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Supplement

Prevention and Control of Hepatitis C

Guidelines and Recommendations

Health Canada Santé Canada

Canada

Guidelines and Recommendations on the Prevention and Control of Hepatitis C

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GUIDELINES AND RECOMMENDATIONS ON THE PREVENTION AND CONTROL OF HEPATITIS C

Preamble

The Laboratory Centre for Disease Control (LCDC) of Health Canada held a National Meeting on the Prevention and Control of Hepatitis C on 6 - 8 December, 1994. Participants included provincial and territorial epidemiologists and laboratory directors, representatives of professional organizations, individual specialists, and representatives of interest groups. This document represents the outcome of that meeting as agreed at the final session; however, certain participants did feel that the recommendations should have been more far reaching in the areas of care and treatment and look-back programs. Copies of the background papers and proceedings of the information sessions held on 6 December, 1994, are available from the LCDC, Bureau of Communicable Disease Epidemiology Bloodborne Pathogens Group, Room 1707, Jeanne Mance Building, Tunney's Pasture, Ottawa, Ontario KIA 0K9 (tel: 613 954 5205). These guidelines and recommendations are also available over Faxlink and Health Infonet/BBS.

1. GENERAL INFORMATION

1.1 Epidemiology

One thousand six hundred and thirty-five cases of hepatitis C were reported to Health Canada's LCDC in 1993. This information includes reports on both acute and chronic cases from only seven provinces / territories.

In the LCDC's Sentinel Health Unit Surveillance System, 305 newly identified cases of hepatitis C (both acute and chronic) were identified in 1994. Preliminary analysis has shown that, of these individuals, 28% had previous blood transfusion as a risk factor; 71%, injection drug use (IDU) as a risk factor, and 14% had both risk factors.

Three out of every thousand new blood donors in Canada in 1993 / 1994 had antibodies to hepatitis C (anti-HCV) (Canadian Red Cross, unpublished data).

Five to 25% of people with new hepatitis C virus (HCV) infections are ill enough to seek medical attention. Estimating the size of the problem of hepatitis C through notification is inaccurate and, as such, the burden of illness and number of deaths from HCV infection in Canada is largely unknown.

1.2 Transmission

The major mode of transmission of hepatitis C, in Canada now, is IDU. Transmission by other routes (e.g., sexual) occurs much less frequently but these risks still need to be accurately defined. Since tests became available and usage commenced in 1990, it has been shown that hepatitis C can be transmitted by the same routes, although not with the same frequency, as other "bloodborne pathogens," such as the human immunodeficiency virus (HIV) and the hepatitis B virus (HBV).

The risk or chance of someone becoming infected with HCV depends on the way in which the person is exposed. An individual exposed through blood or blood product transfusion (prior to screening of blood donors) is the most likely to

become infected, followed by needle sharing in IDU, needlestick injuries (occupational exposure), sexual intercourse, and mother to child (vertical transmission).

Blood/blood product transfusion

In Canada, the risk of infection through blood transfusion has been reduced, but not eliminated, by the testing of donors for HCV. 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. Tests for HCV infection have only been available since 1990. The incidence of post-transfusion hepatitis C in the mid-1980's was 3.1%. This rate had fallen to 1.3% by the late 1980's.

Other modes of transmission

- Rates of infection in those who have *ever* used injection drugs are at least 30%.
- The risk of sexual transmission is low. The rate is estimated to be about 2.5% for prolonged sexual exposure (> 20 years) to infected individuals.
- Estimates on the risk of infection by other routes of transmission also vary. The occurrence of infection after a needlestick accident has been reported to be approximately 4%.
- The risk of transmission between family members (intra-familial transmission) and from mother to child (vertical transmission) is probably very low. If the mother is also HIV positive, the risk of HCV transmission increases.
- HCV has been reported to have been found in semen, saliva and breast milk by some researchers but not others. The importance of these findings is not yet clear.

1.3 Clinical Aspects

Five to 25% of newly infected individuals are symptomatic when first infected; they then recover. As many as 90% of people newly infected with HCV remain healthy for some time but they continue to carry the virus and may be infectious. These persons are at risk of becoming ill at some time in the future as a result of HCV infection.

The most serious sequelae of HCV infection are cirrhosis and hepatocellular carcinoma (liver cancer). For those who develop sequelae, it has been estimated that it may take 10 years to develop symptoms, 20 years to develop cirrhosis, and 30 years to develop cancer of the liver.

Because of the long-term nature of HCV infection, infected individuals may develop and die of diseases unrelated to HCV. This is particularly true of those who acquired HCV as a result of transfusions for life-threatening conditions. Those who acquire HCV as a result of IDU may also die from other causes prior to developing complications from their HCV infection.

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2. SURVEILLANCE

2.1 Background

The purposes of surveillance include the following:

- provision of epidemiologic data, e.g., delineation of disease distribution and trends, natural history and burden of illness (morbidity and mortality), and identification of risk factors
- identification and prioritization of populations for intervention
- guidance in health care planning
- evaluation of impact of control interventions and prevention programs.

There should be reporting (i.e., notification by laboratories and possibly physicians to local medical officer of health as required under public health legislation) of HCV infection in conjunction with enhanced surveillance to further describe the epidemiology of this infection. These twin elements of surveillance are inseparable. In particular, there should be surveillance activities to monitor changes in incidence and patterns of disease.

