

GUIDELINES & PROTOCOLS

ADVISORY COMMITTEE

Clinical Management of Chronic Hepatitis C

Scope

This guideline is for general practitioners, internists, and pediatricians. It recommends a diagnostic work-up for patients with chronic active hepatitis C and referral for treatment to physicians with expertise in hepatitis.

The goal is to:

- prevent the spread of the virus to other persons
- improve the patient's quality of life
- cure the disease where possible

RECOMMENDATION 1: Patient counselling

Counsel patients to prevent spread. See the attached patient guide.

RECOMMENDATION 2: Confirmation of chronic active hepatitis C

Confirm active infection by a qualitative hepatitis C virus RNA (HCV RNA) test, e.g. PCR (polymerase chain reaction).

Confirm chronic hepatitis by an elevated ALT (alanine amino transferase) monthly for three consecutive months.

Note: 60 to 85 per cent of acute infections will result in chronic disease.

RECOMMENDATION 3: Indications for referral for treatment (adults only)

Patients who meet the following criteria should be considered for referral to a physician with expertise in hepatitis treatment.

- Patients whose liver enzymes are elevated – ALT more than 1.5 times upper limit of normal monthly for three consecutive months.
- Patients with unusual associated diseases, such as cryoglobulinemia, porphyria cutanea tarda, or glomerulonephritis (with or without elevated ALT).
- Rarely, patients with end stage liver disease (e.g. cirrhosis) may present with normal ALT levels.

Patients not meeting the above criteria should be monitored.

Children: refer to Recommendation 10.



Notes: Because treatment is between 30 to 70 per cent effective, is lengthy and expensive, and may have side effects, it is important to identify those patients who will benefit. See Recommendation 4.

As ALT, serology and nucleic acid tests are imperfect markers, a liver biopsy is strongly indicated before treatment is initiated.

RECOMMENDATION 4: Relative contraindications to treatment

While all cases should be considered on an individual basis, the following factors are relative contraindications to treatment. If in doubt seek consultation with a specialist.

Relative contraindications to treat with interferon and/or ribavirin:

- non-compliant patient or psychosocially unstable
- ongoing drug or alcohol abuse, however individual situations should be considered
- significant disease, such as heart disease, uncontrolled diabetes mellitus, active psychosis, severe depression, auto-immune disease, active bacterial infection (e.g. osteomyelitis)
- decompensated liver disease
- renal failure or anemia - these patients have a higher risk of adverse effects to ribavirin
- pregnancy or lack of appropriate contraception (male and female, as ribavirin is teratogenic)
- myelosuppression e.g. thrombocytopenia (platelet count less than $80 \times 10^9/L$), neutropenia (neutrophil count less than $0.8 \times 10^9/L$)

RECOMMENDATION 5: Treatment of adult patients

Treatment should be given by a physician with expertise in hepatitis.

The current standard treatment of chronic hepatitis C is combination therapy with interferon and ribavirin. However, therapy with pegylated (long half-life) interferon alone or in combination with ribavirin is under investigation.

The probability of response to and the duration of combination therapy for chronic hepatitis C are dependent on the viral genotype. Viral genotyping should be performed on all patients before treatment initiation, but should only be ordered by the physician with expertise in hepatitis who is initiating treatment.

- For patients with genotype 1, 48 weeks of therapy is indicated if a patient demonstrates undetectable HCV RNA at week 24 using a qualitative HCV RNA test. Approximately 30 per cent of treated patients will clear the virus from the body. If the qualitative HCV RNA is positive after 24 weeks, treatment is usually discontinued.
- For patients with genotype non-1, 24 weeks of therapy is indicated. Approximately 60 per cent of treated patients will clear the virus from the body.

Treatment protocols for chronic hepatitis C are constantly evolving. For a listing of currently available trials in British Columbia, see www.bccdc.org/hepatitis/research.

RECOMMENDATION 6: Monitoring untreated patients

If the ALT is normal or less than 1.5 times the upper limit of normal, repeat the ALT test at three, six, and 12 months.

