THE MANAGEMENT OF VIRAL HEPATITIS

CANADIAN ASSOCIATION FOR STUDY OF THE LIVER

PROCEEDINGS OF A CONSENSUS CONFERENCE HELD IN MONTREAL, QUEBEC IN MARCH 1999

TABLE OF CONTENTS

THE CANADIAN CONSENSUS CONFERENCE ON THE MANAGEMENT OF VIRAL HEPATITIS

This report was written by the CASL consensus conference rapporteur group
See end of article for conference participants and rapporteurs

INTRODUCTION

This report is the proceedings of a consensus conference on the management of viral hepatitis sponsored by the Canadian Association for Study of the Liver and Health Canada. This meeting was open to the public. Experts in various aspects of viral hepatitis were asked to present a review of the medical literature on assigned topics. Three expert panels were convened, consisting of the speakers and other invited experts from the fields of hepatology, infectious disease, epidemiology, virology, medical microbiology and public health. The expert panels debated assigned topics, which corresponded to the reviews presented earlier. Audience participation was sought. Attempts were made to reach consensus on a number of recommendations about the management of viral hepatitis. A "rapporteur" group then synthesized the content of the literature reviews, and the debates and consensus statements into a preliminary document. This was presented to the audience, and additional comments sought to determine how well the document reflected the views expressed in the earlier discussions. The draft document was amended as necessary, and edited to produce this report. All participants were obliged to publicly declare any potential conflicts of interest. The report gives some background and offers recommendations aimed at both the general practitioner and the specialist. The recommendations and other important statements are highlighted in the text. The recommendations are also summarized at the end of the document.

HEPATITIS B VIRUS

1. 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. If the Canadian population can be described by three groups - Native/Inuit, Immigrant and Non-immigrant then the estimated prevalence and number of cases in Canada are shown in Table 1 (1-6). Immigrants constitute the largest group of HBV carriers, particularly those from regions with high endemic rates of HBV, such as Asia. The proportion of HBV infected patients who are HBeAg-positive also varies amongst the different groups (1). HBeAg-positivity ranges from <9% in the Inuit population, to <15% for non-immigrants, to 46% for Asian immigrants and 55% for Indochinese immigrants. The majority of HBeAg-positive cases occur in the young immigrant population.

Following acute HBV infection, the percent-age of infected patients who become carriers varies with age. The risk is greatest in the very young and in the elderly (see later). **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 6 months with or without continuing liver enzyme abnormalities, accounts for the greatest burden of disease.**

Table 1 Hepatitis B in Canada

	Prevalence of HBsAg+	Estimated number of cases in Canada
Native / Inuit	4%	1,640
Immigrant	4.3%	154,160
Non-immigrant	0.2% - 0.5%	49,862 – 124,655
Total		206,000 to 280,000

2. NATURAL HISTORY OF CHRONIC HEPATITIS B

The course of chronic hepatitis B is highly variable, characterized in some patients by exacerbation and remission 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 (7). The first phase, the so-called immuno-tolerant phase, is characterized by high levels of virus in serum, and no or minimal hepatic inflammation (8). 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 (8-11). Seroconversion to anti-HBe-positive may occur during this phase (12), 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 (3). In general, patients who clear HBeAg have a better prognosis than patients who remain HBeAg-positive for prolonged periods of time do (14). About 1%/year of anti-HBe-positive patients will clear HBsAg (15). However these patients remain at risk for hepatocellular carcinoma.

One of the major mechanisms by which sero-conversion occurs (possibly the only mechanism) is by the development of the so-called "pre-core mutant" (16). This is a mutation which arises during the course of infection, and which results in inability of the virus to produce HBeAg. The virulence of this mutant is uncertain. Patients who are anti-HBe-positive with elevated ALT concentrations and detectable HBV DNA almost all carry the pre-core mutant. However, anti-HBe-positive patients with normal ALT levels and undetectable HBV DNA also frequently carry the mutant. It may be that virulence is determined by another related mutation in pre-core mutants.

