

GUIDELINES & PROTOCOLS

ADVISORY COMMITTEE

Clinical Management of Chronic Hepatitis C

Revised 2004

Scope

This guideline is for general practitioners, internists, and pediatricians. It recommends a diagnostic work-up for patients with chronic active hepatitis C and indications for referral for treatment to physicians with expertise in hepatitis. A one-page summary and algorithm are also provided.

The goal is to:

- prevent the spread of the virus to other persons
- improve the patient's quality of life
- eradicate viral infection where possible
- prevent progression to end stage liver disease

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).

Assess disease activity by monitoring ALT (alanine amino transferase) on at least 3 occasions over 6 months.

Note: 75 per cent of acute infections will result in chronic disease.

RECOMMENDATION 3 Assessment and consideration for treatment (adults only)

Assess status of liver disease activity (see ALT below), clinical evidence of fibrosis, symptoms and comorbidity.

Patients who meet the following criteria should be considered for referral to a physician with expertise in hepatitis treatment. Treatment guidelines are continually evolving and, in some cases, referral may be appropriate even if these criteria are not met.

- Consistently elevated liver enzymes - ALT more than 1.5 times upper limit of normal* on at least 2 of 3 measurements within 6 months.
- Unusual associated diseases, such as cryoglobulinemia, porphyria cutanea tarda, or glomerulonephritis (with or without elevated ALT).
- Age less than 50 with genotype 2 or 3 HCV even if presenting with normal or minimally elevated ALT levels.
- Advanced liver disease (e.g. cirrhosis) even if presenting with normal or minimally elevated ALT levels.

* Individual laboratories may have different reference ranges for normal values

Patients not meeting the above criteria should be monitored clinically and with ALT testing as detailed below. See Recommendation 6.

Because treatment is between 45 to 80 per cent effective, is lengthy and expensive, and may have severe side effects; it is important to identify those patients who will benefit. See Recommendation 4.

Liver biopsy is indicated if the results of the biopsy will influence the decision to treat, or if there is concern about other hepatic pathology. It is more often helpful in patients with normal or minimally elevated ALT than in patients who clearly meet treatment criteria.

Children: refer to Recommendation 11.

RECOMMENDATION 4 Contraindications to treatment with pegylated interferon/ribavirin

Absolute contraindications:

- non-compliant or psychosocially unstable patient
active psychosis, major depression, active auto-immune disease, active bacterial infection (e.g. osteomyelitis)
- pregnancy or lack of appropriate contraception (male and female, as ribavirin is teratogenic)

Relative contraindications:

- ongoing drug or alcohol abuse, however individual situations should be considered
- significant comorbidity, such as heart disease or uncontrolled diabetes mellitus
- decompensated liver disease
- renal failure or anemia - these patients have a higher risk of adverse effects to ribavirin
- platelet count less than $70 \times 10^9/L$, neutrophil count less than $1 \times 10^9/L$ (experts sometimes treat patients with lower counts if circumstances warrant).

RECOMMENDATION 5 Treatment of adult patients

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

The current standard treatment for chronic hepatitis C is combination therapy with pegylated interferon and ribavirin.

The probability of response to and the duration of combination therapy for chronic hepatitis C depend on the viral genotype. Viral genotyping should be performed on all patients before starting treatment.

- For patients with genotypes 1, 4, 5 and 6; 48 weeks of therapy is indicated if a patient demonstrates a two log quantitative drop in HCV RNA or has undetectable HCV RNA at week 12. Approximately 45 per cent of treated patients will clear the virus from their bodies.
- For patients with genotypes 2 and 3, 24 weeks of therapy is indicated. This will eradicate the virus in about 80 per cent of treated patients on a long term basis.

Treatment protocols for chronic hepatitis C are constantly evolving. A recent consensus document on the Management of Viral Hepatitis is available at:

www.hepatology.ca/cm/FileLib/ViralHepatitisCanadianConsensus2004.pdf

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 3, 6 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 is more than 1.5 times the upper limit of normal on at least 2 of 3 measurements within 6 months, specialist referral is recommended.

* Individual laboratories may have different reference ranges for normal values.

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 pegylated interferon and ribavirin combination therapy.

Consult with a specialist if the patient has any of the following signs of side effects to treatment:

- 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 virus has been eradicated

Successful treatment is defined as a negative qualitative HCV RNA test six months after the completion of therapy. Repeat the qualitative HCV RNA one 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 unless the patient is a carrier for hepatitis B. HCC only occurs after established cirrhosis in hepatitis C infected patients.

Although the cost benefit of screening has yet to be proven, screening is suggested with abdominal ultrasound annually 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. More sensitive imaging may be required if abnormalities of either alpha-fetoprotein or ultrasound are found. The type of follow-up imaging is best determined by a physician with special knowledge of HCC.