Nationwide surveillance for HCV infection will be of limited value until there is a way to distinguish between acute (recent new infection) from chronic (long-term) infections and until it is possible to accurately estimate HCV-associated morbidity and costs. There is a need to set up pilot projects and sentinel systems to address these concerns and answer other questions on the demographics, risk factors / behaviours and natural history of hepatitis C.

2.2 Recommendations

2.2a

- HCV infection should be added to the list of reportable diseases in all Canadian jurisdictions.
- Reporting should be, at least, from all laboratories in all Canadian jurisdictions.
- Provinces and territories should report nationally numbers of individuals infected (cases) not numbers of positive tests and each HCV-infected individual should be reported only once.
- In addition to receiving notifications from laboratories, provinces and territories may add to their reports notifications of cases from physicians and other sources.

2.2b

- The **surveillance case definition** of HCV infection should be as follows: a person with laboratory evidence of HCV infection, i.e., at the present time a positive test for anti-HCV. (This definition does not allow differentiation between acute and chronic infection, clinical disease (symptomatic disease) from infection (asymptomatic), or describe how infectious an individual is. This definition does recognize that anti-HCV positivity usually represents non-acute infection but does not exclude acute infection, that anti-HCV positivity usually represents infectiousness and that in the absence of widely available tests for viral antigens or viral RNA (i.e., for the presence of virus), anti-HCV positivity is the best currently available indicator of the potential to transmit to others.)

2.2c

- (A minimum of) date of birth, gender and date of report to the public health agency should be reported nationally in all instances of laboratory evidence of HCV infection.
- The local Medical Officer of Health should ensure that every reported case meets the surveillance case definition.
- Efforts should be made at the provincial level to avoid duplicate reporting over time and across health unit jurisdictions.

2.2d

- A national sentinel system should be developed to carry out viral hepatitis surveillance and gather data on risk factors / behaviours from a population representing the demographics of Canada including ethnic origin, country of origin and urban / rural mix. (This could be achieved through expansion of the existing Sentinel Health Unit Surveillance System coordinated by LCDC.)

2.2e

- In addition, surveillance should be carried out using a variety of other mechanisms in order to characterize cases. (For example, to differentiate between acute / non-acute infection and define the natural history of infection through random sampling of routine case reports for further investigation, sentinel physicians, (hepatologists, infectious disease physicians, gastroenterologists) seroprevalence studies of the general population and persons at high risk.)

2.2f

- A standardised reporting form should be developed for enhanced surveillance (i.e., surveillance additional to routine reporting) that would include risk factors / behaviours and elements of natural history, in order to facilitate comparisons between jurisdictions.

2.2g

- Resources commensurate with the tasks outlined above should be made available in all jurisdictions.

2.2h Research recommendations

Areas of research to be addressed are as follows:

- distinction of acute from chronic disease
- description of natural history of infection
- data links to enumerate / characterize co-infections, e.g., HBV & HIV
- standardization of risk factor evaluation across diseases
- easier, accurate tests for prevalence and screening
- investigation of a potential treatment registry
- the merit of case finding in selected high-risk groups
- HCV-related outcomes of needlestick injury
- health risk behaviours.

3. BLOOD/BLOOD PRODUCT TRANSFUSION

3.1 Current Risk of HCV Transmission by Blood/Blood Products [Transfusion-Associated Hepatitis C (TA-HCV)]

3.1.1 Background

Estimates of the current risk of HCV transmission from blood products from window period infections as a result of test characteristics (sensitivity and specificity) follow:

Using first generation (see glossary) enzyme immunoassay (EIA) tests:

- U.S. = 1 in 1500 donor exposures*(1)
- Canada = 1 in 2500 donor exposures(2)

Using second generation (see glossary) EIA tests:

- U.S. = 1 in 5000 donor exposures**
- Canada = 1 in 7500 donor exposures**

These estimates are conservative. Documented risk may be significantly lower. Preliminary results from data being collected in the U.S., show no seroconversions to HCV in 400 patients studied using second generation tests(1). In Canada, EIA 1.0 and recombinant immunoblot assay (RIBA) 1.0 were used to test blood donations from June 1990; RIBA 2.0 was introduced in May 1991 and EIA 2.0 in May 1992.

Current routinely available tests for hepatitis C detect antibody to anti-HCV. Anti-HCV is a proxy for HCV infection and potential infectivitiy.

Although the "window period" is shortened by third generation testing, experience in Europe suggests that the introduction of third generation testing is unlikely to significantly increase the number of HCV-positive donors identified.

* 1 in 1500 donor exposures = 1 person infected as a result of 1500 donations.

** Estimates calculated from first generation test data but using sensitivity of second generation tests.

Estimated "window period" for HCV infections using second generation testing is 12 to 14 weeks [14-week estimate from European studies]; [12-week estimate based on U.S. studies]. With third generation testing, the window period is decreased by approximately one week.

The estimated risk of TA-HCV from a donor in the window period [second generation testing in place] is 1:62,000 units. This estimate is based on U.S. data using documented seroconversion to HCV in repeat blood donors and estimates of the window period.

There is significant concern regarding the validation of HCV infection in transfusion recipients identified as HCV-RNA positive but who remain antibody negative > 20 weeks after exposure, i.e., false-positive laboratory result vs. extended window period. Confirmation of infection in this subgroup will be important in defining the limits of the window period.

