstruation or anal intercourse, although it is noted that in homosexual men, the transmission rates are not comparable to those those of HIV. Similarly, the risk of transmission with the shared use of sex toys is unknown. There is no data on the risk for lesbian transmission, although there is some data suggesting that the rates in women with HIV are very low and are, therefore, likely to be lower still with HCV.

7. Rh immunoprophylaxis

Studies of two large cohorts of women infected following contaminated Rh immunoprophylaxis documented a lack of transmission after 7,000 person-years of unprotected sexual activity, again supportive of a minimal risk.[64] The currently used preparation for Rh immunoprophylaxis (Winrho SDF™ as well as the previously used Winrho™) is devoid of risk from known viral bloodborne pathogens, including HCV, due to modern purification processes.

8. Transmission between family members, household contact

General household contact is not thought to be a risk. Where familial transmission has been observed, such transmission may have been due to inadvertent blood contact (razor, toothbrush), but there is no evidence to implicate the use of these items. HCV antibodies and HCV RNA have both been detected in saliva. However, they are not predictably present and the implications for transmission are not clear.

IV. VIROLOGY, CLINICAL MANIFESTATIONS, COURSE OF DISEASE

There are very few studies defining the natural history of HCV infection, and those available do not always take into account the genotype, geographical area or therapeutic intervention. The long evolution of the disease also makes study design difficult. Despite these limitations, a significant amount of information has been accumulated.

TABLE VI

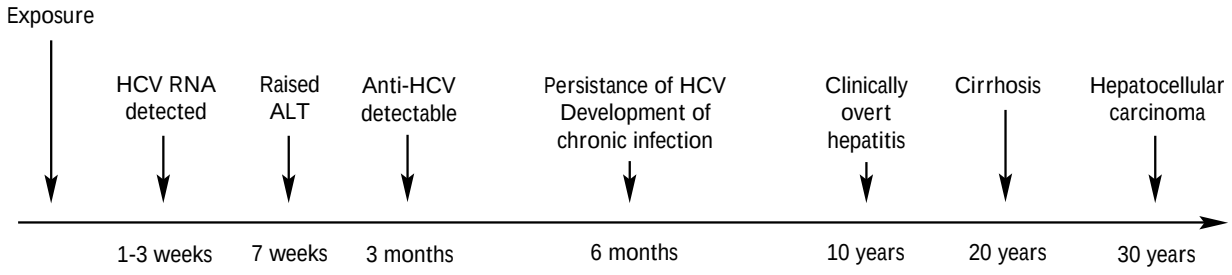
POPULATION STUDIES SHOWING VERTICAL TRANSMISSION RATES OF HEPATITIS C: TOTAL VERTICAL TRANSMISSION AND ACCORDING TO HIV STATUS

YEAR OF PUBL.	COUNTRY	TOTAL STUDY POPULATION	TOTAL HCV RNA POSITIVE	HIV POSITIVE	HIV POSITIVE HCV RNA POSITIVE	HIV NEGATIVE	HIV NEGATIVE HCV RNA POSITIVE
1991	USA (San Francisco)[65]	7/10 (70.0%)	NR*	3/5 (60.0%)	NR	4/5 (80.0%)	NR
1992	Sweden (multicentre)[66]	1/21 (4.8%)	1/21 (4.8%)	NR	NR	1/21 (4.8%)	1/21 (4.8%)
1992	USA (New York)[12]	0/24 (0.0%)	0/16 (0.0%)	0/4 (0.0%)	NR	0/20 (0.0%)	NR
1993	France (Clichy)[18]	0/13 (0.0%)	0/10 (0.0%)	NR	NR	0/10 (0.0%)	0/10 (0.0%)
1993	France (Paris)[17]	0/18 (0.0%)	0/8	NR	NR	0/18 (0.0%)	0/8 (0.0%)
1993	Japan (Kuruke)[16]	0/26 (0.0%)	NR	NR	NR	NR	NR
1993	Scotland (Edinburgh)[67]	4/66 (6.1%)	NR	NR	NR	NR	NR
1994	Japan (multicentre)[21]	3/54 (5.6%)	NR	NR	NR	NR	NR
1994	Japan (multicentre)[21]	1/6 (16.7%)	NR	NR	NR	NR	NR
1994	Taiwan (Taipei)[20]	1/15 (6.7%)	NR	NR	NR	1/15 (6.7%)	NR
1994	Taiwan (Taipei)[68]	NR	NR	NR	NR	2/11 (18.2%)	NR
1995	Italy (Milan)[69]	6/37 (16%)	6/21 (28.6%)	4/20 (20.0%)	4/13 (30.8%)	2/17 (11.8%)	2/8 (25.0%)
1995	Italy (Milan)[70]	14/70 (20.0%)	9/23 (39.1%)	12/53 (22.6%)	NR	2/17 (11.8%)	NR
1995	Italy (Milan)[26]	8/116 (6.9%)	8/64 (12.5%)	8/22 (36.4%)	8/18 (44.4%)	0/94 (0.0%)	0/49 (0.0%)
1995	Italy (Pavie)[71]	17/53 (32%)	NR	14/32 (44%)	NR	3/21 (14.3%)	NR
1995	Italy (Torino)[29]	1/45 (2.2%)	0/43 (0.0%)	1/18 (5.6%)	0/8 (0.0%)	0/27 (0.0%)	0/19 (0.0%)
1995	Japan (multicentre)[28]	2/163 (1.2%)	2/87 (2.3%)	NR	NR	NR	NR
1995	Japan (Tsukuba)[25]	3/31 (9.7%)	3/21 (14.3%)	NR	NR	3/31 (9.7%)	NR
1996	Italy (Chieti)[32]	3/30 (10.0%)	3/10 (30.0%)	NR	NR	3/30 (10.0%)	3/10 (30.0%)
1996	Italy (Udine)[33]	NR	NR	NR	NR	0/25 (0.0%)	0/18 (0.0%)
1996	Sweden (Stockholm)[72]	0/58 (0.0%)	NR	0/2	NR	0/53 (0.0%)	NR
1997	Australia (Camperdown)[73]	NR	6/63 (9.5%)	NR	NR	6/89 (6.7%)	6/63 (9.5%)
1997	Germany (Hamburg)[74]	6/120 (5.0%)	NR	1/6 (16.7%)	NR	NR	NR
1997	Italy (multicentre)[75]	28/245 (11.4%)	NR	25/165 (15.1%)	NR	3/80 (3.7%)	NR
1997	Japan (Kurume)[36]	0/11(0.0%)	NR	NR	NR	NR	NR
1997	Spain (Seville)[34]	6/50 (12.0%)	6/33 (18.2%)	NR	NR	NR	NR
1997	U.A.E. (Al-Ain)[35]	20/65 (30.8%)	20/65 (30.8%	NR	NR	20/65 (30.8%)	20/20 (100.0%)
1998	Australia (Melbourne)[76]	NR	NR	NR	NR	3/91 (3.3%)	NR
1998	Egypt (Mansoura)[43]	2/67 (3.0%)	2/18 (11.1%)	NR	NR	2/67 (3.0%)	2/18 (11.1%)
1998	Italy (Brescia)[77]	6/70 (8.6%)	6/63 (9.5%)	4/22 (18,2%)	NR	2/48 (4.2%)	NR
1998	Italy (Florence)[41]	NR	13/275 (4.7%)	NR	NR	13/403 (3.2%)	NR
1998	Italy (Florence)[6]	2/80 (2.5%)	2/56 (3.6%)	NR	NR	2/80 (2.5%)	2/56 (3.6%)
1998	Italy (Genoa)[38]	NR	4/45 (8.9%)	NR	NR	4/60 (6.7%)	NR
1998	Italy (multicentre)[78]	17/291 (5.8%)	17/207 (8.2%)	9/40 (22.5%)	9/32 (28.1%)	8/251 (3.2%)	8/175 (4.6%)
1998	Japan (Tochigi)[42]	NR	NR	NR	NR	4/65 (6.2%)	4/55(7.3%)
1998	USA (multicentre)[39]	NR	NR	13/155 (8.4%)	13/140 (9.3%)	NR	NR
1998	USA (New York)[79]	7/122 (5.7%)	NR	5/73 (6.8%)	NR	2/49 (41%)	NR
1998	USA (New York)[80]	NR	NR	9/62 (16.4%)	NR	NR	NR
1999	Germany (Hamburg)[81]	3/90 (3.3%)	NR	NR	NR	NR	NR
1999	Italy (Naples)[82]	2/22 (9.1%)	2/14 (14.3%)	2/8 (25.0%)	2/5 (40.0%)	0/14 (0.0%)	0/9 (0.0%)
1999	Tanzania (Ifakara)[45]	1/35 (2.9%)	NR	NR	NR	1/35 (2.9%)	NR
2000	Italy (multicentre)[48]	8/155 (5.1%)	NR	NR	NR	NR	NR
	Totals	179/2,264 (7.9%)	110/1,155 (9.5%)	110/685 (16%)	36/216 (16.7%)	87/1,812 (4.8%)	48/539(8.9%)

