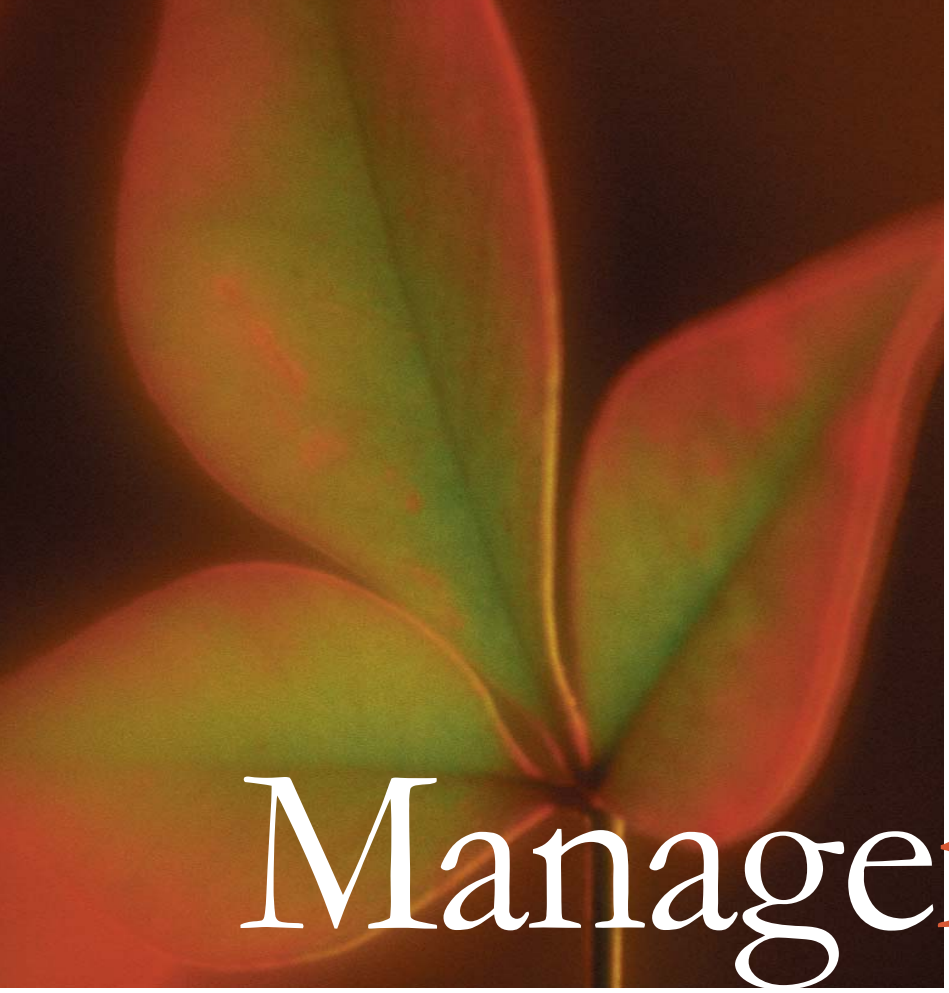

2000

Management of Viral Hepatitis

Recommended Guidelines for Physicians

Canadian Association for the Study of the Liver

The Canadian Association for the Study of the Liver

Consensus Conference on Viral Hepatitis

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Canadian Association for the Study of the Liver

Recommended Guidelines based on the Consensus Conference on the management of viral hepatitis, held 1999, Ottawa, Canada

Issued also in French under the title,
La prisé en charge de l'hépatite virale: lignes directrices recommandées à l'intention des médecins

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Introduction

The guidelines for physicians presented in this handbook are based on the proceedings of the consensus conference on the management of viral hepatitis, which was sponsored by the Canadian Association for the Study of the Liver (CASL) and Health Canada. At this unique event, experts in various aspects of viral hepatitis presented views and findings on the hepatology, infectious disease, epidemiology, virology. medical microbiology and public health.

The full proceedings of the consensus conference document is available on the CASL web site at **www.lhsc.on.ca/casl/cont.htm**

This handbook contains updated information. The recommendations will be of use to both the general practitioner and the specialist.

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Background and Recommendations

For complete information,

the full consensus document is

available on the CASL web site:

www.lhsc.on.ca/casl/cont.htm

1. Hepatitis B

The treatment of chronic hepatitis B is complex and evolving rapidly. Only physicians who are familiar with the disease and its management should undertake to treat chronic hepatitis B. Appropriate therapy may require consultation with experts, as inappropriate therapy can limit future therapeutic options.