Patients with hepatitis B-induced cirrhosis who are anti-HBe-positive have a 97% 5-year survival, compared to a 72% survival for those who are HBeAg-positive (17). Once hepatic decompensation occurs in anti-HBe-positive patients, the survival at 5 years is only 28%, whereas in HBeAg-positive patients the 4-year survival is zero (18). Factors predicting an adverse outcome include active hepatitis, bridging necrosis on biopsy, older age, and persistent HBV DNA in serum (19).

Patients with chronic hepatitis B are at risk for the development of hepatocellular carcinoma (20). The relative risk has been prospectively determined to be about 100, but that is highly dependent on the population being studied. Studies in Asian populations describe a much higher risk than Caucasian populations. However, even in a Caucasian population the 10 year incidence of HCC may be as high as 15% (17).

3. 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 2. Measurements 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. 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, and 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.

Table 2. Initial investigation of the hepatitis B carrier

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

Table 3. Manufacturer's reported dynamic ranges for HBV DNA assays

Method	Working range
Abbott Solution Hybridization Assay	1.6 to~800 pg/ml
Digene 1st Generation Hybrid Capture Assay	5-2000 pg/ml ($1.4x10^6$ –$5.6x10^8$ copies/ml)
Digene 2nd Generation Hybrid Capture Assay Standard test Ultra-sensitive method	 $1.4x10^5$ – $1.7x10^9$ copies/ml $4.7x10^3$ – $5.6x10^7$ copies/ml
Chiron Quantiplex™ bDNA Assay	0.7 – 5000 Meq/ml ($7x10^5$ – $5x10^9$ copies/ml)
Roche AMPLICOR™ HBV Monitor™ PCR Assay	1000 – $1x10^7$ copies/ml

- **Chronic hepatitis B – Special Investigations**

HBV DNA Assays

HBV DNA can be detected in serum by several commercially available methods (see later). Table 3 lists the current tests, their limits and ranges. There is poor inter-assay standardization so that quantification of HBV DNA when tested on different assays can vary by approximately 10 fold or more when testing the same specimen. There is also considerable intra-assay variation so that repeat testing of the same sample will result in a significant difference in results (coefficient of variation for bDNA assay is 10-20%, and for PCR assays is 20-40%). **It is therefore important for the clinician to understand the type of assay methodology used, and its limitations, and that a consistent methodology be used 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 bi-opsy 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. Its use is not recommended for this purpose. Positive immunostaining of hepatocyte nuclei and cytoplasm for HBcAg reliably predicts the presence of HBV DNA in serum.

4. TREATMENT OF THE HEPATITIS B CARRIER

The licensing of the nucleoside analogue, lamivudine, has significantly increased the therapeutic options available for the manage-ment of HBV-infected patients. Clinical trials indicate that the response rates, as measured by HBeAg seroconversion to anti-HBe-positive, after lamivudine therapy in HBeAg-positive patients with elevated liver enzymes range from 17-33%, and are comparable to seroconversion rates documented with interferon therapy (21-23). Loss of HBsAg with lamivudine therapy occurs in less than 5% of patients, compared to 8-33% with interferon (23). 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. It use is associated with the development of viral mutants, the so-called YMDD mutants (24), which may develop in 16-32% of treated patients after one year of therapy (21,22). 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.

The initial trigger for consideration of treatment is an abnormal ALT level. This is defined as an elevated ALT on at least three consecutive occasions over a three-month period. For interferon therapy the cut-off is twice the upper limit of normal, and for lamivudine therapy the cut off is 1.3 times the upper limit of normal.

A response to therapy is defined as loss of HBeAg, development of anti-HBe, clearance of HBV DNA from serum (by the bDNA, solution hybridization or hybrid capture assays), and normalization of the aminotransferases. This response is seen at the end or within 3-6 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 > 18 years of age (see later for rec-ommendations for children).

In the HBeAg-positive patient with abnormal ALT levels liver biopsy is strongly recommended, but not mandatory. 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 (5-6 mu daily or 9-10 mu TIW) for 16 weeks** (25-32). **Lamivudine is given at a dose of 100 mg daily for 52 weeks** (21)**.** 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 (33). 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. Treated patients have a 5-year rate of clearance of HBsAg of 16% vs. 4% in the untreated group (15). The data on the efficacy of lamivudine on clearance of HBsAg are not yet available.

