

GUIDELINES & PROTOCOLS

ADVISORY COMMITTEE

Clinical Management of Chronic Hepatitis B

Scope

This guideline is for general practitioners, internists, and pediatricians. It recommends a diagnostic work-up for patients with chronic active hepatitis B 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 B

Confirm active hepatitis B by positive surface antigen (HBsAg).

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

Confirm chronic hepatitis B with a repeat positive HBsAg six months later.

Note: In adults, less than five per cent of acute hepatitis B infections will result in chronic disease. Chronic carriers may occasionally clear surface HBsAg spontaneously without treatment. If given hepatitis B immune globulin (HBIG) and vaccinated at birth, less than 10 per cent of children of carrier mothers will develop chronic disease. If not given HBIG or vaccinated at birth, 90 per cent will develop 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 1.3 times the upper limit of normal, monthly for three consecutive months.
- Patients with end-stage liver disease (e.g. cirrhosis) who may present with normal ALT levels.

Treatment of patients with chronic hepatitis B is complex and referral to a specialist is recommended.



Patients not meeting the above criteria should be monitored (see Recommendation 6).

Children: refer to Recommendation 10.

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**:

- 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
- myelosuppression e.g. thrombocytopenia (platelet count less than $80 \times 10^9/L$), neutropenia (neutrophil count less than $1 \times 10^9/L$)

Relative contraindications to treat with **lamivudine**:

- Although there are few contraindications, treatment is complex and specialist consultation is recommended.

RECOMMENDATION 5: Treatment of adult patients

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

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

Treatment with interferon for 16 weeks will lead to an antiviral response in 25 to 30 per cent of individuals. Treatment with lamivudine for a year or more will lead to an antiviral response in 15 to 40 per cent of individuals. Prolonged therapy increases the risk of antiviral resistance.

What constitutes a hepatitis B antiviral response is complicated because of viral variability in patients and variability in the interpretation of the different available tests, e.g. ALT, HBsAg, HBeAg, HBV DNA.

Treatment protocols for chronic hepatitis B 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 1.3 times the upper limit of normal, repeat the ALT at three, six, and 12 months.

If the ALT remains normal or less than 1.3 times the upper limit of normal after one year of monitoring, repeat the ALT annually.

If the ALT is more than 1.3 times the upper limit of normal for three consecutive months, specialist referral is strongly recommended.

RECOMMENDATION 7: Monitoring treated patients

The physician with expertise in hepatitis who is actively treating the patient will individualize monitoring depending on the patient's needs.

RECOMMENDATION 8: Determining if the patient is “cured”

Cure is achievable in only a small percentage of patients but disease progression can be modified. The treating specialist will determine the length of treatment (see Recommendation 5).

The chance of clearing HBsAg with treatment is low, but disease progression can be modified by achieving a “sero-conversion”. A sero-conversion means achieving the following:

In patients who are initially HBeAg positive:

- A negative HBeAg
- A negative HBV DNA
- A positive HBeAb (positive anti-HBe), although this is not always possible

In patients who are initially HBeAg negative:

- A negative HBV DNA
- A positive HBeAb (positive anti-HBe)

Patients should have the above test results on three occasions over a three-month interval. Many patients treated with lamivudine achieve sero-conversion by 12 months of treatment, but treatment of 24 to 36 months may result in a higher patient response rate.

The occurrence of a HBV viral resistance mutation (usually at the YMDD locus) during treatment with lamivudine is high:

- 14 per cent by 12 months of treatment
- 30 per cent by 24 months of treatment
- 50 per cent by 36 months of treatment

A mutation is suggested if the ALT and AST become significantly elevated after an initial fall from the pre-treatment level. Prolonged treatment after development of the YMDD mutant is still controversial but improvement in liver pathology with decreased fibrosis may occur if treatment is continued.

RECOMMENDATION 9: Screening for hepatocellular carcinoma (HCC)

HCC may occur in the absence of cirrhosis. The presence of cirrhosis will increase the risk of HCC further. Although the cost benefit of screening has yet to be proven, screening is suggested in all patients age 30 or older with one or more of the following risk factors:

- Infection at birth (perinatal/vertical transmission)
- Male gender
- Duration of infection for multiple decades
- Family history of HCC
- Co-infection with hepatitis C
- Groups at high risk, e.g. Asian, refugee populations

The most important risk factor is chronic infection for multiple decades. In addition, all patients with active disease (elevated AST, ALT) including cirrhosis are at risk.

Suggested screening consists of an abdominal ultrasound and serum alpha-fetoprotein at approximately six-month intervals.

RECOMMENDATION 10: Infants and children

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

All infants born to hepatitis B virus (HBV) carrier mothers (i.e. HBsAg positive) should have received HBIG and the full course of HBV vaccination (0, 1, and 6 months). Vaccine failure in the neonate is rare but does occur (less than 10 per cent) and is probably related to transplacental transmission before birth.