Epidemiology of Hepatitis B in Canada

The prevalence of hepatitis B (HBV) infection varies considerably across Canada because of the heterogeneity of the Canadian population. Immigrants constitute the largest group of HBV carriers, particularly those from regions with high endemic rates of HBV, such as Asia. The majority of HBeAg-positive cases occur in the young immigrant population.

Following acute HBV infection, the percentage of infected patients who become carriers varies with age. The risk is greatest in the very young and in the elderly. Although acute hepatitis B continues to be an important clinical problem in Canada, the majority of acute cases will resolve and clear HBsAg spontaneously. Chronic HBV infection, established when HBsAg is detectable for longer than six months with or without continuing liver enzyme abnormalities, accounts for the greatest burden of disease.

Natural History of Chronic Hepatitis B

The course of chronic hepatitis B is highly variable, characterized in some patients by exacerbations and remissions of inflammatory activity in the liver, in others by continuous active hepatitis of varying degrees of severity, and in yet others by trivial inflammation. The disease can be described by three phases. The first phase, the so-called immuno-tolerant phase, is characterized by high levels of virus in serum, and no or minimal hepatic inflammation. These patients are HbeAg-positive. This is followed by the “active” phase, during which there is intermittent or continuous hepatitis of varying degrees of severity. Seroconversion to anti-HBe-positive may occur during this phase, but cessation of inflammatory activity does not always follow. The third phase is the inactive phase during which viral concentrations are low, and there is minimal inflammatory activity in the liver.

In general, patients who clear HBeAg have a better prognosis than patients who remain HBeAg-positive for prolonged periods of time do.

Patients with chronic hepatitis B are at risk for the development of hepatocellular carcinoma. (For more information on screening, please refer to Section 4, page 13.)

EVALUATION OF THE HBSAG-POSITIVE PATIENT

Who should be tested?

Any patient with clinical or laboratory evidence for either acute or chronic liver disease should be considered as possibly infected with HBV. Individuals engaged in high-risk activities such as intravenous drug use or high-risk sexual activity are at risk, as well as individuals exposed to blood by reason of their occupation. In addition, being a member of a population with a high endemic rate of HBV is a risk factor for infection.

The diagnosis of HBV infection is based on the detection of HBsAg in serum. All HBsAg-positive individuals require further detailed assessment. The objectives are to characterize the nature of the infection and the extent and severity of any underlying liver disease. Other objectives include identifying patients who may benefit from anti-viral treatment, early diagnosis and management of cirrhosis and its complications, timely detection of HBV-associated hepatocellular carcinoma, and immunization of contacts at risk.

Chronic hepatitis B - Initial Investigations

The laboratory tests needed in the initial assessment in all cases of chronic HBV infection are listed in Table 1. Measurement of the aminotransferases provide a measure of ongoing inflammation, whereas the bilirubin, albumin and INR estimate liver function. Anemia, leukopenia or thrombocytopenia may indicate cirrhosis with portal hypertension. A positive HBeAg is associated with the continued presence of actively replicating HBV in the liver and detectable HBV DNA in the blood. Such patients are at risk for ongoing liver injury. *Their blood and body fluids are highly infectious*.

Table 1. Initial investigation of the hepatitis B carrier

Tests of liver inflammation	AST ALT
Liver function tests	Bilirubin Prothrombin time/INR Albumin
Viral serology	HBeAg/anti-HBe Anti-HCV
Other important tests	BUN or creatinine CBC and differential

Anti-HBe-positive patients may have much lower viral loads, which may be undetectable in blood by standard assays. These patients usually have little ongoing liver damage. Anti-HBe-positive patients may be infected with the so-called “pre-core” mutant, which does not produce HBeAg. These patients may have detectable HBV DNA and may develop progressive liver disease leading to cirrhosis, and therefore merit life-long observation. In selected cases additional tests are needed. Anti-HCV should be requested in patients at high risk (IVDU, high risk sexual exposures, origin in countries of high HCV prevalence). For those at risk for hepatocellular carcinoma (long term and childhood infections, positive family history), and those in whom cirrhosis is suspected, an ultrasound is strongly advised.

Chronic hepatitis B - Special Investigations

HBV DNA Assays

HBV DNA can be detected in serum by several commercially available methods. Due to poor inter-assay standardization and considerable intra-assay variation It is important for the clinician to understand the type of assay methodology used and its limitations, and *to use a consistent methodology for all assays*. HBV DNA testing should be limited to those patients being considered for treatment and to evaluate response to treatment. It is not indicated routinely in the evaluation of all HBsAg-positive patients. HBV DNA testing should be readily available to qualified practitioners regularly involved in the treatment of HBV.