In patients treated with interferon, development of anti-HBe with normalization of ALT is a good surrogate marker for clearance of HBV DNA. Therefore, monitoring with HBV DNA is not essential. In patients treated with lamivudine, clearance of HBV DNA is a marker of efficacy of treatment. The ALT response may be delayed or incomplete. Therefore, HBV DNA testing is essential to evaluate the response to therapy. In addition, an increase in ALT levels while on treatment may be a marker of the development of viral resistance to lamivudine, and should be followed by quantitative assessment of hepatitis B viral DNA levels.

In anti-HBe-positive patients with elevated ALT and detectable HBV DNA (pre-core mutant) therapy is more difficult. These patients do not respond well to interferon (33,34). There are reports of extended treatment (6-12 months) interferon with sustained viral clearance. However, this remains controversial. Lamivudine treatment will suppress viral replication in these patients with improvement in ALT (35). However, the relapse rate is high once treatment is stopped. The consensus was that these patients should be treated in expert centers. **Lamivudine therapy for patients who are anti-HBe-positive and HBV DNA-positive is still considered experimental.**

The use of prednisone withdrawal prior to interferon therapy is contraindicated in the management of HBV-associated disease.

Interferon use in the immunosuppressed patient is not effective. In the setting of organ transplant up-regulation of HLA display may also enhance rejection. The optimal management of HBV-infected patients who are immunosuppressed has not yet been defined. These include patients who have been transplanted with an organ other than the liver, or who are being treated for autoimmune disease, or malignancy. Routine screening of patients undergoing organ transplantation is standard practice. At the present time **there is insufficient information to support routine screening of other immunosuppressed patients for HBV infection**. However, patients with risk factors should be screened. **There is also insufficient information to recommend lamivudine anti-viral prophylaxis for immunosuppressed patients who are known to be hepatitis B carriers**.

There are several case reports of the use of lamivudine in patients following renal transplantation and bone marrow transplantation, indicating that suppression of virus is possible, with resolution of the hepatitis (36,37). However, there are no reports of long term outcome, and therefore no recommendations could be made for or against the use of lamivudine in immunosuppressed patients.

SPECIAL CASES

- **Hepatitis D Virus**

Hepatitis D virus (HDV) is a small, defective RNA virus that requires the presence of a coating of hepatitis B surface antigen (HBsAg) for entry into and exit from the hepatocyte. HDV therefore 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. Infection with hepatitis D usually causes an aggressive hepatitis (38).

Interferon at a dose of 9 Mu three times a week for a year can induce a virological response but this is only sustained in 21% of cases when assessed six months after completing therapy (39). Whether or not interferon therapy alters outcome in terms of morbidity or mortality is unknown.

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. Low-dose interferon therapy in such patients (HBeAg-positive) may result in one-third responding with seroconversion and improvement in liver function, but some 20 to 70% of patients have

significant complications from the treatment (40). Lamivudine appears to yield a better response rate, approaching 80%, without significant side effects (JP Villeneuve, personal communication). Whether or not this changes the overall outcome remains to be determined.

Patients with decompensated chronic hepatitis B are candidates for liver transplantation. Prior to the availability of anti-viral therapy re-infection of the graft was common. Chronic hepatitis B post-liver transplant causes aggressive disease and a rapid evolution to cirrhosis and liver failure. Many liver transplant centres are currently treating these patients with lamivudine before transplantation. Some patients may improve sufficiently to avoid or delay the need for transplantation. Timing of the introduction of lamivudine is important. Waiting times for liver transplantation are long. Prolonged use of lamivudine pre-transplant may allow the appearance of the YMDD-variant. These patients develop HBV DNA in serum once more, and may lose their opportunity for transplantation. Therefore the possibility of improved liver function must be balanced by the risk of emergence of viral resistance. Furthermore some patients in transplant studies experience a return of active hepatitis after developing YMDD-variant HBV; and may progress to liver failure and death. Loss or partial loss of lamivudine virologic efficiency in patients with advanced disease and/or immunosuppression may also be associated with more frequent or more severe disease progression than is observed in non-decompensated patients.