3.1.2 Recommendations

3.1.2a

- To lessen the current risk of disease transmission by blood / blood product transfusion, reduction in the use of blood and blood products should be given a high priority by agencies in "the blood system" and agencies responsible for physician practice. Reduction could be achieved by the following:
  - development of clinical practice guidelines
  - physician education
  - establishment of computerized information systems for look-back and utilization reviews
  - funding and regulation of autologous transfusion programs at Canadian Red Cross centres and hospitals.

3.1.2b Research recommendation

- Accurate determination of the (residual) risk of TA-HCV infection is dependent on the number of HCV-RNA positive, anti-HCV negative donors among current donors. Studies examining this issue should be given priority.

3.2 Identification of Those at Risk of Having Acquired TA-HCV

3.2.1 Background

The risk of post-transfusion hepatitis C in the late 1980's was in the order of 3%, but it is estimated that a small proportion of Canadians with HCV infection were probably infected through blood / blood product transfusion before 1990, from donors identified since 1990 as infected with HCV (U.S. estimate < 5%)[3].

After consideration of the need to identify those at risk of having acquired HCV infection and after consideration of the different methods by which this might be carried out, the following recommendations were made.

3.2.2 Recommendations

3.2.2a

- Because there may be drawbacks as well as benefits in identifying those at risk of infection, consideration must be given to the potential advantages and disadvantages of a previously transfused individual knowing she / he is HCV infected before any program is undertaken.

Benefits include the following:

- Treatment opportunity. There is some evidence to suggest that patients may respond better to interferon if treated early in the course of their infection. The long-term efficacy of interferon treatment on the natural history of disease is unknown and such data will require decades to accumulate.
- The proportion of TA-HCV individuals identified is likely to be higher if done now rather than in the future, perhaps permitting earlier treatment to a larger number of persons.
- Individuals may make socioeconomic decisions based on knowledge of HCV

seropositivity, e.g., job changes / estate planning.

Disadvantages include the following:

- There is the stigma that is associated with the 'HCV-infected' label.
- Major anxiety is related to finding out the disease is present without options for treatment.

3.2.2b

- There should be a two-pronged general education program for the public and physicians coordinated at the national level and put in place throughout Canada.
- A public campaign should be developed in consultation with all stakeholders, including consumer groups.

A *general education* campaign should include the following:

- targeting physicians with information on
  - reportability of HCV infection
  - identification of infected individuals
  - testing procedures
  - counselling, treatment, and follow-up of infected individuals
  - guidelines for use of blood / blood products.

(The target audience for an education campaign would be general practitioners, family physicians, internists, infectious diseases specialists, gastroenterologists, hepatologists, laboratory medicine specialists, and other health care workers. Case-finding by physicians will lead to notification, which will aid surveillance of HCV infection.)

- providing information to the general public on
  - HCV disease (natural history of infection)
  - how the infection is transmitted, i.e., who is at risk
  - risks of past / present IDU, and blood / blood product transfusion
  - steps to prevent infection (primary prevention)
  - steps to prevent spread (secondary prevention)
  - self-evaluation of level of personal risk of infection
  - advisability of consultation with personal physician, if at risk.

3.2.3 Rationale

The two-pronged campaign will have the maximum effect of informing those at greatest risk of having acquired infection, i.e., blood / blood product transfusion recipients and IDUs, as well as those who are at greatest risk of acquiring the disease in the future, i.e., IDUs.

The two-pronged education strategy will provide information to all those at risk for HCV infection, including those who have had a blood transfusion. This strategy ensures equitable population-wide access to information on the risks and prevention of HCV infection, and the need to seek counselling by those identified at risk.

In contrast, targeted and general look-back programs will only identify previous recipients of blood / blood products, which in the case of a targeted program constitute a small proportion of total HCV infections in Canada. These programs address only secondary prevention and individual case management for blood-related cases. Limiting action to such strategies offers no opportunity for primary prevention of new infections or identification of existing HCV infections (non-blood related) in the general population.

The Canadian Red Cross Society has recommended targeted and general look-back programs in an attempt to identify recipients of blood transfusion or blood products from donors identified as being RIBA 2.0 positive since 1990, and to inform them that they may have been HCV infected and that they should be tested. Persons thus identified have a high likelihood of being

HCV infected and, therefore, may possibly benefit from appropriate case management. With regard to disease control in the Canadian population, however, the use of transfusion look-back programs to identify those at risk of HCV infection is marginal compared to a general education program.

NOTE:

a) Any look-back programs must be associated with a careful implementation plan, including ensuring adequate resources are available for agencies involved, such as the Canadian Red Cross, hospital blood banks, and laboratories providing anti-HCV testing.

b) Cost/benefit analyses should be put in place to evaluate the effectiveness of any look-back programs implemented, with rapid reallocation of resources if effectiveness is poor. A better estimate of the number of surviving TA-HCV infected individuals in Canada is required for these analyses.