Liver Biopsy

Biochemical or serological tests, including HBV DNA, cannot predict histopathology with adequate precision. Therefore liver biopsy may be required to determine the severity of permanent liver injury (fibrosis or cirrhosis).The biopsy appearances may help in choosing appropriate therapy.

Ancillary tests

The detection of IgM anti-HBc in the serum is not a reliable surrogate for HBV DNA testing and is not recommended for this purpose.

TREATMENT OF THE HEPATITIS B PATIENT

In 1992, interferon alpha-2b was approved by the US Food and Drug Adminstration (FDA) for use in treating chronic HBV infection. Nucleoside analogues were first tested for treatment of hepatitis B two decades ago, but the first-generation agents did not effectively suppress viral replication and had serious side effects. Interferon alpha-2b produces sustained remission in 35% of patients with chronic hepatitis B.

The licensing of the nucleoside analogue, lamivudine, has significantly increased the therapeutic options available for the management of HBV-infected patients. Clinical trials indicate that the response rates range from 17-33%, and are comparable to seroconversion rates documented with interferon therapy. Response to lamivudine therapy is associated with improved liver histology. Preliminary results suggest that combined therapy with interferon and lamivudine has no advantage over the use of interferon or lamivudine alone. Lamivudine is well tolerated with minimal side effects. Its use is associated with the development of viral mutants, the so-called YMDD mutants which may develop in 16-32% of treated patients after one year of therapy. Although these mutants often appear to be less virulent than the wild-type HBV, they have been associated with rapidly progressive liver disease in some patients. There are no data on the long-term benefits of lamivudine therapy. We do not currently have good guidelines as to when to stop treatment with lamuvidine.

The initial trigger for consideration of treatment is an abnormal ALT level, defined as an elevated ALT on at least three consecutive occasions over a three-month period. A response to therapy is defined as loss of HBeAg, development of anti-HBe, clearance of HBV DNA from serum and normalization of the aminotransferases. This response is seen at the end or within three to six months of the end of interferon therapy, whereas on lamivudine therapy this response is usually seen while still on treatment.

The recommendations below apply only to patients over 18 years of age.

- Liver biopsy is strongly recommended, but not mandatory in the HBeAg-positive patient with abnormal ALT levels.
- Treatment is recommended regardless of the stage of fibrosis. However, the degree of fibrosis may influence the choice of therapy.
- Therapy may be with either interferon or lamivudine. Interferon is given at a dose of 27-35 mu weekly (5-6mu daily or 9-10 mu TIW) for 16 weeks. Lamivudine is given at a dose of 100 mg daily for 52 weeks. Factors which should be considered in choosing an appropriate regimen include age, pre-treatment liver histology (amount of fibrosis), HBV viral load, and the potential side effects of the drugs. Other important considerations are the risk of development of mutant viruses, and its implications for future antiviral therapy, and the likelihood of pregnancy. Interferon therapy results in a delayed but enhanced clearance of HBsAg compared to untreated patients.

SPECIAL CASES

Hepatitis D Virus may be acquired as a co-infection simultaneously with hepatitis B or as a super-infection in a patient who already is a carrier of HBV. Patients with active hepatitis D should be treated in expert centres.

Decompensated Hepatitis B Cirrhosis: Patients with decompensated HBV-associated liver disease have a poor prognosis, particularly those with active viral replication. They should be referred to a liver transplant centre for treatment.

Chronic Hepatitis B in Children: The risk of chronicity in hepatitis B infections in newborns and early childhood is high. In addition, most infants and young children infected with hepatitis B have normal aminotransferases and are not candidates for therapy. Children who are first infected at over seven years of age have a low risk of developing chronic disease. The prognosis of hepatitis B in children is generally good. The indications for treatment are similar to those in adults. There is no information on the use of lamivudine in children. Normally treatment should not begin before two years of age.

2. Hepatitis C Virus

Hepatitis C virus (HCV) is a single-stranded, positive-sense RNA virus belonging to the Flaviviridae family. Like many other RNA viruses, HCV has an inherently high mutation rate, resulting in considerable genetic heterogeneity throughout the genome. This genetic heterogeneity subdivides the hepatitis C virus into six major genotypes that vary in distribution worldwide. Genotype 1 appears to be the predominant type in Canada.