* not recorded

FIGURE 2

TIME COURSE OF HCV INFECTION AND ITS COMPLICATIONS



A. THE ORGANISM

Hepatitis C virus is a single stranded RNA, enveloped virus from the *Flaviviridae* family. It is characterized by a wide range of genomic heterogeneity and multiple distinct types (Table VII). For each of these genotypes several subtypes exist, differing from each other by about 20 percent of their sequence. The generally accepted classification scheme describes six major genotypes and over 30 subtypes.[3,83,84] In North America types 1a and 1b are the most common in non-migrant people, but there are regional variations. Immigrants to Canada may have acquired different genotypes in their country of origin. The subtypes are also geographically distributed. After infection the virus has been shown to mutate into genetically distinct populations referred to as "quasi species," which carries important consequences for the development of chronic disease, immune response, and vaccine development. HCV does not seem to induce an effective, protective immune response.

HCV is easily destroyed by heat and is probably quite an unstable virus. Although survival in the environment is not known, the modes of transmission do not suggest fomite survival.

B. NATURAL HISTORY

The natural history of HCV infection is complex. Due to the paucity of symptoms in the acute phase, early diagnosis of the disease is often not possible. In addition, most infected patients remain asymptomatic for years. In general, the course of HCV infection is slowly progressive. About 15 percent of HCV infected individuals recover spontaneously; an additional 25 to 30 percent have an asymptomatic illness with persistent normal aminotransferases and generally benign histological lesions; hence about 40 percent of patients recover or have a benign outcome.[3] For some, however, HCV is a chronic, debilitating, symptomatic disease.

TABLE VII

CHARACTERISTICS OF HCV

- single stranded RNA virus
- enveloped
- six major genotypes
- at least 30 subtypes
- produces "quasi species" or diverse populations in the same individual patient

1. Course of infection

See Figures 2 and 3.

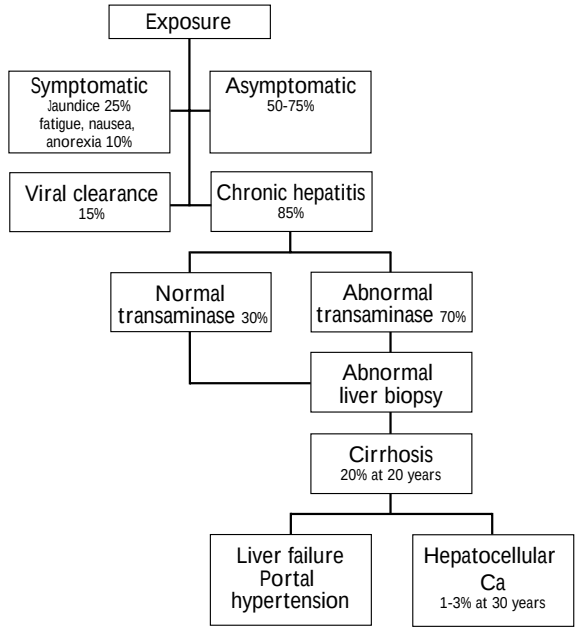
2. Pathology

a) Liver biopsy: liver biopsy features may be categorized into lobular and portal tract changes. Tissue is described by grade of inflammation (mild, moderate, severe) and stage of fibrosis from 0 (no fibrosis) to 4 (cirrhosis).

- **lobular changes** suggest widespread liver damage. HCV antigen and RNA can be isolated in the cytoplasm of infected cells. Cellular atypia may also be present and may represent a precursor to the development of carcinoma.

FIGURE 3

POSSIBLE SEQUELAE OF EXPOSURE TO HCV



- **portal tract changes** include nodular aggregates of lymphocytes in germinal centres and bile duct lesions.

The basic cellular damage from HCV probably occurs through an immunologic pathway, although a direct cytopathic effect may play a more minor role.

b) Liver function: most patients with chronic HCV will have raised aminotransferase levels, although this does not appear to correlate with disease severity or progression.

Thirty percent of patients with HCV RNA may, however, have normal transaminases, and despite this still have significant histopathologic changes on liver biopsy. The long-term prognosis for this particular group remains uncertain but would appear to be less severe.