3.2.4 Other issues

3.2.4a

The working group that considered issues of bloodborne transmission during the meeting discussed further programs that might be carried out in addition to a general education program. The group felt that the following prioritization might be considered for these programs:

1) Targeted look-back (standard, Canadian Red Cross initiated identification of infected donors). Recipients of previously donated blood from donors found to be anti-HCV positive would be targeted for anti-HCV testing.
2) Encouraging the routine practice-based review of patient transfusion histories by physicians and the discussion regarding anti-HCV testing with all patients who received blood prior to the introduction of EIA 2.0 testing in May 1992.
3) Trace-back from cases of TA-HCV infection with notification of the Canadian Red Cross and hence identification of donors leading to a targeted look-back.
4) Targeted look-back (extended), i.e.,persons identified by any agency as being anti-HCV positive are questioned about prior blood donation, and where necessary, targeted look-back is undertaken.
5) Testing of stored specimens taken from donors before routine second generation testing began in 1992 (Canadian Red Cross initiated, with subsequent targeted look-back, if appropriate).

3.2.4b Recommendation

- That routine testing of transfusion recipients for anti-HCV at > 6 months post-transfusion should <u>not</u> be carried out. (The current risk of TA-HCV infection is estimated to be low given present blood screening procedures. Further data to document this risk in the setting of second generation anti-HCV testing will be available from the U.S. before similar studies could be initiated in Canada. Therefore, the routine testing of all prospective transfusion recipients for anti-HCV before and after transfusion is a high-cost, low-yield endeavour).

3.2.4c Research recommendation

- High priority should be given to initiating pilot studies to look at hospital programs designed to identify those at high risk of transfusion-related infections; individuals with a long life expectancy receiving multiple transfusions, e.g., neonates and pediatric surgery patients; in particular, to study the necessity, cost, feasibility and yield of such programs.

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4. MODES OF TRANSMISSION OTHER THAN BLOOD/BLOOD PRODUCT TRANSFUSION

4.1 Health Care Settings

4.1.1 Recommendations

- The recommendations for the prevention of bloodborne infections in health care settings, which have already been made (CCDR 1992;18:177-84) and updated in the draft document "Preventing the

Transmission of Bloodborne Pathogen Infections in Public Service Facilities 1994", should apply to HCV.

- Universal precautions should be regarded as the minimum standard of practice for preventing transmission of bloodborne pathogens in all health care settings. Universal precautions must be clearly and consistently defined wherever they are described.

4.1.1a HCV testing for health care workers

- Mandatory testing of health care workers is not justified based on current scientific evidence.
- Health care workers who have had a previous significant exposure* to blood and body fluids or who have personal risk factors, e.g., IDU, should be encouraged to voluntarily seek HCV testing.
- Voluntary testing of health care workers who have no personal risk factors, based on perceived or potential occupational risk for transmitting HCV, e.g., persons performing invasive procedures, should not be done.

4.1.1b HCV-infected health care workers

- Any health care worker with an infectious disease that could put a patient at risk should be encouraged to voluntarily seek medical evaluation with respect to the potential for transmission of the infection to patients. Seeking medical evaluation is a fundamental ethical principle for health care workers infected with HCV to follow.
- Current guidelines and legislation dealing with confidentiality should be reinforced and followed.
- Reporting of anti-HCV positive health care workers to their professional organizations should be done only within the requirements of current legislation.
- Medical evaluation of an infected health care worker should be the responsibility of the health care worker's primary care physician. Primary care physicians who care for HCV- infected health care workers are encouraged to seek advice on assessment of risk for the transmission of infection in the health care setting.
- A consultation mechanism that can be easily accessed by a primary care physician should be established, ideally in each province. (This mechanism should ensure confidentiality and allow for input from public health, licensing bodies and / or professional associations, experts in infectious diseases and infection control, and others as judged appropriate to the situation. Participants in this process need not know the health care worker's identity. An existing provincial reporting / consultation system may be adapted to serve as the consultation mechanism.)
- Criteria used to assess seropositive health care workers should include the medical evaluation, knowledge, application of infection control practices, and risk for injuries from sharp objects in the context of the individual's occupation.
- Supportive non-threatening programs through licensing and / or professional organizations should be developed to assist seropositive health care workers whose practices are modified because of their infection status. Career counselling and, if necessary, job retraining should be encouraged to promote the utilization of the health care worker's skills and knowledge.

* Exposure to blood and body fluids via non-intact skin or needlestick injury.

4.1.1c Disclosure of infected health care worker's status

- Routine disclosure of an infected health care worker's serologic status is not justified.
- A patient should be notified when a significant exposure to an infected health care worker has occurred. There is no need to disclose the identity of the source of the exposure.

4.1.1d Occupational post-exposure management

- Because a significant exposure to blood or body fluids from an infected person may lead to HCV infection, all such exposures should be fully documented.
- A working group should be established to develop a national post-exposure protocol for HCV.
- Immune serum globulin should not be used in post-exposure management.
- HCV should be added to the national surveillance program for occupational post-exposure to HIV.

4.1.1e Institutional issues

- Since there are no perceived benefits, routine screening for HCV should not be carried out in an institutional setting, e.g., acute and long-term care and correctional facilities.

4.2 Personal Services

4.2.1 Recommendation

- Since hepatitis C and other bloodborne infections are transmissible through personal services, such as tattooing, body piercing and electrolysis, national guidelines and a national strategy should be developed for the prevention of bloodborne infections in these settings.