Over the next 10-20 years chronic hepatitis C is predicted to become a major burden on the health care system in Canada as patients who are currently asymptomatic with relatively mild disease progress to end-stage liver disease and develop hepatocellular carcinoma.

Information on the rates of development of chronicity after an initial HCV infection comes largely from studies of post-transfusion hepatitis. In these studies viral clearance from serum occurred in about 20-30% of patients initially infected with hepatitis C. It is not known whether this is also true for hepatitis C acquired through other routes.

To be confident that viral clearance has been achieved, PCR-based assays must be used. Negative HCV RNA by PCR assays indicate viral clearance from serum, but give no information about the state of HCV in the liver or in other privileged niches such as lymphocytes. Thus, given the current state of knowledge complete viral clearance cannot be ascertained with certainty. Patients who are anti-HCV-positive who have spontaneously developed negative HCV RNA by PCR should continue to be monitored at intervals for the presence of liver disease.

The outcome of chronic hepatitis C virus infection is not well defined. A proportion of patients will ultimately develop cirrhosis and hepatocellular carcinoma. Reports have suggested that the lifetime risk of cirrhosis in HCV carriers is between 20-50%; several factors have been identified which increase this risk, including alcohol consumption.

Hepatitis C RNA testing

As with HBV DNA testing, there is a large inter-assay and intra-assay variation with HCV RNA testing. The physician should be familiar with the characteristics of the assay being used, and the use of a particular assay should be consistent. This variability must be considered when adapting results from the published literature to local practice.

There are two types of assay for hepatitis C viral RNA.

- *Qualitative tests give a positive or negative result.*
- *Quantitative tests give the viral concentration or viral load.*

The only qualitative assay available is the Roche AMPLICOR™ assay. Quantitative assays available include the Chiron bDNA assay and the Roche Monitor ™.

Use of HCV RNA testing

Qualitative HCV-RNA testing is not essential to make the diagnosis of hepatitis C in typical patients who are anti-HCV positive. HCV RNA testing is indicated in patients who are anti-HCV-positive with persistently normal ALT levels. Interpretation of the results of such testing is given in Table 2. HCV RNA testing is also sometimes necessary in patients who are immunosuppressed, and who have unexplained elevations of the aminotransferases. In these patients there may be a false-negative anti-HCV assay.

Qualitative HCV RNA may also be used to determine whether infants of infected mothers are also infected, and in resolution of indeterminate serological testing. Qualitative HCV RNA monitoring is also useful in assessing the response to therapy.

Quantitative HCV RNA testing is not generally required.

Table 2. Interpretation of hepatitis C virus RNA testing in anti-HCV-positive patients.

ALT CONCENTRATION	HCV RNA RESULT	INTERPRETATION
Normal	Positive	- Patient is infected, with undetectable liver disease
Normal	Negative	- False-positive anti-HCV - Spontaneous viral clearance - False negative HCV RNA - Dormant infection with no or minimal liver disease
Elevated	Positive	- Infected with active liver disease,
Elevated	Negative	- False-positive - Spontaneous viral clearance - False negative HCV RNA - Dormant hepatitis C infection, but some other cause for liver disease

Sexual transmission of the hepatitis C virus

Direct percutaneous inoculation is the most efficient mode of transmitting HCV, although sexual, household, occupational and vertical transmission of HCV may also occur. HCV intra-spousal transmission appears to be rare in the absence of a parenteral risk in the partner. In case-control studies, sexual co-habitation with an anti-HCV-positive person was not identified as a risk for infection, therefore *HCV is not considered to be a sexually transmitted disease*. Some factors, however, such as sexual promiscuity, HIV and HSV2 co-infections are associated with sexual transmission of hepatitis C.

The infected person should inform sexual partners and testing should be offered to the sexual partner. Patients should be advised to avoid sharing items of personal hygiene. In short-term sexual relationships condom use is advised. Unprotected sex during menstruation should be avoided by infected females as the virus may be present in menstrual blood. Couples should be given information about the risks of transmission, and about precautions which may reduce the risk of transmission. The committee recommends neither for nor against the use of condoms in stable monogamous relationships, leaving the decision to the informed couple.

Mother-to-Infant Transmission of the Hepatitis C Virus

Rates of transmission of hepatitis C from mother to newborn infant vary between 0 and 3%, according to different reports. Two risk factors have been identified: HIV infection in the mother, and high maternal viral load.