Low dose interferon is not recommended in decompensated hepatitis B cirrhosis. Patients with decompensated chronic hepatitis B should be referred to a liver transplant center, and treatment with lamivudine coordinated with the transplant center.

- **Extra Hepatic Manifestations of Hepatitis B:**

Glomerulonephritis

Both acute and chronic HBV infections have been associated with membranoproliferative glomerulonephritis, in which immune complexes are deposited in the basement membrane of the glomerulus. Interferon therapy is very effective for hepatitis B-induced membranous glomerulonephritis, but response is poor in those with membranoproliferative glomerulonephritis (41,42). In membranoproliferative glomerulo-nephritis HBeAg clearance occurs in the same proportion of patients as with standard indications for chronic liver hepatitis B. Corticosteroid therapy is contraindicated. There are no reports on the use of lamivudine in these patients.

The indications for interferon therapy in patients with hepatitis B-induced membranproliferative glomerulonephritis are the same as for hepatitis B patients without glomerulonephritis, i.e., the indication for treatment is the liver disease**. In membranous glomerulonephritis, the renal disease *per se* is an indication for interferon therapy** (because the response rate is so good)**. No recommendations for or against the use of lamivudine could be made.**

- **Chronic Hepatitis B in Children**

The risk of chronicity in hepatitis B infections in newborns and early childhood is high (see table 4). In addition, most infants and young children infected with hepatitis B have normal aminotransferases and are not candidates for therapy (8,43).

Children who are first infected at ages over 7 years of age have a low risk of developing chronic disease. The prognosis of hepatitis B in children is generally good, cirrhosis and hepatocellular carcinoma are only rarely seen in the childhood years. Spontaneous sero-conversion from HBeAg to anti-HBe antibody occurs in between 6-12% of infected children per year. In randomized controlled trials treatment with alpha-interferon in children resulted in 35% clearance of HBV DNA and HBeAg (11% in controls) and 7% clearance of

HBsAg (1% in controls) (44). **Optimal treatment is between 3-6 mu/m2 of interferon TIW for 6 months. 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, because of the side effects of alpha-interferon. In older children the side effects of interferon appear to be well-tolerated. Weight loss can be offset by dietary interventions.

Table 4

EARLY CHILDHOOD HBV INFECTION	
RISK OF CHRONICITY	
Age at Infection (years)	Proportion who become carriers (%)
<1	70-90
2-3	40-70
4-6	10-40
>7	6-10

4. COMMENT

The treatment of chronic hepatitis B is complex, and is 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, because inappropriate therapy may limit future therapeutic options.

HEPATITIS C VIRUS

Hepatitis C virus (HCV) is a heterogeneous, 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 (47). Genotype 1 appears to be the predominant type in Canada (46-49). Quasispecies are closely related variants of a single genotype within a single individual, which arise from mutations that occur during viral replication. Quasispecies diversity may increase with time and contribute to interferon resistance and viral persistence.

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 (e.g., lymphocytes). Thus, given the current state of knowledge complete viral clearance cannot be ascertained with certainty. Therefore, **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 (50-52). However, the proportion of patients at risk for this outcome has not been accurately determined. Various reports have suggested that the lifetime risk of cirrhosis in HCV carriers is between 20-50%. Although several factors have been identified which increase this risk, e.g., alcohol consumption (53-55), the magnitude of increase in risk has not been well defined. Furthermore, the rate at which disease progresses has also not been completely defined (56-58). Some studies have indicated that after 17 years of infection the prevalence of cirrhosis is no more than 2% (60). Other studies have indicated that the mean duration between infection and the first diagnosis of cirrhosis is about 20 years (50). The differences in these studies are accounted for by referral bias. As a result there is considerable uncertainty about the rate of disease progression.