4.3 Injection Drug Use

4.3.1 Recommendations

- Because IDU is the major mode of transmission of HCV, all IDUs should be counselled according to current guidelines regarding prevention of HIV transmission, regardless of serostatus.
- Education regarding the use of clean needles should be expanded to include all related equipment and paraphernalia.
- Access to specific programs, such as needle exchange and detoxification, should be improved if the future burden of this disease is to be reduced.

4.4 Accidental Needlesticks

4.4.1 Recommendation

- The proposed working group to develop a national post-exposure protocol for HCV should consider community needlestick accidents. (*A consensus was not reached on testing for HCV in community-acquired needlestick injuries. Each circumstance will have to be considered separately before national guidelines are produced.)*

4.5 Sexual Transmission

4.5.1 Recommendations

4.5.1a

- Whereas the magnitude of the risk of sexual transmission of HCV has not been established but appears to be much lower than that of HIV or HBV, current knowledge does not warrant partner notification / contact tracing; however, HCV-infected persons have a personal responsibility to inform potential sexual partner(s) that there is a risk of infection [up to 2.5% with long-term (> 20 years) sexual exposure].

4.5.1b HCV-positive individuals with multiple sexual partners

- Despite the lack of good supporting scientific data on the efficacy of risk

reduction activities in the prevention of transmission of HCV, an HCV-infected person should be provided with information that may reduce the risk of sexual transmission. This information should include the range of safer sex practices.

4.5.1c HCV-positive individuals in long-term sexual relationships

- Because the risk of transmission may increase with repeated sexual exposures, long-term sexual partners should be offered testing by their physician.
- Despite the lack of good supporting scientific data on the efficacy of risk reduction activities in the prevention of transmission of HCV, an HCV-infected person should be provided with information that may reduce the risk of sexual transmission. This information should include the range of safer sex practices. Information should also be provided on the estimates of risk.

4.6 Mother-to-Infant Transmission

4.6.1 Background

Because current data indicate that vertical, intrapartum and horizontal transmission is rare and the mechanism (in utero, parturition, or breast feeding) has not been established and because of the lack of information, specific recommendations against pregnancy and breast feeding cannot be made.

4.6.2 Recommendations

- Information on the risks as they are presently known should be given to HCV-infected women of childbearing age.
- Immune serum globulin should not be given to infants of HCV-infected mothers post-partum.

4.7 Household Transmission

4.7.1 Background

There are insufficient data to make specific recommendations regarding HCV transmission to household contacts.

4.7.2 Recommendation

- Because of a theoretic risk, advice based on standard guidelines for avoiding exposure to blood should be provided, e.g., avoid sharing razors, toothbrushes and other personal hygiene items.

4.8 Identification of Persons at Risk for Having Acquired HCV by Modes Other Than Blood/Blood Product Transfusion

4.8.1 Recommendation

- Professional societies should make a concerted effort to educate health care providers about the following:
  - known and potential risks for HCV infection
  - the need to ascertain complete behaviour risk histories from patients
  - the appropriate evaluation of at-risk patients for evidence of infection
  - current status of investigations on use of alpha-interferon to treat HCV.

4.9 Research Recommendations

Further research is required on the risk of the following:

- sexual transmission
- household transmission
- maternal-to-child transmission through
  - breast feeding
  - Caesarian section
  - delivery
  - amniocentesis.
- Survival of virus in the environment (including effective disinfectants); however, it is recognized that this is not technically possible at the present time.

- Viral infectivity (serologic assays), i.e., quantification of infectious dose.

5. INFORMATION FOR USE IN CASE MANAGEMENT

5.1 Guidelines on Factors to Consider in the Identification of Persons with Increased Likelihood of HCV Infection; Indicators of Risk

- history of previous IDU ever
- known blood / blood products transfusion in Canada before May 1992 (the date after which both EIA 2.0 and RIBA 2.0 tests of blood donors were in use)
- multiple transfusions (at any time), e.g., those with thalassemia and hemophilia
- needlestick injury associated with a known HCV-infected source
- children of HCV-infected mothers
- organ and tissue transplant recipients
- abnormal aminotransferases
- cryptogenic cirrhosis or alcoholic cirrhosis
- hepatocellular carcinoma (hepatoma)
- mixed cryoglobulinemia
- glomerulonephritis of unknown origin
- porphyria cutanea tarda.

NOTE: *Clinical judgement is needed in making a decision to test individuals who are infected with other bloodborne pathogens, e.g., hepatitis B acquired through vertical transmission.*

5.2 Guidelines on the Further Investigation of HCV-Infected Persons

5.2.1 Background

Individuals will come to medical attention through two routes: 1) by identification of elevated aminotransferases at insurance time or routine examination; or 2) by identification of anti-HCV positivity through screening or investigation of illness. The follow-up for each group is different.

5.2.2 Guidelines

- If a person is identified because aminotransferases are elevated, HCV testing should be done as part of diagnostic work-up
- If a person is identified anti-HCV positive by screening or disease investigation, carry out the following tests:
  - aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gammaglutamyltransferase (GGT), and liver function tests, i.e., albumin, international normalized ratio of prothrombin time (INR), and bilirubin.

NOTE: *Liver biopsy is strongly suggested if ALT remains elevated for > 6 months or if there is clinical evidence of cirrhosis. The biopsy findings should be reported in terms of severity of disease according to the scheme of Scheuer and Desmet, and not by using the now outdated nomenclature of "chronic active" and "chronic persistent" hepatitis.*

- Prior to testing an individual there must be informed consent, including communication of the nature and consequence of an HCV test (including provisions for pre- and post-test counselling).
- Physicians must inform their patients of their anti-HCV antibody status as soon as practically possible once the information becomes available.