Delivery by caesarian section has not been shown to prevent transmission of HCV. Transmission from breast milk has not been documented. *Breast feeding is considered safe* and is not contraindicated.

Anti-HCV testing in the neonate is not helpful, because there is passive transfer of antibody across the placenta. This may take 12-18 months to clear. Testing for hepatitis C infection within the first 18 months of life should be by PCR assays. There is limited information concerning chronicity after neonatal transmission; clearance of the virus may occur more frequently than in adult infection.

Therapy for Chronic Hepatitis C

The prime indication for treatment in chronic hepatitis C is an ALT level more than 1.5 times the upper limit of normal on three consecutive occasions over more than three months. Patients with ALT levels below 1.5 times the upper limit usually have mild disease and an excellent prognosis. Treatment may not be required. The only method to stage hepatitis C accurately is by liver biopsy. Many factors have to be taken into consideration before deciding to treat a patient. Recommended is:

- an assessment of whether the patient will ever develop cirrhosis and liver failure
- assessment of patients over age 50, where competing causes of mortality are more or
- less likely to cause death.

  liver biopsy may also be required in patients in whom treatment is not being considered, in order to assess the extent of liver injury.

Response to treatment should be defined in virologic terms as the use of ALT levels to define response is no longer recommended. Successful treatment is indicated by clearance of hepatitis C virus RNA from serum (by sensitive PCR-based assays) six months after the completion of therapy.

Dose and Duration of Treatment

The recommended treatment for chronic hepatitis C is with a combination of interferon alpha 2b and ribavirin. The dose of interferon is 3mu TIW, and the dose of ribavirin is 1000 mg for patients weighing less than 75kg, and 1200 mg daily for patients weighing more than 75 kg. The use of interferon alpha 2a or other interferons in combination with ribavirin has not been reported. Overall, about 40% of patients treated with this combination will have a sustained response. Patients with genotype 2 or 3 have about a 65% response rate. Patients with genotype 1 have about a 30% response rate. The response rates in other genotypes are not as well defined.

Response rates are also improved with lower viral loads ($<2 \times 10^6$ copies/ml by the NGI assay), in patients aged under 40 years, in females, and where there is an absence of fibrosis.

Treatment duration with interferon and ribavirin is determined by the viral genotype. Patients who carry genotypes 2 or 3 may be treated for 24 weeks. Patients carrying any other genotype should be treated for 48 weeks. Viral load may be used to predict response to therapy, but the data on viral load as an indicator of duration of treatment were weaker than for genotype, and viral load should not at this stage be used to determine duration of therapy.

A small number of patients treated with interferon and ribavirin who ultimately become long term responders first clear HCV RNA between 12 and 24 weeks of therapy; this differs from the response in interferon monotherapy. There is as yet insufficient data to recommend whether the 12-week stop rule described for interferon monotherapy (see below) also applies to combination therapy. Approximately 14% of patients with positive HCV RNA assays at 12 weeks will become sustained responders. However, it is clear that patients who fail to clear HCV RNA by 24 weeks of treatment will not become sustained responders. Therefore, a positive HCV RNA assay after 24 weeks of therapy is an indication to stop treatment. Interferon monotherapy should now be reserved for patients who cannot tolerate ribavirin (e.g., patients with anemia).

The intended treatment duration of interferon monotherapy is 48 weeks. Response is assessed at three months using the qualitative HCV RNA test. Failure to clear HCV RNA after three months of therapy predicts inability to develop a sustained response. Treatment should be stopped if the HCV RNA is positive at three months.

Monitoring During Therapy

The addition of ribavirin to the therapy increases the likelihood of side effects. Ribavirin predictably causes hemolysis. The hemoglobin level falls within the first two to four weeks, then stabilizes in most patients. Ribavirin dose reduction is recommended if the hemoglobin falls below 100gm/l. Routine monitoring for adverse effects includes a CBC weekly for the first month, then CBC monthly and TSH every 3 months (there is an increased incidence of thryroiditis on interferon therapy, particularly in patients with chronic hepatitis C). Symptoms should be monitored by the ALT and the HCV RNA concentration. ALT is an imperfect surrogate marker for viral clearance, so that HCV RNA testing is mandatory at the appropriate time points (12 or 24 weeks of therapy, and 24 weeks after completion of therapy). Qualitative HCV RNA testing is adequate to determine response. Quantitative HCV RNA is not required. The most commonly reported side effects of interferon alpha-2b/ribavirin therapy include flu-like symptoms, anemia, depression and alopecia. Laboratory tests may indicate changes in hemoglobin, neutrophil counts, platelet counts, thyroid function and uric acid.