C. SEQUELAE

1. Hepatic complications

a) Cirrhosis: cirrhosis will occur in about 20 percent of chronically infected patients. The mean interval between exposure and development of cirrhosis ranges from three to 44 years and appears to be longer in patients with histologically diagnosed mild activity compared to those with a higher grade of inflammation, especially if severe. It is generally agreed that cirrhosis is a late manifestation and unlikely to occur before the first decade post-exposure. Liver biopsy is useful to stage disease in those with HCV RNA and elevated transaminases, and is the only reliable method to diagnose cirrhosis as there may well be no other clinical evidence. The presence of severe fibrosis and necroinflammatory changes is predictive of the development of cirrhosis.[3,58] The prognosis is also linked to the severity of fibrosis as a function of time or duration of disease. The main complication of cirrhosis is portal hypertension leading to bleeding œsophageal varices, ascites, and hepatic failure.[85-87]

b) Hepatocellular carcinoma: hepatocellular carcinoma may develop with further disease progression as a late and infrequent manifestation in cirrhotic patients. It occurs with an annual incidence of approximately one percent of those with cirrhosis, although rates vary with geographical location and have been reported as high as 11 percent. It has been shown to occur from 15 to more than 45 years post-exposure. The pathophysiology remains unclear, with repeated necroinflammatory insults and a direct carcinogenic effect of HCV both being postulated.[88]

2. Extra-hepatic complications

HCV infection has also been associated with several conditions, possibly by triggering an autoimmune response:

- cryoglobulinaemia (essential mixed type II)
- membranous glomerulonephritis
- porphyria cutanea tarda
- aplastic anaemia

Associations have also been suggested with Sjögren's disease, Mooren's corneal ulcer, B-cell non-Hodgkin's lymphoma, thyroiditis, and immune thrombocytopenic purpura.[1,89-91]

D. CO-FACTORS

The natural history of HCV may be influenced by the presence of viral and host factors.[84,92]

1. Viral load/viraemia

There is no clear correlation between the level of HCV RNA, genotype, and disease progression. Quantitative HCV RNA levels and genotype are used to determine treatment protocol. In general, patients with higher levels of viraemia (more than 2 million copies/ml) are relatively less likely to respond to therapy, as are those with genotype 1 compared to genotype 2 or 3. Therefore, duration of treatment for types 2 or 3 is six months regardless of the level of viraemia. In patients with type 1, current data suggests that six months treatment is sufficient if there is a low level of viraemia, but 12 months is required if high.[84,92]

2. Histology

Higher necroinflammatory grading or fibrosis appears to be associated with accelerated progression to cirrhosis. In cases of severe inflammatory changes, a risk as high as 90 percent for the development of cirrhosis has been reported.[84,92]

3. HIV co-infection

Recent reports have shown the negative effects of co-infection with HIV and are thought to indicate a poorer prognosis for both diseases. It is suggested that, in the presence of HIV, HCV behaves as an opportunistic infection in which progressive liver disease is the principal manifestation. It has been shown that HIV positive patients who acquire HCV have a higher risk of developing progressive liver disease, and those with AIDS-defining immunodeficiency higher still. In addition, patients co-infected with HCV and HIV who also have progressive liver disease have a more rapid progression to AIDS. The interactions between these two viruses are complex and should be managed by experts in the field.[58,84,92]

4. Alcohol

Consumption of alcohol is the most important external co-factor for disease progression, both in biochemical and histological severity. Consumption of more than two units per day increases the rate of progression to cirrhosis threefold. For this reason, abstinence is strongly advised. (A unit is equivalent to one glass of wine or a half pint of beer.)

E. GENDER AND AGE EFFECTS

1. Gender

In most adult studies, male sex has been associated with greater disease severity. The potentially more benign course in young women is supported by two studies of women who became infected following Rh immunoprophylaxis prior to the availability of a

TABLE VIII

LONG-TERM OUTCOME FOR WOMEN INFECTED WITH HCV

	Kenny-Walsh[93]	Wiese[94], Muller[95]
n	376	350
Years at follow-up	17 years	10, 18 years
Incidence chronic hepatitis	90% (mild, moderate)	62% (10 yrs) 49% (18 yrs)
Cirrhosis	2.4%	0%
Hepatocellular carcinoma	0%	0%

purification process.[82,92] The researchers reported that although most infected women developed chronic hepatitis, it was usually not severe and the incidence of complications such as cirrhosis was very low, even after many years of follow-up (Table VIII).

2. Age

Advancing age has been associated with increased histological severity and a possible decreased interval to the development of late manifestations such as cirrhosis.[82]

F. PREGNANCY

Currently there is no data to suggest that pregnancy alters the course of HCV. Indeed, most pregnant women are asymptomatic and only a minority (10%) have elevated transaminases. It has been hypothesized that endogenous production of interferon, partly by the fetoplacental unit, may account for the lower levels of transaminases in pregnant women.[5,96-100] There does not appear to be an increase in frequency of adverse pregnancy outcomes in women with HCV. Vertical transmission, however, is a risk, and so far it would appear that most children infected in this way develop chronic hepatitis.

G. INFECTION IN CHILDREN

Infection in children is acquired either by transfusion (although this has become very rare in the era of systematic screening for HCV infection in all blood donations) or by perinatal transmission from an infected mother. Recent studies with long-term follow-up of children infected by either mechanism have shown that infection in children is associated with milder disease than infection in adults.[5,100-102] The clinical course in these children is characterized by low or normal transaminase levels, less severe histological changes and a lower percentage with persistent presence of HCV RNA. Follow-up in some of these studies is close to twenty years. However, some children have fibrosis on liver biopsy and fibrosis progresses with age and duration of illness. Thus, it is possible that some individuals infected in early childhood will eventually progress to end stage liver disease.[101,103,104]

V. ASSESSING A WOMAN'S RISK FOR HCV

A. SCREENING

1. Universal screening

The screening of medical disorders usually requires that certain conditions be present (Table IX). Although HCV is of major public health importance, universal screening is not currently recommended in Canada.[2] However, this policy may change with new developments in the field of HCV infection and universal screening may become invaluable to the general population.[84,105,106] The prevalence remains low in both the general (1-3%) and pregnant (0.68-4.5%) populations. Antibody screening tests are available but do not differentiate between acute and chronic infection. Interferon and ribavirin therapy has shown some encouraging results but the response to treatment is neither universal nor sustained in the general population. At the moment there is insufficient data on the safety of interferon in pregnancy. **Ribavirin is a known teratogen.** There are no documented measures capable of influencing maternal-fetal transmission. However, there may be great benefit from counselling regarding risk reduction strategies including abstinence from alcohol consumption, immunization against hepatitis A and B, and for injection drug users, needle exchange programmes, alternative routes of administration or methadone maintenance therapy.

2. Targeted screening

For the above reasons, a targeted screening approach has been adopted by Health Canada and individuals listed in Table X should be counselled in favour of screening.[2] Similarly, routine screening is not currently recommended in pregnancy but women falling into these categories should be offered testing. Even with this approach, between 40 and 60 percent of infected women will remain unidentified.

B. COUNSELLING

The health care provider has a unique and integral role to play in providing women living with HCV with clear, evidence based information regarding hepatitis C infection.

1. Emotional and psychosocial issues

The emotional and psychosocial impact of a diagnosis of hepatitis C on a woman and her family should not be underestimated. Some will take the diagnosis in stride but for others the knowledge will

TABLE IX

CONDITIONS FOR USE OF A SCREENING TEST

- Disease must be of public health importance
- A sensitive and specific test must exist for its detection
- Therapeutic and preventive measures must be available
- Direct and indirect screening costs must be acceptable to the individual and society

TABLE X

INDIVIDUALS TO BE OFFERED SCREENING FOR HCV

- Injection drug user—this should include anyone who has ***ever*** injected drugs
- Patient on haemodialysis
- Patient with persistently elevated ALT
- Recipients of clotting factor concentrates before 1988*
- Recipients of blood components or solid organs before 1992*
- Recipients of blood components or solid organs from HCV (+) individual
- Person with significant exposure to blood of HCV (+) individual or that of individual at high risk
- Prisoners in correctional facilities
- Infants of HCV infected mothers
- Older children of HCV(+) mothers if there is reason to believe vertical transmission may have occurred
- HIV positive individuals
- Individuals with tattoos (especially performed in prisons)

* applicable dates in Canada

be devastating and more damaging than the actual disease. The general lack of knowledge concerning HCV infection among medical practitioners and the public, and the way in which the "bad news" is broken, will both influence the subsequent course. There are many fears that may need to be addressed: about health and life, about transmission and relationships with loved ones, and about stigma or discrimination. There may also be a sense of guilt and feelings of violation.