Follow-up testing should be performed at approximately three months after the HBV vaccination series is completed, as follows:

- HBsAg to detect vaccine failures
- anti-HBc (total) to detect previous infection
- anti-HBs to confirm vaccine effectiveness or failure

RECOMMENDATION 11: Needlestick injuries

Hepatitis B

Verify the immune status in the needlestick recipient and consider HBIG and a hepatitis B vaccine booster as appropriate. The risk of transmission is about 25 per cent. The risk of chronic infection after a needlestick injury, however, is almost zero in immunized populations.

HIV

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

For further information see the Centres for Disease Control and Prevention (US) web site at http://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 B and another 40,000 persons are chronically infected with hepatitis C. Without treatment about 15 to 30 per cent of chronic hepatitis B and C 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

Interferon or lamivudine treatment can convert 25 to 35 per cent of HBe antigen positive patients to positive anti-HBe (positive HBeAb) and decrease the long-term risk of cirrhosis.^{1,2,3,4,5} Prolonged treatment with lamivudine for up to four years increases the probability of response but also increases the risk of antiviral resistance 30 to 50 per cent. This undesirable outcome may alter lamivudine's treatment effectiveness. For HBV, unlike HCV, complete 'cure' is not yet possible for most patients.

Evidence

Most data are based on randomized controlled trials. However, long-term follow-up has been limited to interferon treated patients. Data on lamivudine treated patients suggest similar improvements in outcome but the duration of therapy and the importance of antiviral resistance remain unclear. Also the test methodologies to assess HBV antiviral effectiveness are not well standardized.

Benefits, harms, and costs

Given the long-term risks of HBV-associated liver complications, the relatively well-tolerated regimens of lamivudine favour its use over interferon, which is associated with a high rate of side effects. Therapy is approximately \$1800/year per patient treated. However, questions remain regarding how long to treat, what are the risks, what are the implications of antiviral resistance, and how to measure the treatment response.

Guideline benefits and risks

Both HBV and HCV 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 HBV and HCV place patients at risk of poor outcome due to hepatic damage. 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

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2. Niederau C, Heintges T, Lange S, et al. Long-term follow-up of HBeAg-positive patients treated with Interferon alfa for chronic hepatitis B. *The N Engl J Med* 1996;334:1422–7.
3. Pianko S, McHutchison J. Chronic hepatitis B: new therapies on the horizon? *Lancet* 1999; 354:1662–3.
4. Lai CL, Chien RN, Leung NWY, et al. A one-year trial of lamivudine for chronic hepatitis B. *N Engl J Med* 1998;339:61–8.
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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.

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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.

Clinical Management of Chronic Hepatitis B Summary

- 1. Patient counselling:** Counsel to prevent spread.
- 2. Confirmation of chronic active hepatitis B:** Do HBsAg.
If +, repeat at 6 months.
If HBsAg remains +, do ALT.
If ALT > 1.3 times upper normal limit,
do ALT monthly for 3 consecutive months.
- 3. Indications for referral for treatment (adults):** If ALT > 1.3 times upper limit for 3 consecutive months.
- 4. Relative contraindications to treatment:** Non-compliant patient, drug or alcohol abuse, significant disease etc.
- 5. Treatment of adult patients:** The physician with expertise in hepatitis treats with interferon or lamivudine.
- 6. Monitoring untreated patients:** Repeat ALT at 3, 6, 12 months, then annually.
- 7. Monitoring treated patients:** Individualized depending on patient's needs.
- 8. Determining if the patient is "cured":** Only a small percentage of patients are cured, but disease progression can be modified by sero-conversion.
- 9. Screening for HCC:** Screen patients age 30 or over with one or more risk factors.
- 10. Infants and children:** Refer to a pediatric specialist with expertise in viral hepatitis.
- 11. Needlestick injuries:** The risk of transmission is about 25 per cent, but the risk of chronic infection is almost zero in immunized persons.

Hepatitis B

A GUIDE FOR PATIENTS

June 2002

What is hepatitis B?

Hepatitis B is a liver disease caused by infection with a virus. In adults, less than five per cent of new infections will go on to long-lasting (chronic) liver disease. Treatment of chronic disease can lessen damage to the liver.

How is hepatitis B spread?

- Having sex with an infected person
- Contact with the blood of an infected person
- To a baby during delivery by an infected woman
- Transfusion of blood products – this is rare, however, you should inform your doctor if you have ever received blood or are a donor

What will help me get better?

- Don't use alcohol (alcohol is a liver toxin)
- Eat well to help your liver heal
- Don't use illegal drugs – if using drugs, do not share or re-use needles
- Get vaccinated for hepatitis A if you have no prior 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
- Ask your sexual partner(s) to be tested for hepatitis B immunity (you have a high risk of spreading the virus to them)
- Ask your sexual partner(s) to get vaccinated, if they are not immune to hepatitis B
- Tell your other health care providers, e.g. dentist or laboratory technician that you are infected with hepatitis B
- Use condoms 100 per cent of the time, unless your partner is immune

You cannot spread hepatitis B by:

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

If you are a mother carrying hepatitis B:

- Be sure that your baby is vaccinated at birth, at one month, and at six months.
- Breastfeeding is safe for babies who have been vaccinated and who have received hepatitis B immune globulin (HBIG) at birth

For updated information:

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