Contraindications to Therapy

In assessing whether a patient is a good candidate for therapy with interferon and ribavirin, it is essential to consider the benefits and risks for that individual. Factors that may decrease the likelihood of long term benefit from treatment include shorter life expectancy such as older age, co-morbid conditions, decompensated liver disease, and active alcohol or substance abuse. Ideally patients should abstain from alcohol completely while on treatment. Factors that may predispose to a higher risk of adverse events include major psychiatric disorders, cardiovascular diseases such as significant arrhythmias, major congestive heart failure, uncontrolled hypertension or ischemic heart disease, active autoimmune diseases, poorly controlled seizure disorders, diabetic retinopathy (interferon can exacerbate diabetic retinopathy), thyroid disease (relative contraindication).

Ribavirin is teratogenic, so patients on combination therapy (both male and female) and their partners must use adequate contraception. Patients in whom poor compliance is expected, or in whom there is a significant risk of re-infection (as in active substance abuse) may not be suitable candidates for treatment. Other conditions such as severe asthma, psoriasis and past history of autoimmune diseases or psychiatric disorders are relative contraindications.

Absolute contraindications to therapy with interferon and ribavirin are decompensated liver disease, active alcohol abuse, pregnancy or lack of appropriate contraception and expected non-compliance.

SPECIAL CASES

Thalassemia: Patients with thalessemia can be offered therapy with the understanding that during treatment there is likely to be a 40 to 90% increase in their transfusion requirements. It may be possible to reduce the ribavirin dose.

Hemophilia: Patients with hemophilia can be offered therapy. Pre-treatment assessment should include a liver biopsy.

Methadone maintenance: Patients on methadone maintenance should not be excluded from treatment.

Prisoners: Therapy for incarcerated patients should be based on their expected compliance and risk of re-infection.

TREATMENT FAILURES

Relapse after interferon monotherapy: These are patients in whom the ALT normalized or in whom viral clearance occurred transiently during interferon monotherapy, but who relapsed after completion of therapy. Such patients should be offered treatment with interferon and ribavirin. The expected response rate is similar to naïve patients

Non-responder to interferon monotherapy: These are patients in whom the ALT did not return to normal during therapy, or in whom viral clearance from serum was not achieved. There are several treatment options for these patients, each with a response rate of 10-15%. Options include re-treatment with interferon and ribavirin, treatment with consensus interferon, or induction therapy with interferon. There is insufficient information to make a recommendation on the effectiveness of any of the therapeutic options for patients who were non-responders to interferon monotherapy.

Failure of combination therapy: Patients who fail to respond or who relapse after combination therapy should be managed in consultation with a centre with expertise in this area. There are no proven treatment options for these patients at present, but they may be candidates for experimental therapies.

Hepatitis C Infection in Children

In past years, hepatitis C was found with high prevalence in children who received multiple transfusions of blood derived products before testing for hepatitis C was introduced. Currently, age-related distribution of infection is likely related to different patterns of exposure. Vertical transmission in infants and body piercing, tattooing and drug abuse in adolescents are the most common routes of infection. The rate at which the initial infection becomes chronic in infants is still unknown. Although progression of the disease seems to be more benign in children than in adults, some children do develop significant fibrosis. The indications for treatment in children with hepatitis C have not been adequately defined. Chronic hepatitis C in children should not be treated except in controlled trials.

Acute hepatitis C

Since 1991, routine screening of blood products has reduced the incidence of acute HCV following transfusion to negligible levels. Therefore, acute HCV infection is now seen mainly in individuals who have received an accidental needle stick injury. Although risk for infection is relatively low at less than 5%, because the majority of these individuals are health care workers, every effort should be made to make an early diagnosis, and thereby minimize the risk of nosocomial transmission.

Based on expert opinion, the recommendation is that health care workers or others subjected to needle-stick injury or equivalent exposure should be tested by anti-HCV at the time of the injury and at 12 weeks or later to detect infection. Treatment should be with standard combination therapy of interferon and ribavirin for the standard duration, despite the lack of studies proving efficacy. Given the urgent need to gather data on such cases it is strongly recommended that patients with acute hepatitis C be treated in the setting of a clinical trial or a registry.