Factors that increase the risk of progression to cirrhosis include age over 40, consumption of even moderate amounts of alcohol (53-55**), and increased age of acquisition of infection.** Patients infected by transfusion are also thought to have more aggressive disease, but in this cohort having a transfusion may be a surrogate marker for increased age at acquisition of disease, since the transfused population is considerably older than the average population. **The risk of progression to cirrhosis also appears related to the degree of liver inflammation and fibrosis seen at the time of a biopsy. Patients with persistently normal ALT have a lower likelihood of progression to cirrhosis** (56,60,61). There is no clear association of disease progression with genotype or viral load. Co-infection with HIV is associated with higher viral loads, and a more rapid progression to cirrhosis (see later). Co-infection with hepatitis B is associated with a greater risk of HCC than either disease alone (see later).

Predictions of disease progression depend on the assumption that the rate of disease progression is linear, and that it takes an equal amount of time to progress from e.g., stage 1 fibrosis to stage 2 fibrosis as from stage 3 to stage 4 fibrosis. This assumption may not be correct.

Once cirrhosis has developed the 10 year survival is about 80%. However, the rate of development of complications of cirrhosis over the same time period is about 40% (62).

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. Predictions in the USA indicate that there will be a 60% increase in the incidence of cirrhosis, a 68% increase in hepatoma incidence, a 279% increment in incidence of hepatic decompensation, a 528% increase in the need for transplantation, and a 223% increase in liver death rate. There are no comparable studies to assess the future health burden in Canada, but since the demographics in the US and Canada are similar, we can expect a similar increase in these disease states in Canada.

1. HEPATITIS C RNA TESTING

As with HBV DNA testing, there is a large inter-assay and intra-assay variation with HCV RNA testing. Once more the requesting physician should be familiar with the characteristics of the assay being used (table 5), 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 (lower limit of sensitivity 100 copies/ml). Quantitative assays available include the Chiron bDNA assay and the Roche Monitor™ assay, which measures down to 1000 particles/ml. The most recent studies on therapy using interferon and ribavirin or PEGylated interferon use the National Genetics assay, which although commercially available requires the sample to be sent to the NGI lab. There is approximately a 10-fold difference between the Monitor and the NGI assay, so that $2x10^6$ copies/ml in the NGI assay is equivalent to about $2x10^5$ copies/ml in the Monitor assay. This becomes important when comparing viral load data between published studies and individual patients.

2. 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 normal ALT levels. Interpretation of the results of such testing is given in table 6. 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 (see later), 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 routinely required for all patients. There was no consensus as to the requirement for quantitative HCV-RNA testing prior to treatment. Viral load is a predictor of response to therapy, but the panel felt that viral load should not be used to assess duration of therapy (see later). High viral loads should not be a deterrent to initiating treatment.

Table 5. Manufacturer's reported dynamic ranges for HCV RNA assays

Method	Working range
Roche AMPLICOR™ HCV Monitor™ (Quantitative) PCR Assay	$1\text{-}2x10^3 – 5x10^7$ copies/ml
Roche AMPLICOR™ HCV (Qualitative) PCR test	100 copies/ml (lower limit of sensitivity)
Chiron Quantiplex™ bDNA HCV RNA Assay version 2	0.2 – 120 Meq/ml ($2x10^5 – 1.2x10^9$ copies/ml)
NGI (National Genetics Institute) HCV SuperQuant™	100 - $5.0x10^7$ copies/ml

Table 6 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

3. SEXUAL TRANSMISSION OF 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 (63-67). **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 (66,67). It is not clear whether the probability of transmission between partners increases with decades of marriage and/or age (68,69). This does not necessarily represent sexual transmission.

The infected person should inform sexual partners. 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. Couples should be given information about the risks of transmission, and about precautions which may reduce the risk of transmission. The committee neither recommends nor recommends against the use of condoms in stable monogamous relationships. It is up to the couple to make a decision, based upon the best information that can be provided to them.