Prior to testing, the patient's perceived risk of infection should be established, possible symptoms assessed, and level of knowledge concerning HCV transmission and prevention ascertained. The patient should be adequately counselled prior to testing. The tests should be explained and a discussion of how the patient might cope with a positive result should take place. Referrals to support sources should be made and the possible implications of informing others with respect to relationships, jobs or life insurance be discussed. Emphasis should be given to the fact that HCV does not necessarily pose an immediate threat to life. The opportunity to discuss healthy lifestyles and harm reduction behaviour should be taken.

The diagnosis should always be delivered personally to the patient in a sensitive, supportive manner by a well informed health care provider, allowing sufficient time for questions. Results should never be communicated by telephone, answering machine or through a receptionist. During the consultation, the patient's understanding of a positive diagnosis should be checked. Assurance that shock is a common reaction should be given. A further discussion of features of the illness, diagnostic procedures, and medical care may be necessary. Referrals to support resources in the form of both professional and self-help organizations will be invaluable, as will written information. Follow-up appointments should be offered for further discussion. Partners, family, and friends should be invited to attend if appropriate.[106,107]

2. Risk reduction behaviours

These should be discussed with all patients with HCV as appropriate in a sensitive fashion (Table XI).

3. Gynaecological issues

a) General points: the effects of HCV on a woman's reproductive health will depend on the status of her disease. In the absence of significant liver disease there may be no symptoms. However, if significant liver disease or cirrhosis are present, abnormal menstrual cycles or infertility may be seen, secondary to anovulation. If cirrhosis has resulted in chronic estrogen excess, dysfunctional bleeding or endometrial hyperplasia may also be seen. Indeed, any of these symptoms may be a presenting feature of HCV infection.

It may be important at initial diagnosis, especially if infection is occurring in the context of injection drug users or multiple partners, to seek out and treat coincident sexually-transmitted pathogens. It is recognized that women on interferon therapy commonly suffer recurrent yeast infections. Recommendations for Pap smears remain unchanged.

TABLE XI

RISK REDUCTION BEHAVIOURS

- Current IV drug users should be offered participation in needle exchange programmes, treatment programmes, with discussion of needle sharing, needle cleaning*, etc. Remember that many patients may not be current users
- Alcohol consumption should be discussed and abstinence advised
- Recommend vaccination against hepatitis A and B if the patient is non-immune
- Involvement in a support group is of great value
- Social, educational, and employment activities should continue as normal
- Encourage safer sexual practices in those with multiple partners. There is insufficient evidence to recommend changes in current sexual practice in long-term monogamous relationships
- Refrain from blood, organ, tissue or semen donation
- The sharing of razors and toothbrushes should be avoided, although there is no evidence to suggest that general household contact may lead to transmission.
- Tattooing in unlicensed parlours not adhering to recommended Health Canada infection control guidelines may carry a small risk of transmission and should be avoided.

* not recommended as a good preventive measure, a last resort only.

b) **Contraception:** there are no contraindications to **barrier methods** of birth control or to the **intrauterine device**. Couples in exclusive, monogamous relationships should be advised that sexual transmission is uncommon. In the context of multiple sexual partners, condom usage should be encouraged.

Progesterone only based contraceptives would be appropriate for women with HCV.

Combined pills may be prescribed to most women infected by HCV with the exception of those with cirrhosis or hepatic failure when hepatic metabolism may be altered. There is no evidence that hormonal contraceptives further compromise the infected person who has a functional liver.

c) **Hormone replacement therapy:** there is little information on the effects of hormone replacement therapy on women with HCV. Oral preparations are metabolized in the liver and the presence of liver dysfunction may significantly alter pharmacokinetics. Given that these preparations may be used continuously for many years, regular evaluation of liver function (as recommended for all HCV patients) should accompany their use. Consideration could be given to the use of transcutaneous preparations which avoid the first pass effect in the liver. Recommendations should be tailored to the individual based on the need for hormone therapy and the liver function. Consultation with a colleague with expertise in the management of liver disease should be sought.

d) **Assisted reproduction:** women living with HCV who desire medical or surgical assistance with reproduction will need counselling regarding the issues related to HCV infection.

All HCV positive women should be offered preconception counselling. If **ovulation induction** is required, carefully monitored **clomiphene** therapy may be considered except in cases of severe liver dysfunction. The use of **gonadotropins** for ovulation induction should only be carried out in consultation with a reproductive endocrinologist, but would not necessarily be contraindicated in the context of HCV infection.

In vitro fertilization or **intrauterine insemination** is not contraindicated for an HCV positive woman. However, ethical dilemmas arise in discordant couples where the male partner is infected and the woman is not. As HCV has been detected in semen, and although purification of the semen with standard sperm washing techniques appears to decrease the viral load but not eliminate it,[108] there is a concern that HCV transmission will occur during the assisted reproductive process. Unfortunately this particular mode of transmission has not been well studied and there are no accurate figures to report. The current Canadian Fertility and Andrology Society guidelines exclude semen donors who are hepatitis C positive.[109] Individual infertility clinics have specific policies regarding treatment. All women seeking these therapies should be aware of the risk of becoming infected with HCV and fully informed consent obtained.

4. Effect of HCV infection on pregnancy

Although there is currently little data on HCV infection in pregnancy, the available data does not suggest an increased risk of congenital malformation, fetal distress, stillbirth or prematurity. Women with HCV and their fetuses are at no greater risk of obstetric or perinatal complications compared with other women. There is no contraindication to pregnancy on the grounds of HCV alone.[100,110-112]

5. Effect of pregnancy on HCV

Very little is reported on the effects of pregnancy on the course of HCV infection. The majority of women appear to be unaffected. Fewer than ten percent display elevated transaminases, and in most cases a decrease in ALT during pregnancy has been noted with a rebound postpartum.[100,112] It is postulated that endogenous production of interferon by the fetoplacental unit may play a role in the benign course of disease during pregnancy. Cholestasis of pregnancy may be more common among HCV infected women.[46] Rarely, women may present with advanced liver disease and complications such as oesophagal varices and coagulopathy, posing risks for bleeding with delivery and the possibility of variceal rupture. These cases should be managed in tertiary care settings.