3. Combined Infections

Hepatitis B and Hepatitis C

The prevalence of combined infections with these two organisms in Canada is unknown. Various studies have demonstrated that the outcome of combined infection is more severe than infection with either virus alone. In most patients one infection predominates, while the

other is dormant. Thus in HBV-dominant disease the HBV DNA is detectable while the HCV RNA is not, and vice versa. Occasionally both diseases may be active. The risk of HCC is also increased compared to the risk with hepatitis B or hepatitis C alone.

There are few reports of treatment. In patients with one infection dominant and the other dormant, the indications for treatment and the dose and duration of treatment are identical to when the dominant infection exists alone.

Hepatitis B and HIV

Since hepatitis B and HIV are spread via similar routes, patients often have evidence of infection with both agents. However, only about 10% of HIV-positive subjects are chronic carriers of hepatitis B.

In the presence of HIV infection hepatitis B replication is increased, liver disease is more common, and tends to be more rapidly progressive. However, until the advent of highly active anti-retroviral therapy most patients who were co-infected with hepatitis B and HIV died of AIDS, rather than complications of hepatitis B. This may no longer be true now that more effective anti-HIV therapy is available. Interferon treatment of hepatitis B in HIV-positive patients has been largely unsuccessful. Lamivudine therapy is effective in suppressing viral replication, but at present there are no reports of long term outcome after lamivudine therapy in this population. Chronic hepatitis B in HIV-infected patients must not be treated with lamivudine monotherapy as it will result in the rapid emergence of resistant HIV virus.

Hepatitis C and HIV

Hepatitis C infection occurs in HIV-positive patients with parental risk factors with a frequency between 50-90%. Progression to cirrhosis is rapid with increasing degrees of immunosuppression. Treatment with interferon monotherapy has a success rate not much different than for hepatitis C in the absence of HIV There are no data on the use of combination therapy with interferon and ribavirin in these patients. There are no recommendations about therapy in patients co-infected with hepatitis C and HIV.

4. Screening for Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a well known complication of chronic hepatitis B (HBV) infection. The risk appears to be related to the duration of infection. Once HCC develops, the prognosis is very poor. Survival of patients with symptomatic untreated tumours beyond three years is rare.

Apart from cirrhosis, other factors that increase the patient's risk for developing HCC include long duration of infection, male gender, age greater than 55 years, continued alcohol consumption and co-infection with HBV and HCV. Response to interferon treatment may confer a protective effect against the development of HCC. Although routine screening for HCC in patients with HCV is not as widespread as for patients with HBV, this is still practiced in certain community groups.

In the absence of documented benefit of mass screening, the committee makes no recommendations for or against screening for HCC in HBsAg-positive patients, nor for patients with chronic hepatitis C. Screening may be justified in high risk cases (presence of cirrhosis, long duration of infection, HBV/HCV co-infection, past curative resection for HCC, family history of HCC [HBV only]).

5. Recommended Vaccination Guidelines

HEPATITIS B

At present B vaccination policies vary by province across Canada. All provinces include some form of universal vaccination, offered either to all newborns, or to adolescents, as well as vaccination of individuals at high risk of acquiring hepatitis B. Since high risk situations are not always adequately identified, there is a risk that some susceptible individuals will not receive vaccination. Strategies aimed at pre-teens fail to protect against horizontal transmission in children who reside in communities where hepatitis B is endemic.

Recommended: a universal hepatitis B vaccination policy should aim to eliminate vertical (mother to child) transmission, as well as horizontal transmission in early childhood. The policy should also protect against hepatitis B risks imposed by environment, behaviours, or occupation.

The vaccination strategy for Canada should be:

- Universal vaccination of all neonates, combined with screening of all pregnant women.
- Newborns of infected mothers should be given hepatitis B immunoglobulin in addition to the vaccine.
- A "catch-up" program should be instituted for all children and young adults who have not yet been vaccinated.
- The policy should be standardized and national so that vaccination is assured for all children when their families move between provinces.
- Serologic testing post-immunization is not recommended routinely, but is advised for those with continual or repeated exposures such as infants of infected mothers, sexual partners of chronic carriers and those with occupational exposure. For further details see the *Canadian Immunization Guide*, Fifth edition, 1998.

HEPATITIS A

The age distribution and number of hepatitis A-susceptible individuals in Canada has changed over the last twenty years. An increasing percentage of adults have never been exposed to hepatitis A and remain at risk of infection. Hepatitis A in childhood is usually a trivial disease. However, in adults hepatitis A can be severe with considerable morbidity, and even mortality.
Hepatitis A vaccines are safe and effective.