5.3 Prognosis

- The majority of HCV-infected individuals remain persistently infected (i.e., HCV-RNA positive).
- Per decade, it is estimated that 10% of HCV-infected individuals develop cirrhosis.
- Twenty percent of HCV-infected individuals who are evaluated at one

point in time have biopsy-verified cirrhosis (cross-sectional point prevalence studies).

- The proportion of HCV-infected individuals who develop hepatic decompensation each year is not known.
- The risk of cirrhosis increases also with excessive alcohol use (threshold not known) and, as such, alcohol consumption should be reduced to a maximum of no more than one alcoholic beverage per day.
- The risk of cirrhosis increases with duration of infection
  - severity of disease as identified on a liver biopsy
  - concurrent infection with HBV, delta-hepatitis, HIV or HAV.

5.4 Hepatocellular Carcinoma

- The risk of hepatocellular carcinoma increases with all types of cirrhosis. (Substantial increases in hepatocellular carcinoma incidence associated with both hepatitis B and hepatitis C are projected for the next 10 to 20 years).
- In North America hepatocellular carcinoma is frequently associated with cirrhosis due to hepatitis C. Hepatocellular carcinoma is rare in hepatitis C without cirrhosis and it is uncertain whether hepatitis C, without cirrhosis, confers additional risk for this cancer.

5.5 Other Diseases

- Other diseases (e.g., mixed cryoglobulinemia, glomerulonephritis, and porphyria cutanea tarda) associated with HCV infection occur only in a small subpopulation. It is not necessary to routinely investigate for these diseases.

5.6 Guidelines for the Follow-Up of Identified HCV-Infected Individuals

- If the liver aminotransferases are persistently normal, i.e., on 3-4 serial tests within 1 year, follow up with yearly ALT tests.
- If aminotransferases are elevated and treatment is not currently indicated, follow up with 6-monthly bilirubin, albumin, INR, and ALT tests.
- If an individual has established cirrhosis, the risk of liver failure requires specialist follow-up because of complications, such as ascites, variceal bleeding and hepatic encephalopathy.
- All individuals infected with HCV who are not currently immune to HBV, should be offered hepatitis B immunization to prevent any further liver damage. For the same reason, those who are at high risk for hepatitis A should be offered hepatitis A immunization.
- Investigate other diseases associated with HCV infection when clinically relevant.
- Routine case finding for hepatocellular carcinoma needs further study and cannot be routinely recommended with the current state of knowledge.
- Nucleic acid tests, e.g., PCR, are not currently part of routine follow-up, but when tests are standardized and validated they may become a useful part of management, especially in individuals with normal ALTs.

5.6 Recommendation

- Whereas there is a need to anticipate both the technologic and human resource needs that will evolve as increasing numbers of Canadians are diagnosed with HCV infection, a mechanism should be found to address issues related to concerns of long waiting lists and a potential lack of related specialists. (Specific issues to be addressed include, but should not necessarily be limited to, the number of practising specialists with expertise in hepatitis [primarily

hepatologists, gastroenterologists, infectious disease physicians and medical microbiologists], the number of fellowship positions with appropriate hepatology training, the amount of hepatology training in gastroenterology training programs, training and information sharing with primary care health care workers [family physicians and nursing], and the equipment and facilities needed to adequately manage HCV-infected persons).

5.7 Treatment

5.7.1 Guidelines

- The published consensus statement[4,5] on the treatment of chronic hepatitis in individuals infected with HCV remains a good guideline given the current state of knowledge.
- Nonetheless, interferon treatment is not indicated for most subjects and additional studies, currently underway and planned, may result in changes in these recommendations in the near future.
- Hepatitis C is the second most common reason for liver transplantation. Patients with hepatitis C and liver failure remain candidates for liver transplantation. Transplantation is usually successful and recurrences of hepatitis C infection in the transplanted liver usually result in mild disease.

5.7.2 Recommendations

- When treatment is indicated there should be equity of access to interferon therapy in the different provinces across Canada.
- Whereas liver transplantation is currently limited by donor availability and the need for liver transplantation may outstrip the capacity to provide donor livers in the next 10 to 20 years, there should be discussions between governments, professionals with an interest in liver disease, e.g., through the Canadian Association for the Study of the Liver, or the Canadian Liver Foundation, and funding agencies to set an agenda for research in hepatitis C, including the need to support, plan and fund adequate studies to clarify optimum therapy, indicators of therapeutic efficacy (i.e., monitoring therapy), and indicators to predict how individuals will respond to therapy (e.g., HCV-RNA levels and genotype).

5.8 Research Issues

- Technology for diagnosis, immediate management and follow-up of HCV-infected individuals
- Quality of life issues throughout the natural history of HCV
- Determination of the efficacy and cost efficiency of screening for hepatocellular carcinoma
- Treatment:
  - definition of optimal therapy
  - predictors of response, including overall morbidity and mortality
  - evaluation of the efficacy of delivery of services, and the effect of various interventions
  - natural history of infection
  - prognosis of ALT normal subjects
  - long-term natural history for those treated and not treated with interferon
  - prognosis of PCR negative, anti-HCV positive subjects
  - prognosis for transfusion-related hepatitis C in recently infected persons
  - epidemiology of HCV in aboriginal populations
  - epidemiology of HCV in high-risk groups with an emphasis on IDUs since they will, in time, constitute the vast majority of infected individuals

- natural history in those infected at a young age and utility of early identification and treatment.