6. Effect on the neonate

Reported rates of vertical transmission vary from zero to 36 percent, with an average of five to six percent in otherwise healthy women.[4,6,7,63] The risk of transmission in those also infected with HIV is up to 44 percent (Table VI). Although the available evidence points to the intrapartum period as the main time of transmission, the relative importance of intrauterine versus intrapartum transmission remains to be established. Several studies have documented a significantly greater risk of vertical transmission with maternal HCV viral copies above 1,000,000/ml.[21,110] A transmission risk of about five percent is generally reported, but it may be as high as 36 percent in the presence of a high maternal viral load.[21]

HCV has not been shown to be teratogenic. Infants born to HCV positive mothers do not show any more neonatal complications than other infants with the same risk factors (such as prematurity, born to injection drug users). Children who become infected are likely to become chronically so. It should be noted that all neonates will have detectable maternal antibodies. For details concerning the testing of infants please see Section VIII.E.2: Infant testing.

7. Breastfeeding

HCV RNA and anti-HCV antibodies have both been detected in colostrum and breast milk.[36,62] However, in multiple series no case of transmission through breastfeeding has been documented. Therefore, it is generally felt that breastfeeding is not contraindicated.

VI. DIAGNOSTIC TESTS

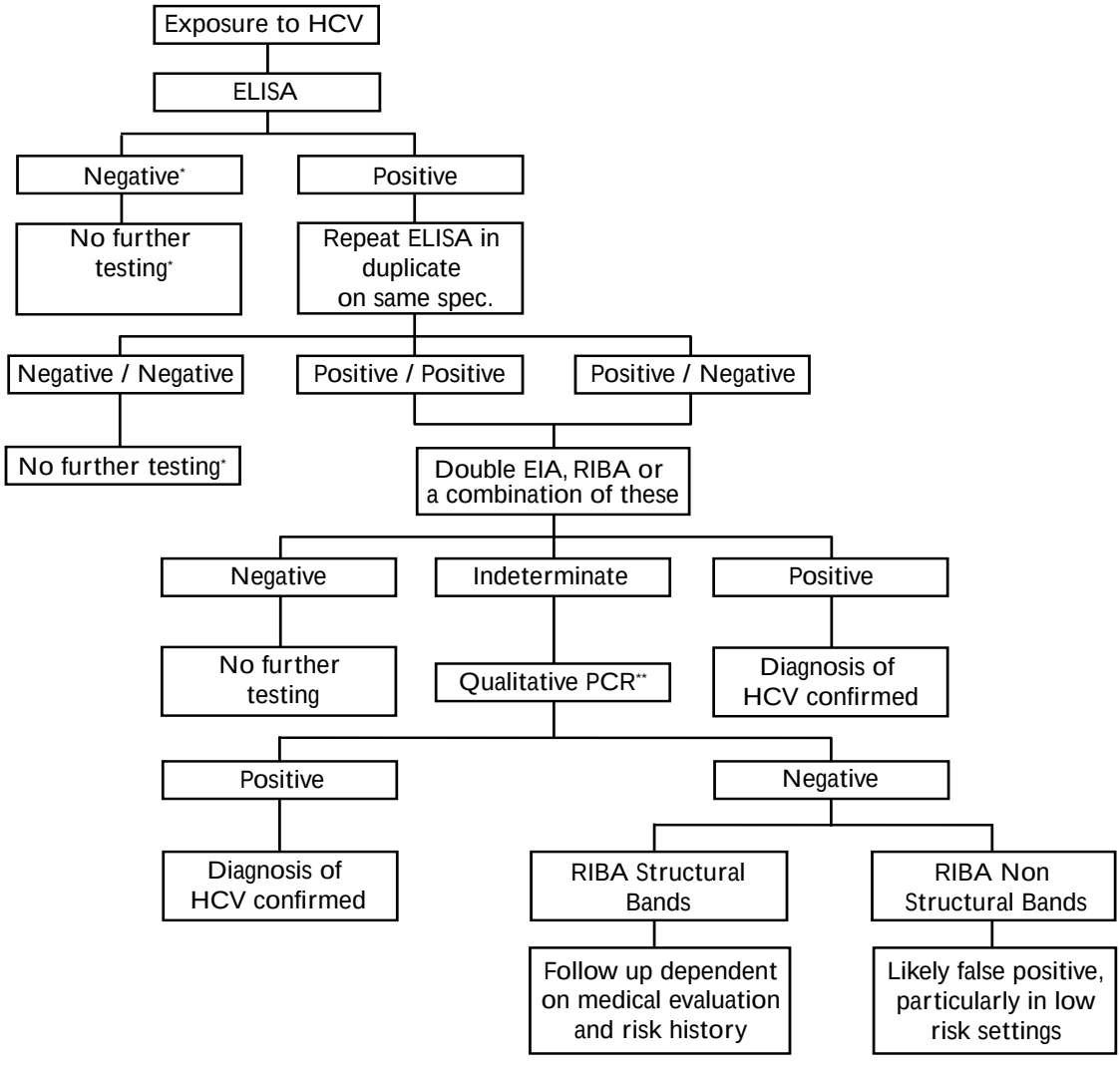
A. SEROLOGY

Screening of individuals for HCV relies on the detection of HCV antibodies using enzyme immunoassays (EIA) to detect antibodies to specific recombinant HCV antigens. Third generation ELISA screening is currently used routinely throughout Canada. It is reliable in most immunocompetent people who replicate HCV but is less sensitive in haemodialysis and immunocompromised patients. Over 90 percent of tests will be positive in the presence of established infection, with the test becoming positive approximately three months after exposure. False positives may occur in the presence of rheumatoid factor and false negatives are generally explained by the timing of the test. Patients with indications for screening who were tested prior to the general introduction of third generation ELISA screening may benefit from re-testing.

To make a definitive diagnosis, the ELISA should be repeatedly reactive and followed by a positive confirmatory test involving either a RIBA, a two ELISA algorithm or a nucleic acid amplification test (Figure 4).[2]

FIGURE 4

ALGORITHM FOR SCREENING FOR HCV INFECTION



* Unless exposure occurred in the last 3 months.
** Newborns of HCV positive mothers can only be diagnosed accurately using qualitative PCR. Immunocompromised and haemodialysis patients can also require qualitative PCR.
Adapted from: LCDC, CCDR 1995;21(S2):15.

B. QUALITATIVE POLYMERASE CHAIN REACTION (PCR)

Qualitative HCV RNA testing must be performed in individuals with confirmed anti-HCV antibodies in the presence of normal ALT. It is not usually necessary where ALT is raised. This test may also be useful in the diagnostic evaluation of immunocompromised patients and can be used to detect HCV in infants of HCV positive mothers where a positive anti-HCV result may represent persisting maternal antibodies.

C. QUANTITATIVE PCR AND GENOTYPING

These are not routine tests and are only recommended to tailor therapy to the individual patient. Quantitative PCR is being used as a research tool to assess the risk of transmission but the results are not yet transposable to clinical practice.

VII. THERAPEUTICS

A. GENERAL

HCV-infected women should be encouraged to have a normal well balanced diet and to restrict alcohol consumption to less than two units per day. Support or treatment programmes may be offered to that effect.