4. MOTHER-TO-INFANT TRANSMISSION OF HEPATITIS C VIRUS

Rates of transmission of hepatitis C from mother to newborn infant vary between 0 and 3% according to different reports (70-73)**.** Two risk factors have been identified, HIV infection in the mother, and high maternal viral load (70,73). It is controversial whether caesarian section prevents transmission of HCV. Results of testing breast milk for HCV RNA are conflicting. However, 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 very limited information in the literature con-cerning the rate of chronicity after neonatal transmission. Clearance of the virus may occur more frequently than in adult infection.

5. 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 (60). Treatment may not be required. Interferon monotherapy treatment in this group is largely ineffective. There are no data on the use of interferon and ribavirin combination therapy in this group.

Although the ALT is the trigger for considering treatment, other factors may also influence the decision whether to treat or not. **A liver biopsy is recommended for grading and staging of the liver disease.** When treating immunosuppressed patients such as renal or bone marrow transplant recipients, a biopsy is mandatory to confirm the diagnosis. If the biopsy is normal or shows minimal disease then treatment may not be necessary. An adequate biopsy consisting of at least 3-5 portal zones is necessary for assessment. Many other factors have to be taken into consideration before deciding to treat a particular patient. Most important is to try to make an assessment of whether the patient will ever develop cirrhosis and liver failure, or particularly in patients over age 50, whether 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.

It is recommended that response to treatment be defined in virologic terms. The use of ALT levels to define response to treatment is

no longer recommended. **Successful treatment is indicated by clearance of hepatitis C virus RNA from serum (by sensitive PCR-based assays) 6 months after the completion of therapy (sustained response).** There is now evidence showing that this response is durable, in that serum HCV RNA remains negative for years (74). ALT levels return to normal, and the incidence of complications of cirrhosis and hepatocellular carcinoma are reduced. Survival is improved.

- **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 3 mu TIW, and the dose of ribavirin is 1000 mg for patients weighing less that 75 kg, and 1200 mg daily for patients weighing more than 75 kg (75-77)**.** 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 (76,77). 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 ($<2x10^6$ copies/ml by the NGI assay), age less than 40 years, absence of fibrosis and female gender (77).

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** (53,54)**.** 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. An algorithm has been developed using several of the favourable response factors listed above (77). However, the algorithm has not been prospectively validated, and should not be used to determine treatment duration.

Unlike interferon monotherapy, 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. 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 2-4 weeks, then stabilizes in most patients. Ribavirin dose reduction is recommended if the hemoglobin falls below 100 gm/l. Routine monitoring for adverse effects includes a CBC weekly for the first month then CBC monthly and TSH every 3 months (there is a increased incidence of thryroiditis on interferon therapy, particularly in patients with chronic hepatitis C). Symptoms should be monitored monthly during treatment.

Treatment response is 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.

- **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 e.g. older age, co-morbid conditions, decompensated liver disease, and active alcohol abuse (abuse within previous 6 months). 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). Interferon can cause an autoimmune thyroiditis. However, patients who are hypothyroid cannot suffer any further harm. Other factors increasing the risk of adverse events include myelosuppression, such as thrombocytopenia and neutropenia. Therapy should not be instituted if the platelet count is less than $80x10^9$/l or the neutrophil count is less than $1.0x10^9$/l. Renal failure and anemia increase the risk of adverse effects from the ribavirin. Ribavirin is teratogenic. Patients on combination therapy 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 e.g. active substance abuse may not be suitable candidates for treatment.

Other conditions, which are relative contraindications, include severe asthma, psoriasis and past history of autoimmune diseases or psychiatric disorders.

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. Data on the need to aggressively reduce hepatic iron by chelation to optimize response to treatment is controversial. Alternatively these patients may be better off waiting for the long acting interferons to become available.

- **Hemophilia**

Patients with hemophilia can be offered therapy (78,79). Pre-treatment assessment should include a liver biopsy that may be performed by the transjugular or by plugged percutaneous route with clotting factor coverage.

- **Methadone maintenance**

Patients on methadone maintenance should not be excluded from treatment.