5.8.1 Research Recommendation

- It is strongly suggested that a national database be established to provide the framework for studies of the natural history of this disease.

6. LABORATORY DIAGNOSIS

6.1 Testing

6.1.1 Recommendations

- EIA should remain the test of choice for initial assessment of specimens. (Currently available EIA tests are based on the immunologic response to infection and are an accurate indirect measure of infection and infectivity. They are at the present time the most practical tests for the first-line detection of HCV infections and are more than 90% sensitive for the detection of established infection.)

- Because of false positive reactions, supplemental testing should be used. [False positive EIA test results do occur. In low-risk populations, i.e., blood donors, patients tested because of previous transfusion history, the proportion of reactive tests that are falsely positive can be greater than 50%. The specific nature of the supplemental test[s] used will vary according to circumstances].

- Tests based on nucleic acid detection, e.g., PCR, can be useful in specific circumstances. [The EIA test has certain limitations. In immunocompromised persons, including dialysis patients, HIV-infected persons and transplant recipients, the antibody response to infection may be blunted, and in acute infections, there is a window period of weeks to months between infection and appearance of detectable antibodies. The window period (HCV-RNA positive, anti-HCV negative) in immuno-competent individuals is 5 to 8 weeks, on average. Nucleic acid detection tests can detect acute infection within 1 to 2 weeks of exposure. In children born to infected mothers, antibody tests do not permit diagnosis of infection in the first months of life because of passive transfer of maternal antibodies].

- Because nucleic acid testing is technically complex, the technique needs further standardization and requires critical specimen handling and processing for accurate determination of the results.

- Although nucleic acid-based testing of HCV can shorten the time to diagnosis of acute HCV infection (i.e., reduce the window period), at the present time nucleic acid tests should not be used routinely because the results do not affect the management of patients or the public health response; however, in immunocompromised persons and children of infected mothers, nucleic acid tests may be the only way of detecting HCV infection.

6.2 Quality Assurance

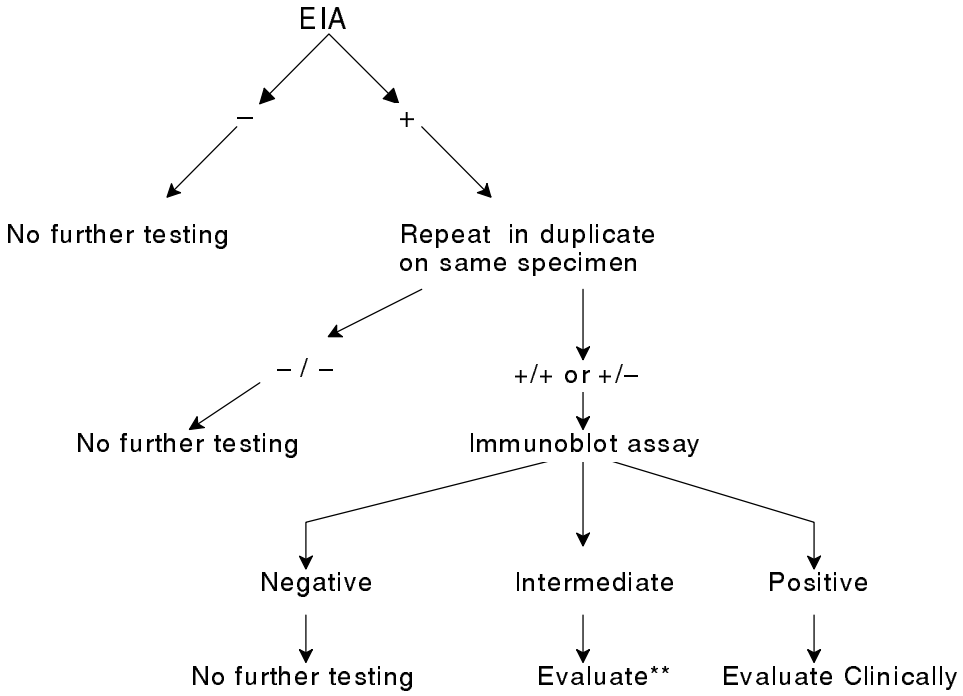
6.2.1 Recommendations

- All laboratories providing serologic testing services for HCV infection should have access to, and participate in, external quality control programs for EIA and RIBA.

- An external quality control program for nucleic acid detection technologies must be developed. All laboratories providing such services should participate in this program.