B. SPECIFIC ANTI-VIRAL THERAPY

Dual ribavirin and interferon therapy is the current standard treatment, and may give a superior response rate to interferon alone. A sustained response with long-term viral clearance is obtained in 30 to 40 percent of cases. Anti-viral treatment is not currently advocated in pregnancy and there is no evidence that interferon may affect vertical transmission rates.

Alpha interferon 2b three times a week has been shown to produce a five to 20 percent viral clearance. No teratogenicity or reproductive toxicity has been reported in human pregnancy despite an abortifacient effect in rhesus monkeys at 90 to 360 times the human dose. There may be a case for its use in pregnant women with advanced liver disease as part of a well-planned clinical research protocol. Inadvertent exposure in early pregnancy is probably not an issue.

Ribavirin is teratogenic and embryolethal in almost all species and is contraindicated for use in pregnant women. Inadvertent exposure may be an indication for termination although there is no actual data on which to draw at present. Women considering ribavirin therapy should be advised of the need for effective contraception.

C. MATERNAL IMMUNIZATION

As infection with HCV carries a significant risk of progressive liver disease, every effort should be made to avoid further conditions with the potential for liver damage. Serious consideration should be given to immunizing pregnant women against both hepatitis A and B. Superinfection with hepatitis A poses a serious threat to patients with chronic HCV. In a series published in 1998, 41 percent of superinfected patients developed fulminant liver failure, and all but one died.[113]

A combined vaccine is also available. For further information regarding these immunizations, please refer to the Canadian Immunization Guide[114] or the Health Canada websites (see Sections XII.A and B: On-line information sites).

D. PRINCIPLES OF PRESCRIBING IN HCV-INFECTED WOMEN

In the absence of cirrhosis, patients with chronic HCV infection should not be treated differently from the general population. Even in cases with cirrhosis, drug metabolism will be normal while liver function is maintained. Hepatic function should be assessed biochemically with INR, albumin, and bilirubin, and clinically with the presence or absence of ascites, encephalopathy, and portal hypertension. In the presence of an abnormality in one or more of these parameters, prescription of medication should be carefully considered in conjunction with a hepatologist.

VIII. CARE OF PREGNANT WOMEN LIVING WITH HCV

A. PRECONCEPTION CARE

Ideally prenatal care should begin at a preconception consultation with a physician knowledgeable in the management of hepatitis C or infectious diseases in pregnancy. It should involve a discussion of the natural history of the disease, implications for the pregnancy, consequences for the fetus, risk of vertical transmission, therapies, and risk reduction behaviours. Possible routes of infection should be discussed in a non-judgmental, sensitive fashion after having established rapport with the patient.

As in all preconception visits, a complete medical history and physical examination should be performed, but with particular reference to issues of importance to hepatitis C, including:

- Current medical history: diagnosis, stage, and course of disease, presence of complications
- Past medical history: other liver conditions
- Past obstetric history: transfusions, cholestasis, HELLP
- Drug history:
  - prescription medication that may be potentially hepatotoxic (see Section VII.D: Principles of prescribing in HCV infected women)
  - interferon and ribavirin therapy
  - non-prescription medication – acetaminophen
  - drug abuse – whether the patient has ever injected drugs
- Alcohol history: it is important to emphasize the negative effect of alcohol on the course of disease. Consumption above two units per day accelerates the progression of HCV infection and abstinence represents the best option for all women.
- Liver function: current test results should be obtained and reviewed with the woman.
- Immunity to hepatitis A and B should be determined and immunization offered as appropriate.

- Given that transmission may be related to the presence of circulating HCV RNA, a recent qualitative test may be of use in this discussion. If HCV RNA is negative, then the vertical transmission rate would appear to be decreased almost to zero. Quantitative tests are not yet validated for predicting individual risk. In view of the sophistication of these tests, their interpretation should probably be discussed with a specialist.
- Combined therapy must have been completed for at least six months before embarking on pregnancy.[115] The teratogenicity of ribavirin is well documented and inadvertent exposure should result in counselling regarding options. Pregnancy termination is an option to be considered. Information to help the patient receiving interferon consider options remains sparse.[116-119]

B. PRENATAL CARE

Women aware of their HCV positive status should consult their physician early during the course of pregnancy for comprehensive prenatal care. Early assessment of both general physical health and liver function will identify those patients most likely to benefit from a multi-disciplinary team approach. As only about 30 percent of the HCV infected population is aware of the diagnosis, early pregnancy is also an opportune time to identify further cases through risk assessment and targeted screening tests, as previously discussed.

1. General points

Prenatal care should follow standard guidelines with consideration given to the following points:

- It is worthwhile to continue to seek risk factors at initial and subsequent prenatal visits as previously discussed. Anti-HCV antibodies are not protective and the acquisition of different strains can and does occur, making the implementation of risk reduction strategies worthwhile.[120]
- Frequency of visits should be determined on an individual basis according to the medical and obstetric condition of the patient.
- Patients should refrain from consuming alcohol.
- It may be wise to avoid the use of drugs which are potentially hepatotoxic or require extensive metabolism in the liver during the pregnancy.

2. Laboratory investigations

In addition to routine prenatal laboratory investigations, the following specific tests should be requested in a patient with HCV in early pregnancy:

- Liver function tests, aminotransferases
- Albumin
- Bilirubin
- INR
- Anti-HBs
- Anti-HA total or IgG
- HCV RNA qualitative test

3. Monitoring the pregnancy

- Liver function including transaminases should be measured in each trimester. Baseline values will be useful to distinguish between HCV related liver dysfunction and that from pregnancy induced complications such as gestational hypertension/HELLP syndrome or cholestasis of pregnancy.[121-123]
- There is no report of an increase in incidence of preterm labour, IUGR or fetal distress in the pregnancies of women with HCV in the absence of other contributing factors.[14,31] Consequently, no specific recommendations can be made for fetal assessment during pregnancy.

4. Ultrasound diagnosis

Indications for diagnostic ultrasound evaluation will not differ from that of the general pregnant population, as no association between HCV and fetal dysmorphism has been made.

5. Invasive procedures

There is no data regarding procedures such as amniocentesis, fetal blood sampling, or chorionic villous biopsy, and the risk of vertical transmission.[124] It is the view of the panel that women with undetectable HCV RNA by qualitative PCR may not carry an increased risk of vertical transmission following these procedures. In the presence of HCV RNA, the indication and risk of abnormality must be balanced against the potential increase in transmission risk. The risk of maternal fetal haemorrhage during amniocentesis is approximately ten percent.

C. INTRAPARTUM MANAGEMENT

1. Mode of delivery

Even though a few retrospective studies have suggested a lower transmission rate after Caesarean section, the evidence is not conclusive to recommend it as a protective intervention. Women with HCV should therefore be allowed to deliver vaginally unless obstetric reasons dictate otherwise. As in all labours, universal precautions should be observed. There is no need to isolate either mother or infant.

2. Induction of labour

HCV infection is not an indication for induction of labour. Labour should be allowed to begin spontaneously in the absence of other indications. Similarly, augmentation should be performed according to local practices.

Although there is no data regarding the duration of membrane rupture and vertical transmission rates, it would seem sensible to maintain membrane integrity as long as possible to avoid fetal exposure to potentially infected cervico-vaginal secretions. Similarly, episiotomy should require careful consideration.