If the ALT remains normal or less than 1.5 times the upper limit of normal after one year of monitoring, perform a follow-up qualitative HCV RNA test (e.g. PCR) at 12 months. If the HCV RNA test is:

- positive, repeat the ALT annually
- negative, repeat once at 24 months
- negative two years in succession, no further testing is required unless the patient has been exposed to new risk factors

If the ALT becomes elevated more than 1.5 times the upper limit of normal for three consecutive months, specialist referral is recommended.

RECOMMENDATION 7: Monitoring treated patients

The physician with expertise in hepatitis who is actively treating the patient may follow the schedule given in Appendix 1 to monitor patients treated with interferon and ribavirin combination therapy.

The following are signs of side effects to treatment. Consult with a specialist if:

- hemoglobin drops below 100 g/L (70 per cent of the lower limit of normal)
- absolute neutrophil count falls below $0.8 \times 10^9/L$ (40 per cent of the lower limit of normal)
- platelet count drops more than 20 per cent

RECOMMENDATION 8: Determining if the patient is cured

Successful treatment is defined as a negative qualitative HCV RNA test six months after the completion of therapy. A qualitative HCV RNA should be repeated a year later. If it remains negative this is considered a cure.

RECOMMENDATION 9: Screening for hepatocellular carcinoma (HCC)

Screening for HCC is not recommended in the absence of cirrhosis. HCC only occurs after established cirrhosis.

Although the cost benefit of screening has yet to be proven, screening is suggested with abdominal ultrasound and serum alpha-fetoprotein at approximately six-month intervals. Mild to moderate elevations in alpha-fetoprotein may occur due to the inflammation in the liver and not necessarily from HCC. Abnormalities of either alpha-fetoprotein or ultrasound indicate the necessity for further, more sensitive imaging. The type of follow-up imaging is best determined by a physician with special knowledge of HCC.

RECOMMENDATION 10: Infants and children

All infants and children should be referred to a pediatric specialist with expertise in viral hepatitis. The diagnostic testing is complex and the treatment guidelines are controversial.

A qualitative HCV RNA test at six weeks is recommended to demonstrate whether or not active infection is present in the neonate. A negative HCV antibody test at 12 months virtually rules out transmission to the child, although in less than 5 per cent of cases, maternal antibody can remain in the neonate for 15 to 18 months.

Note: The risk of perinatal transmission from a chronic HCV carrier mother is approximately six per cent and may increase two to three-fold when the mother is HIV co-infected. Horizontal transmission in families is rare.

RECOMMENDATION 11:

Needlestick injuries

Hepatitis C

The use of immune globulin in the needlestick recipient is not recommended. The immune globulin is specifically screened to remove antibodies to hepatitis C and has not been shown to be of benefit. Routine prophylaxis is not currently recommended. The risk of transmission is less than 5 per cent.

If acute infection is detected refer to the Rationale, second paragraph under Evidence.

HIV

Refer to the web site of the BC Centre for Excellence in HIV/AIDS at:
<http://cfeweb.hivnet.ubc.ca/guide/page/sectg/tbgs.html>

For further information see the Centres for Disease Control and Prevention (US) web site at:
www.cdc.gov/ncidod/hip/Blood/Exp_to_Blood.pdf

Rationale

Burden of Disease

In British Columbia, approximately 40,000 persons are chronically infected with hepatitis C and another 40,000 persons are chronically infected with hepatitis B. Without treatment about 15 to 30 per cent of chronic hepatitis C and B carriers will develop cirrhosis and end-stage liver disease, hepatocellular cancer or require liver transplantation over the next 2 to 4 decades. Approximately 100 individuals die of end-stage liver disease in B.C. per year (about three-quarters are due to hepatitis). The cost of end-stage liver disease, including lost income, is estimated at \$1,000,000 per person and the cost of liver transplantation is \$100,000 to \$200,000 per person.

Outcomes

Combination therapy with interferon and ribavirin can eliminate HCV RNA from blood and improve hepatic histopathology in approximately 30 per cent of genotype 1 patients treated for 48 weeks and in 60 per cent of patients with non-genotype 1 treated for 24 weeks.¹ Most individuals (>90 per cent) who clear HCV RNA remain negative after therapy is stopped.² Newer pegylated interferons,^{3,4} with ribavirin may enhance 'cure' by a further 10 to 20 per cent.