6.3 Recommended Algorithms

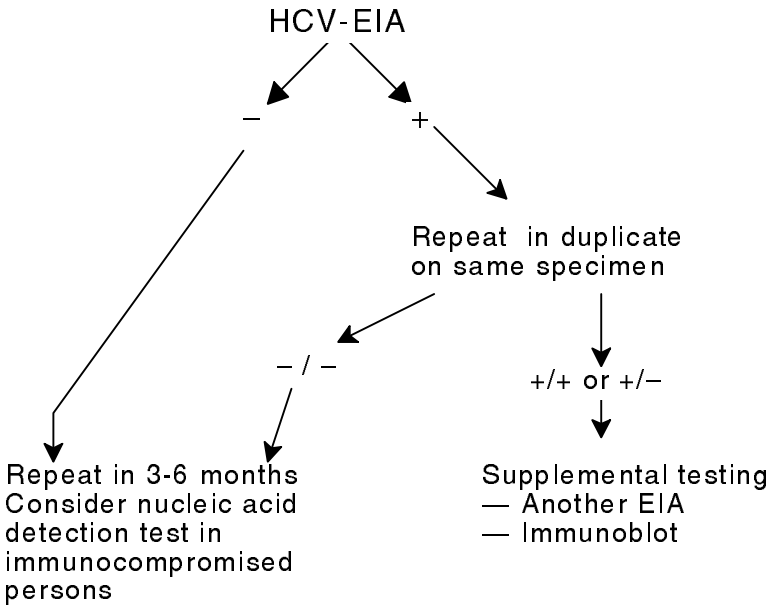
6.3.1 Screening*



* Applicable also to blood, organ, tissue, and sperm donors.
** Nucleic acid detection methods can be useful in resolving indeterminate immunoblot results.

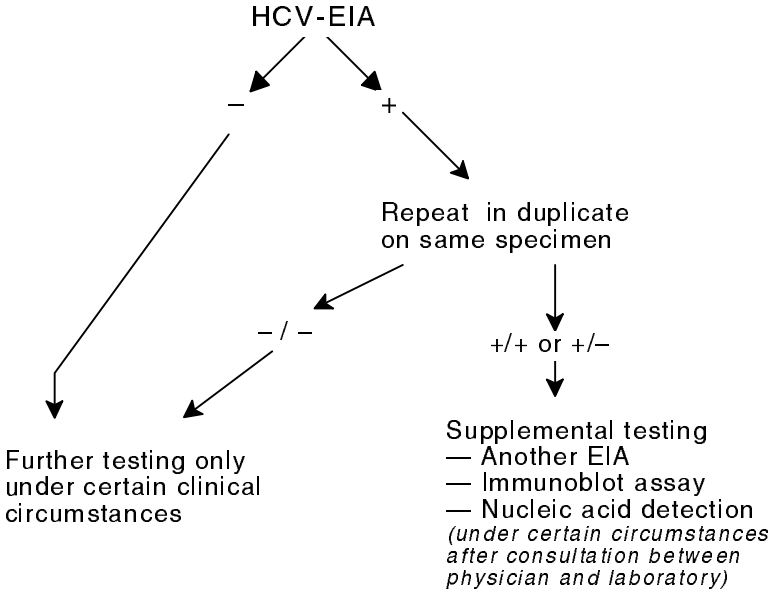
6.3.2 Acute infections

- Rule out hepatitis A (anti-HA-IgM)
- Rule out hepatitis B (HBsAg ææanti-HBcIgM)



6.3.3 Chronic Liver Disease

- Exclude hepatitis B carriage (HBsAg)



7. RESEARCH RECOMMENDATIONS

Questions to answer:

- Does acute infection without antibody response exist in immunocompetent persons? If so, how frequent is it?
- What is the role of viral load determination and genotype determinations in the clinical care of patients?
- What is the genotype distribution in infected Canadians?
- What is the utility of pooling sera for the purpose of population screening studies using antibody techniques?
- Can double EIA algorithms be used to determine infection status of screened individuals?
- What is the optimal follow-up protocol for infants of infected mothers?
- Are saliva and urine useful as specimens for seroepidemiologic studies?
- Is HCV nucleic acid quantification and detection of specific viral HCV genotypes useful in establishing prognosis and assessing the efficacy of HCV treatment programs?

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3. Alter M. *Current epidemiology*. In: *Proceedings of a national meeting on the prevention and control of hepatitis C,* 6-8 Dec 1994, Ottawa, Ontario. In press.
4. The CASL Hepatitis Consensus Group. *Treatment of chronic viral hepatitis with alpha-interferon: a consensus conference report*. Can J Infect Dis 1994;5:107-12.
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GLOSSARY

First (1.), second (2.0) and third (3.0) generation tests: denotes stages in the production of new tests. A new generation would denote a significant advance, e.g., in the specificity and/or sensitivity of a test.

General look-back: identification of all recipients of blood, e.g., from a specific institution, inform recipients and suggest seeking advice regarding testing from family physician.

Injection drug use: taking of illicit or street drugs using a needle, e.g., intravenously, sub-cutaneously.

Marginal utility: a term from health economics denoting a little extra benefit gained from a particular activity.

Polymerase chain reaction (PCR): method of detection of hepatitis C DNA. A positive PCR test on a blood sample is indicative of the presence of virus and, therefore, of infectivity.

Targeted look-back: identification of anti-HCV donor by Red Cross — if previous donations, inform hospitals that were issued blood from these donations, hospitals inform recipients and suggest seeking advice regarding testing from family physicians.

Trace-back: identification of person with hepatitis C. If previously received blood/blood product transfusion, inform Red Cross. Donor is identified. Red Cross informs hospitals that were issued blood from donor. Hospitals inform recipients and suggest seeking advice regarding testing from family physician.

Window period: period of time within which a person is potentially infectious and a screening test will fail to identify the infection.