3. Intrapartum fetal assessment

Intrapartum fetal assessment should follow the clinical guidelines established by the SOGC.[125] Intermittent auscultation or

external monitoring is to be preferred, although no case of fetal infection has been linked to the use of a scalp electrode. However, as internal monitoring, including scalp pH measurement, constitutes a skin breaking procedure, it should be used only if deemed absolutely necessary for the assessment of fetal well-being.

D. POSTPARTUM MANAGEMENT

1. General points

Basic hygiene and the disposal of potentially infected material should be discussed with the patient.

2. Breastfeeding

HCV RNA and anti-HCV antibodies have been detected in colostrum and breast milk. However, in multiple series no case of transmission through breastfeeding has been documented. It is generally felt that breastfeeding is not contraindicated.[36,62]

3. Contraception

Effective future contraception should be discussed as part of obstetrical care. For further discussion please see Section V. B. 3b: Contraception.

E. CARE OF THE NEWBORN

1. General care

Infants may be cared for according to usual hospital procedure while universal precautions are practiced. There is no need for the mother to alter normal child care routines and the use of gloves, masks or extra sterilization is unnecessary. HCV is a bloodborne pathogen and is not transmitted by urine or stools.

2. Infant testing

As passive transfer of maternal antibodies (IgG) occurs transplacentally, all infants of mothers with HCV will be positive for anti-HCV at birth. Uninfected infants should usually have cleared these antibodies by 12 to 15 months of age. The higher the level in the mother, the longer they will take to clear. Earlier verification of infection status is possible, usually starting at two to three months of age, and relies on the identification of circulating HCV RNA by qualitative PCR. It should be remembered that early diagnosis is unlikely to alter the course of events, as the disease in children tends to follow a benign course and therapy is not indicated. However, a negative test may serve to alleviate parental anxiety.

3. Infant immunization

In addition to routine immunizations, immunization for hepatitis B should be commenced in the postnatal period. If the mother is HBsAg positive, appropriate active and passive immunoprophylaxis should be given in the form of hepatitis B immunoglobulin and hepatitis B vaccine. Vaccination against hepatitis A should be given at about one year of age.

A paediatric or infectious diseases consultation is advised to deal with the specific issues regarding testing and immunization.[126]

IX. OCCUPATIONAL EXPOSURE, UNIVERSAL PRECAUTIONS AND INFECTION CONTROL

A. OCCUPATIONALLY ACQUIRED INFECTION IN HEALTH CARE WORKERS

The epidemiology and magnitude of risk for acquiring HCV infection occupationally are not fully known.

Cases of occupationally acquired infection in health care workers have been reported after diverse medical procedures. Most of the reported infections among health care workers from occupational exposure[127,128] are thought to be secondary to needle stick accidents, although two reports of infection following conjunctival splashes have recently been published (Table XII).[127] Some studies seem to indicate a higher prevalence of HCV infection in health care workers and report seroprevalence rates of between two and 4.4 percent, which may suggest an increased risk of acquiring infection occupationally. A prospective American study examining clinical cases reported a threefold increase in incidence of HCV in health care workers compared to the general population over a two year period. However, a recent European study of 5,064 employees from 22 general hospitals reported a seroprevalence of 0.41 percent, lower than that of the general population. There was a strong association in these health care workers with previous blood transfusion and clinically overt hepatitis.[129]

Estimates of post-exposure risk vary from study to study.[127,130,131] Studies prospectively following patients to six months post-exposure report no seroconversion in 24 health care workers exposed by needle stick to 25 viremic patients: three out of 50 and two out of 53 exposed by needle stick became anti-HCV positive at six months.

A French study, using a model based on very similar HCV prevalence rates to Canada's, estimated the probability of HCV transmission from an infected patient to an uninfected surgeon during any single exposure prone procedure to vary between one in 2,381 to one in 23,810. The annual cumulative risk was calculated as ranging from 0.01 percent to 0.1 percent.[132] Between two and 21 surgeons out of a total of 20,000 are estimated to acquire HCV infection annually through their occupation.

The best protection against bloodborne pathogens is prevention. This is particularly true for hepatitis C, since no vaccine or immunoglobulin prophylaxis as yet exists. Universal precautions should be applied to all patients to eliminate the need for special identification and isolation of patients (Table XIII).

B. THE INFECTED HEALTH CARE WORKER

There is much controversy surrounding this issue. Although several instances of transmission from health care worker to patient have been reported, overall the recorded risk is incredibly low.[133] As long as exposure prone procedures are not performed, an infected health care worker can probably continue to participate in patient care. Health care workers do not need to be screened routinely for hepatitis C.

TABLE XII
RISK OF ACQUIRING BLOODBORNE INFECTION FOLLOWING NEEDLE STICK INJURY

Source of infection	Risk (%)
HBe Ag positive	30
HCV	1.8
HIV	0.3

X. RECOMMENDATIONS

a) Screening

- Universal screening for HCV is not recommended, although targeted screening should be offered to all women falling into any at-risk category. Testing should take place following adequate counselling and informed consent of the patient. (III B)

b) Preconception and early pregnancy care

- Ideally, preconception or early pregnancy evaluation should include determination of risk of infection with hepatitis C, counselling, and testing as appropriate. (III B)
- Patients aware of their HCV positive diagnosis should be evaluated before embarking on pregnancy for complications that may compromise maternal health during pregnancy. (III B)
- Pregnancy is not generally contraindicated on grounds of HCV infection alone. (Although it is contraindicated in the context of ribavirin therapy.) (III B)

c) Care during pregnancy

- There is a risk of vertical transmission which is greater if the woman is also infected with HIV. (II-2)
- Antenatal care will need to be tailored individually to meet the specific needs of the individual woman's medical and obstetrical condition, including the monitoring of liver function. (II-2 A)
- Alcohol should be avoided. (II-2 A)
- Immunization against hepatitis A and B should be provided as required. (II-2 A)
- Routine Caesarean section is not recommended as a specific intrapartum measure to reduce the risk of vertical transmission. (II-2 D)
- Breastfeeding is not contraindicated. (II-3 B)

d) Care of infant

- All infants born to HCV positive mothers should be evaluated for evidence of hepatitis C infection. (III A)

e) Contraception and hormone replacement therapy

- Barrier methods should be recommended to those with multiple sexual partners. (II-3 B)
- The extent of liver disease should be carefully evaluated before considering the use of hormonal contraception or hormone replacement therapy. (III B)

f) Universal precautions

- Universal precautions/routine practices and additional precautions are recommended in dealing with all patients for the protection of both health care worker and patient (II-2 A) (Table XIII).