Evidence

The outcomes are based on randomized controlled trials and the use of the most sensitive current HCV RNA detection tests. Measurement of outcomes of interferon/ribavirin treated patients at Vancouver Hospital in B.C. confirm the results. Recognized limitations of the data include the fact that efficacy has largely been demonstrated in individuals with elevated serum transaminases and in individuals compliant with treatment. Compliance correlates with the availability of a supporting infrastructure to administer and monitor the relatively toxic treatment.

Recent evidence suggests that early treatment of recently acquired (< 3 months) infections may be beneficial. The effectiveness of early treatment requires further verification – the evidence is limited at present.⁵ If in doubt, refer to a physician with expertise in hepatitis treatment.

Benefits, harms, and costs

The main benefit from therapy is the potential of a cure. Data collected at Vancouver Hospital demonstrates the baseline quality of life of HCV infected patients is below normal for the Canadian population on most domains of the standardized SF-36® quality of life form. During therapy there is a further deterioration in the quality of life followed by a return to the normal population baseline in responders. Thus therapy has severe side effects as well as significant benefits on the quality of life in responders. Improved clinical outcomes are expected based on short-term improvements in liver pathology, but the effects on long-term risk of cirrhosis and liver cancer have not yet been proven. Also the cost of therapy is approximately \$10,000 to \$20,000 based on the infecting genotype. This must be balanced against current and future expenditures without treatment. Because treatment can cure HCV infection, subsequent transmission of HCV may be prevented. Therefore optimal strategies for prevention and treatment need to be devised.⁶

Guideline benefits and risks

Both HCV and HBV diagnosis and therapy are rapidly evolving and there is critical need to provide information to practitioners to assist in diagnosis, care and follow-up. Untreated chronic HCV and HBV place patients at risk of poor outcome due to hepatic damage and long-term medical costs. Given the medical complexity of hepatitis and the variation in knowledge and practice, guidelines are necessary for accurate diagnosis and follow-up. This guideline is expected to improve case-finding and support evidence-based clinical interventions.

References

1. Lauer GM, Walker BD. Medical Progress: Hepatitis C virus infection. *N Engl J Med* 2001;345:41-52.
2. Schvarcz R, Glaumann H, Reichard O, Weiland O. Histological and virological long-term outcome in patients treated with interferon-alpha2b and ribavirin for chronic hepatitis C. *J Viral Hepat* 1999;6:237-42.
3. Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon Alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000;343:1666-72.
4. Heathcote EJ, Shiffman ML, Cooksley WG, et al. Peginterferon Alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000;343:1673-80.
5. Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med*.2001;345:1452-1457.
6. Garnett GP, Bartley LM, Cameron DW, Anderson RM. Both a 'magic bullet' and good aim are required to link public health interests and health care needs in HIV infection. *Nat Med* 2000;6:261-2.

Sponsors

This guideline was developed by the Guidelines and Protocols Advisory Committee, approved by the British Columbia Medical Association and adopted by the Medical Services Commission.

Effective Date: June 1, 2002

Planned Review Date: June 1, 2004

Guidelines and Protocols Advisory Committee
1515 Blanshard Street 1-2
Victoria BC V8W 3C8

Phone: (250) 952-1347
Fax: (250) 952-1417

E-mail: hlth.guidelines@gems6.gov.bc.ca
Web site: www.healthservices.gov.bc.ca/msp

The principles of the Guidelines and Protocols Advisory Committee are:

- to encourage appropriate responses to common medical situations
- to recommend actions that are sufficient and efficient, neither excessive nor deficient
- to permit exceptions when justified by clinical circumstances.

Appendix 1: Schedule for Monitoring Patients Treated with Interferon and Ribavirin Combination Therapy

GENOTYPE	TEST	TIME
All genotypes	<ul style="list-style-type: none"> • Genotyping • Qualitative HCV RNA • TSH, if not already done (thyroid stimulating hormone) 	Baseline
All genotypes	<ul style="list-style-type: none"> • Monitor weight 	Baseline and each office visit
All genotypes	<ul style="list-style-type: none"> • CBC (complete blood count) and differential • Platelets • AST (aspartate amino transferase) • ALT (alanine amino transferase) • GGT (gamma glutamyl transferase) • Alkaline phosphatase • Total bilirubin 	<p>Every 2 weeks for 2 months.</p> <p>Then monthly until 1-month post-treatment.</p>
Genotype 1	<ul style="list-style-type: none"> • Qualitative HCV RNA 	<p>Weeks 20* and 48</p> <p>If week 20 HCV RNA is negative continue treatment for additional 24 weeks.</p> <p>If negative at week 48 repeat HCV RNA at weeks 72 and 96.</p> <p>Treatment course 48 weeks.</p>
Genotype non-1	<ul style="list-style-type: none"> • Qualitative HCV RNA 	<p>Weeks 24, 48, and 72</p> <p>Treatment course 24 weeks.</p>