Recommended: Current recommendations by NACI with regard to populations in whom vaccination is appropriate remain pertinent. They are as follow. Recommended usage for pre-exposure prophylaxis against hepatitis A.

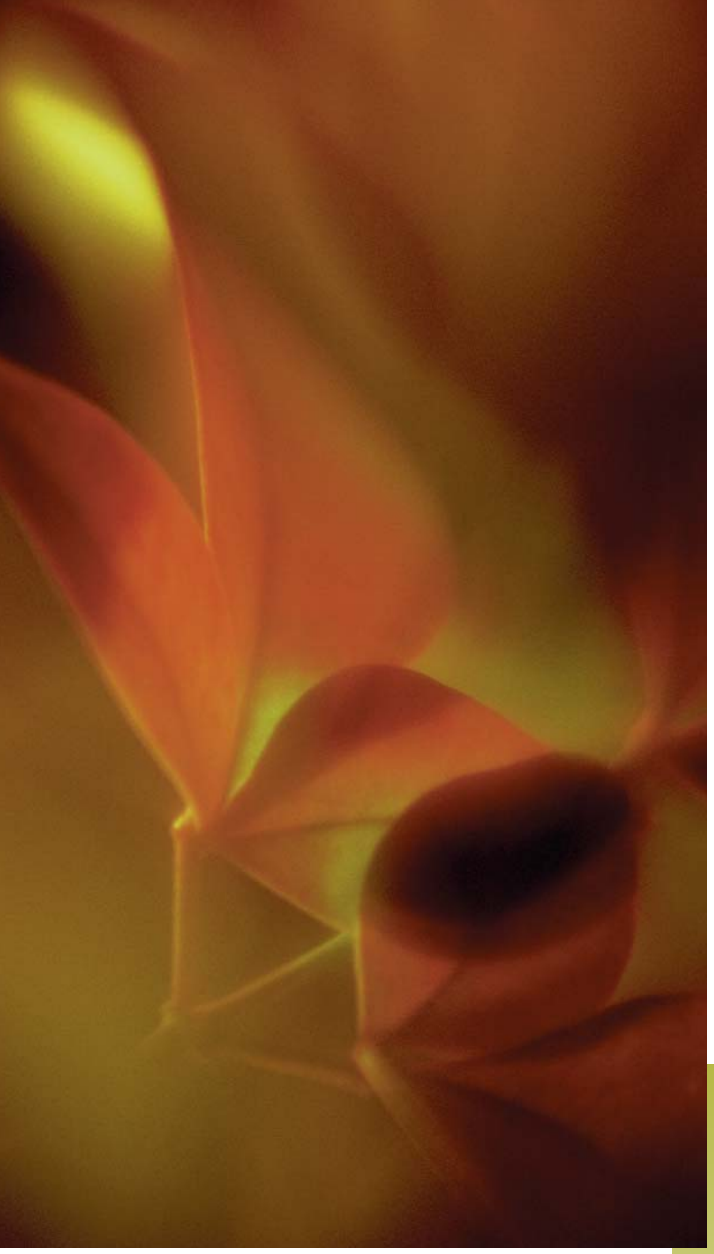
- Travellers to countries where hepatitis A is endemic, especially when travel involves rural or primitive conditions
- Residents of communities with high endemic rates or recurrent outbreaks of HAV
- Members of the armed forces, emergency relief workers and others likely to be posted abroad at short notice to areas with high rates of HAV infection
- Residents and staff of institutions for the developmentally challenged where there is an ongoing problem with HAV transmission
- Inmates of correctional facilities in which there is an ongoing problem with HAV infection
- People with life-style determined risks of infection, including those engaging in oral or intravenous illicit drug use in unsanitary conditions
- Men who have sex with men
- People with chronic liver disease who may not be at increased risk of infection but are at increased risk of fulminant hepatitis A
- Others, such as patients with hemophilia A or B receiving plasma-derived replacement clotting factors; zoo-keepers, veterinarians and researchers who handle non-human primates; certain workers involved in research on hepatitis A virus or production of hepatitis A vaccine.

The Canadian Association for the Study of the Liver

About CASL

The Canadian Association for the Study of the Liver (CASL) represents a multidisciplinary group of doctors, scientists and health care providers whose expertise focuses on the liver. CASL is committed to providing national leadership in all aspects of research, teaching and patient care as pertains to the liver.

Our goals are to improve the quality of health care; support education; promote research; provide a forum for research dialogue; and enhance our role as a world leader in hepatology.



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Recommended Guidelines for Physicians

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