RECOMMENDATION 10 Management of persons co-infected with HIV

Patients who are co-infected with HCV and HIV constitute a very complex sub-population of HCV infected patients that requires unique clinical considerations. These include:

- different thresholds for initiation of HCV treatment
- heightened monitoring and follow-up, particularly with regards to potential drug interactions (e.g. co-administration of ribavirin with either ddl or AZT), and adverse effects
- a lower treatment response rate due to immune suppression.

Consult a physician knowledgeable in HCV and HIV co-infection before initiating treatment.

RECOMMENDATION 11 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 6 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 12 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, consult a physician with expertise in hepatitis treatment. Early treatment of recently acquired infections may be beneficial, but is controversial.

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 20 - 40 years. 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.¹

Outcomes

Combination therapy with pegylated interferon and ribavirin can eliminate HCV RNA from blood and improve hepatic histopathology in approximately 45 per cent of genotypes 1, 4, 5, and 6 patients treated for 48 weeks and in 80 per cent of patients with genotypes 2 and 3 treated for 24 weeks.²⁻⁴ (Note: genotype 1 is the most common in BC.) Most individuals (> 95 per cent) who are HCV RNA negative six months after the end of therapy remain virologically negative.⁵

Evidence

The outcomes are based on randomized controlled trials and the use of the most sensitive current HCV RNA detection tests.^{2,3} 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 mos.) infections may be beneficial. The effectiveness of early treatment remains controversial.^{6,7} If in doubt, the patient should be referred to a physician with expertise in hepatitis treatment.

Benefits, harms, and costs

The main benefit from therapy is the potential of a virological cure and improved quality of life.^{8,9} 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.⁴

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.¹⁰ 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.

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Sponsors

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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.

Hepatitis C

A GUIDE FOR PATIENTS

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 the virus for the rest of their lives and some develop serious liver damage. Treatment can cure hepatitis C, but it is lengthy, has side effects, and may not be suitable for all patients.

How is hepatitis C spread?

- Usually by contact with the blood of an infected person
- injection drug use. If using drugs do not share or re-use needles
- To a baby during delivery by an infected woman (generally low risk)
- Having sex with an infected person (rare)
- Through transfusion of blood products (rare since 1991). Inform your doctor if you have ever received or donated blood.

What will help me get better?

- Don't use alcohol – it accelerates liver damage in patients with hepatitis C.
- 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:

The risk of giving the virus to the baby through breastfeeding is very low
Make sure that your baby is tested at 6 weeks and at one year

For further information:

- Visit the Guidelines and Protocols Advisory Committee web site:
www.healthservices.gov.bc.ca/msp/protoguides/gps/index.html#H Look for Hepatitis
- Visit the BC Centre for Disease Control web site: <http://www.bccdc.org/topic.php?item=60>

Appendix 1: Clinical Management of Chronic Hepatitis C

Schedule for Monitoring Patients Treated with Pegylated Interferon and Ribavirin Combination Therapy