* HCV RNA is tested at week 20 to ensure sufficient turnaround time for result to be available for week-24 Pharmacare decision.

Clinical Management of Chronic Hepatitis C Summary

- 1. Patient counselling:** Council to prevent spread.
- 2. Confirmation of chronic active hepatitis C:** Do PCR.
If +, do ALT.
If ALT > 1.5 times upper limit do monthly x 3 months.
- 3. Indications for referral for treatment (adults):** Refer if ALT > 1.5 times greater than normal for 3 consecutive months, or cryoglobulinemia, porphyria, cutanea tarda, etc.
- 4. Relative contraindications to treatment:** Non-compliant patient, drug or alcohol abuse, significant disease, etc.
- 5. Monitoring untreated patients:** If ALT normal or < 1.5 times upper limit, repeat ALT at 3, 6 and 12 months.
If ALT normal or < 1.5 times upper limit at 12 months, do PCR.
If PCR +, repeat ALT annually.
If PCR negative, repeat ALT once at 24 months.
If PCR negative 2 years in succession, do no further testing.
- 6. Treatment of adult patients:** Combination therapy with interferon and ribavirin.
- 7. Monitoring treated patients:** AST, ALT, HGB, platelets, WBC, neutrophils, etc.
- 8. Determining if the patient is cured:** By a negative HCV RNA 6 months after completion of therapy.
- 9. Screening for HCC:** If cirrhosis is established, screen with abdominal ultrasound and serum alpha-fetoprotein at 6-month intervals.
- 10. Infants and children:** Refer to pediatric specialist with expertise in viral hepatitis.
- 11. Needlestick injuries:** Risk of transmission is less than 5 per cent. Routine prophylaxis is not recommended.

Hepatitis C

A GUIDE FOR PATIENTS

June 2002

What is hepatitis C?

Hepatitis C is a liver disease caused by infection with a virus. Some people have no symptoms or long-term effects from the infection. However, most individuals carry it for the rest of their lives and some develop serious liver damage. Treatment can cure hepatitis C, but it is lengthy and has side effects.

How is hepatitis C spread?

- Usually by contact with the blood of an infected person
- Rarely by having sex with an infected person
- An infected woman can spread hepatitis C to her newborn baby during delivery
- Although rare since 1991, hepatitis C can be spread through transfusion of blood products – you should inform your doctor if you have ever received or donated blood

What will help me get better?

- Don't use alcohol – alcohol is a liver toxin
- Don't use illegal drugs. If using drugs, do not share or reuse needles
- Eat well to help your liver heal
- Get vaccinated for hepatitis A and/or B if you have had no previous infection or immunity
- The value of herbal remedies remains unknown

How can I protect others from getting infected?

- Don't let others come in contact with your blood, e.g. a bloody nose or cut
- Don't share needles or other equipment for intravenous drug use, tattooing, or body piercing
- Don't share spoons or straws for intranasal cocaine use
- Don't share anything that might have blood on it, like a razor or toothbrush
- Tell your health care providers, e.g. dentist or laboratory technician, that you are infected with Hepatitis C
- Tell your sexual partners, although you have a low chance of spreading the virus to them
- Use condoms especially for short-term sexual relationships and multiple partners
- Use condoms during menstruation (because of possible spread through blood)

You cannot spread hepatitis C by:

- Coughing, kissing or hugging
- Sharing eating utensils or drinking glasses

If you are a mother carrying hepatitis C:

- You may breastfeed as the risk of giving the virus to the baby is very low
- Make sure your baby is tested at six weeks and at one year

For updated information:

- Visit the BC Centre for Disease Control web site:
<http://www.bccdc.org/hepatitis/education/guidelines.shtml>