TABLE XIII
UNIVERSAL PRECAUTIONS/ROUTINE PRACTICE AND ADDITIONAL PRECAUTIONS

- Thorough hand washing (10-30 seconds) with soap and warm water before and after all patient contact.
- Cover all skin lesions properly before giving patient care.
- Wear gloves using thicker orthopaedic gloves or double gloving may be helpful.
- Use protective eye wear and gowns when blood or body fluid splashes are anticipated (Caesarean and vaginal delivery).
- Minimize contact with sharps and dispose of them with caution. Never recap needles and ensure rigid disposal box for sharps is nearby and handled appropriately.
- Use a "no touch" technique when passing sharp instruments during surgical procedures.[129]
- Wear gloves until baby's first bath with antiseptic soap and during all post delivery care of umbilical cord for first 48 hours.
- Ensure comprehensive education for all health care workers in preventive techniques for avoiding blood exposure.
- Report all occupational exposures to Health Services as soon as possible so the exposed person can receive adequate counselling.

Post exposure procedure

- When safe and appropriate, stop activity and assess injury. Allow a penetrating wound to bleed as much as possible. Wash skin with soap and water (without using a brush). For non-intact skin disinfect with either a 70 percent alcohol solution or fresh solution of hypochloride 5 percent (household bleach) diluted to one in ten. Ocular splashes should be irrigated with water or normal saline.
- Obtain patient's consent for baseline anti-HCV antibody test, as well as HBsAg and anti-HIV if appropriate, if this information is not available already.
- Having received proper counselling, the health care worker should undergo baseline anti-HCV testing. The test should be repeated at six months with ALT level.
- If an anti-HCV result is repeatedly positive, a confirmatory test should be performed.
- If the health care worker has seroconverted, referral for follow-up should be provided.

TABLE XIV[134]

QUALITY OF EVIDENCE ASSESSMENT	CLASSIFICATION OF RECOMMENDATIONS
The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.[134] I: Evidence obtained from at least one properly randomized controlled trial. II-1: Evidence from well-designed controlled trials without randomization. II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940's) could also be included in this category. III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Exam.[134] A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination. B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination. C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds. D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination. E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

XI. FUTURE NEEDS IN CANADIAN RESEARCH

- What is the actual seroprevalence of anti-HCV antibodies in women of reproductive age and during pregnancy?
- What is the natural evolution of hepatitis C infection in pregnant women?
- What factors and co-factors that contribute to vertical transmission can be identified?
- Does elective Caesarean section reduce transmission rate?
- Is there a place for interferon therapy to prevent intrauterine or intrapartum HCV transmission?
- What is the long term natural evolution of HCV infection in children?
- What is the risk of transmission between sexual partners?
- What psychosocial impact does HCV infection have on families?
- What is the role of breastfeeding in the transmission of HCV?
- What is the role of the placenta in preventing vertical transmission of hepatitis C?
- What is the long term effect of oral contraception and hormone replacement therapy on patients with hepatitis C?

XII. SUGGESTED FURTHER READINGS AND OTHER RESOURCES

A. FOR HEALTH PROFESSIONALS

1. Books/guidelines

Reesink HW (ed). Hepatitis C, 2nd ed, S. Karger AG Basel, 270 p. 1998.

Ministère de la Santé et des Services sociaux. *Information à l'intention des médecins: L'hépatite C.* Québec,1999. (English version forthcoming)

Canadian Paediatric Society. Vertical transmission of the hepatitis C virus: current knowledge and issues. Paediatr Child Health 1997;2(3):227-31.

Hepatitis C prevention and control: a public health consensus. Can Commun Dis Rep 1999; 25S2:1-22.

Prevention and control of hepatitis C: guidelines and recommendations. Can Commun Dis Rep 1995; 21S2:1-18.

Centre for Disease Control. Morbidity and mortality weekly report. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Atlanta, GA: US Department of Health and Human Services.1998;47:RR-19.

World Health Organization (WHO) Weekly Epidemiological Record, Seroprevalence map: 2000;75(3).

2. On-line information sites

- Health Canada:
  Publications of the Bloodborne Pathogens Division
  http://www.hc-sc.gc.ca/hpb/lcdc/bid/bbp/public-e.html
- The Hepatitis C Page of the Disease Notification On-Line
  http://cythera.ic.gc.ca/spansweb/ndis/diseases/hepc-e.html
- Infection Control Guidelines
  http://www.hc-sc.gc.ca/hpb/lcdc/dpg-e.html#infection

- Canadian Hemophilia Society
  http://www.hemophilia.ca/
- Canadian Paediatrics Society
  www.cps.ca/english/statements/ID/id97-01.html
- WHO Reports/publications:
  www.hc-sc.gc.ca/hpb/lcdc/publicat/ccdr/00vol26/ dr2605eb.html

B. FOR PATIENTS

1. Books

Dolan M, Murray-Lyon IM, Tindall J. The Hepatitis C Handbook. North Atlantic Books, 1999.

Everson GT, Weinberg H, Vierling JM. Living with Hepatitis C: A Survivor's Guide. Hatherleigh Press 1999. (Distributed by Schering Company Inc.)

2. On-line information sites

While these sites contain useful information, they are not intended to replace consultation with a well informed health care provider.

- Health Canada:
  http://www.hc-sc.gc.ca
- The Hepatitis Information Network:
  http://www.hepnet.com/hepc.html
- Hepatitis C Forum:
  http:// www.hepatitis-c.de/hepace.htm
- Hepatitis C Facts:
  http://members.bellatlantic.net/~clotho/cfaq.htm
- 50th Annual Meeting of the American Association for the Study of Liver Disease (AASLD):
  http://www.hivandhepatitis.com/conferences/aasld.html
- Sandi's Crusade Against Hep C:
  http://members.home.net/smking/index.htm#toc
- National Center for Infectious Diseases—Viral Hepatitis C:
  http://www.cdc.goc/nciod/diseases/hepatitis/c/index.htm
- British Liver Trust:
  http://www.britishlivertrust.org.uk/blt.html
- Society of Obstetricians and Gynaecologists of Canada:
  http://www.sogc.org

3. On-line support sites

- HEPC Mailing List:
  http://www.hepatitis.org.uk/s-list

C. ORGANIZATIONS

Canadian Liver Foundation (CLF)
Head Office,
2235 Sheppard Ave. East, Suite 1500,
Toronto ON M2J 5B5
1-800-563-5483
Web site: http://www.liver.ca

Montréal Chapter
1200 avenue McGill College, Bureau 2210-A
P.O.Box 66/C.P. 66
Montreal QC H3B 4G7
(514) 876-4171

The Hepatitis C Society of Canada,
National Office
383 Huron Street
Toronto, ON M5S 2G5
1-800-652-HEPC (4372),
Montreal Office: (514) 769-9040
Web: http://web-idirect.com/~hepc
E-mail: hecsc@idirect.com

Canadian Hemophilia Society
625 President Kennedy Avenue, Room 1210
Montreal QC H3A 1K2
National Office:1-800-668-2686
http://www.hemophilia.ca

La Fondation de l'hépatite C du Québec
1185 Rolland Ave.
Verdun, QC H4H 2G5
Eileen Martin, Director, Tel: (514) 769-9040
E-mail: fhcq@qc.aibn.com

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Front cover photograph: Standard thin section electronic microscopy of HPBALL cell harvested on day 25 postinoculation. Cytoplasmic vesicles containing virus-like particles (arrow) associated with amorphous material (open arrow). (Bar = 100 nm)