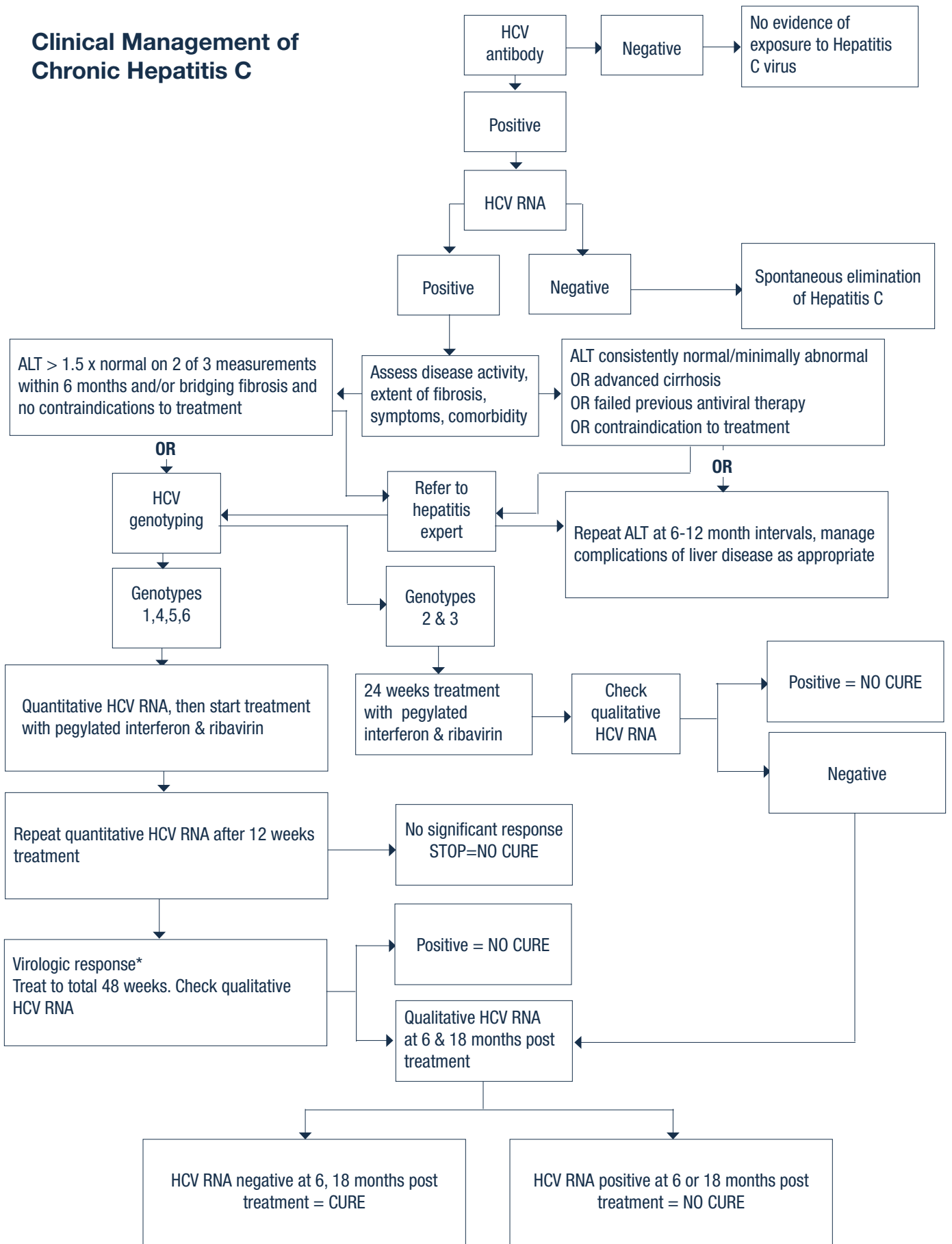
GENOTYPE	TEST	TIME
All genotypes	<ul style="list-style-type: none"> • Genotyping • Qualitative HCV RNA • TSH, (thyroid stimulating hormone) if not already done 	Baseline
All genotypes	<ul style="list-style-type: none"> • Monitor weight 	Baseline and each office visit
All genotypes	<ul style="list-style-type: none"> • Hematology profile • AST (aspartate amino transferase) • ALT (alanine amino transferase) • GGT (gamma glutamyl transferase) • Alkaline phosphatase • Total bilirubin 	Every 2 weeks for 2 months. Then monthly until 1-month post treatment
Genotypes 1,4,5,6	<ul style="list-style-type: none"> • Quantitative HCV RNA • Qualitative HCV RNA 	At baseline & week 12. Therapy for 48 weeks is indicated if a patient demonstrates a two log quantitative drop in HCV RNA or has undetectable HCV RNA at week 12. At week 48. If negative repeat at 6 & 18 months post treatment.
Genotypes 2, 3		At week 24. if negative, repeat at 6 & 18 months post treatment

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

Summary: Clinical Management of Chronic Hepatitis C

- 1. Patient counselling:** Counsel to prevent spread. See patient guide.
- 2. Confirmation of chronic active hepatitis C:** Do qualitative HCV RNA
If positive, do ALT on at least 3 occasions over 6 months
- 3. Indications for referral for treatment (adults):** Refer if ALT > 1.5 times upper limit on at least 2 out of 3 measurements within 6 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 qualitative HCV RNA.
If qualitative HCV RNA positive, repeat ALT annually.
If qualitative HCV RNA negative, repeat qualitative HCV RNA once at 24 months
If qualitative HCV RNA negative 2 years in succession, no further testing required.
- 6. Treatment of adult patients:** Combination therapy with pegylated interferon and ribavirin.
- 7. Monitoring treated patients:** Hematology profile, AST, ALT, GGT, alkaline phosphatase, total bilirubin at baseline, then at weeks 2, 4, 6, 8, 12, 16, 20, etc. until 4 weeks after completion of treatment.
See genotype specific HCV RNA monitoring information in Appendix 1.
- 8. Determining if the patient is cured:** By 2 negative qualitative HCV RNA tests 6 and 18 months after completion of therapy.
- 9. Screening for HCC:** If cirrhosis is established, screen with abdominal ultrasound (annually) 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.

Clinical Management of Chronic Hepatitis C



* Quantitative HCV RNA undetectable or at least 100-fold lower than baseline