- **Prisoners**

Therapy for incarcerated patients should be individualized 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. **These patients should be offered treatment with**

interferon and ribavirin (80)**.** 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%. These include re-treatment with interferon and ribavirin, treatment with consensus interferon (81), 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 mono-therapy.**

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. Up to 30% of these children appear to have spontaneous resolution of their infection.

Although progression of the disease seems to be more benign in children than in adults, some children do develop significant fibrosis. Uncontrolled trials suggest that the response rate to interferon may be as high as 33-50%(82-84). The response to combination therapy (interferon and ribavirin) is unknown. 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, the routine screening of blood products has decreased the prevalence 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 a risk for infection is relatively low at <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. There are no data to indicate which testing algorithms, using serological tests or PCR assays, are more cost effective. HCV RNA may become positive as early as 2 weeks after exposure. Anti-HCV usually becomes positive 10 weeks after exposure. There has been a suggestion that early treatment of acute hepatitis C with interferon monotherapy C may enhance the likelihood of response compared to chronic hepatitis C (85-87). There is no information as to whether this is true for interferon and ribavirin. The possibility of an enhanced response to early therapy has to be balanced against the theoretical 20% chance of spontaneous clearance of the virus. **No recommendations can be made about the timing of therapy of acute hepatitis C**. The following recommendation is therefore based on expert opinion, rather than evidence from the medical literature.

Healthcare 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 prospective 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.

COMBINED INFECTIONS

1. HEPATITIS B AND HEPATITIS C

The prevalence of combined infections with these two organisms in Canada is unknown. Elsewhere the prevalence ranges between 3.4-18.3% in series of patients with hepatitis C (88-90). Various studies have demonstrated that the outcome of combined infection is more severe than infection with either virus alone (91,92). 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 (93-96). There are few reports of treatment (97). 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 disease exists on its own. For example, **in patients who are HBeAg-positive with detectable HBV DNA, undetectable HCV RNA and elevated aminotransferases, treatment is with interferon 27-36 mu weekly for 4 months.** Conversely, **if the HBV DNA is undetectable, and HCV RNA is present, the treatment is with interferon and ribavirin for 24 or 48 weeks, as dictated by the hepatitis C genotype**.

2. 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 (31,32,98). 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. Since lamivudine is a component of highly active anti-retroviral therapy, patients co-infected with both viruses may receive appropriate treatment for the hepatitis B as a fortunate, but not necessarily intended, result of HIV therapy. **Chronic hepatitis B in HIV-infected patients must not be treated with lamivudine monotherapy.** Lamivudine monotherapy will result in the rapid emergence of resistant HIV virus.

3. HEPATITIS C AND HIV

Hepatitis C infection occurs in HIV-positive patients with a frequency between 50-90%. Co-infection results in hepatitis C viral loads that are higher than in the absence of HIV (99,100). Progression to cirrhosis is also more rapid (100). Treatment with interferon monotherapy has a success rate not much different than for hepatitis C in the absence of HIV (about15%)(101-104). 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.**

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. Thus Asian patients who acquire the disease in childhood, by virtue of the long duration of the disease, are at a significantly higher risk of developing HCC than Alaskan natives or Caucasians (20,105-107). The cumulative probability of developing HCC in patients who are HBsAg-positive has been estimated to be 6% at 5 years and 15% at 10 years. Once HCC develops, the prognosis is very poor. Survival of patients with symptomatic untreated tumours beyond 3 years is rare (108).

The enthusiasm to screen patients with HBV for HCC is based on the premise that earlier detection can offer these patients a chance for potential cure. There are 2 large North American studies of screening in hepatitis B carriers (107,109). One suggests that screening is very effective at finding curable tumours, whereas the other suggests otherwise.

The risk of developing HCC in a non-cirrhotic patient with hepatitis C (HCV) is trivial. Once cirrhosis is present, the cumulative probability of developing HCC is estimated to be 1.4 to 3.3% per year (50,62). Apart from cirrhosis, other factors that increase the patient's risk for developing HCC include long duration of infection, male gender, greater than 55 years, continued alcohol consumption and co-infection with HBV. Response to interferon treatment appears to 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. Much of what is known about screening for HCC in patients with HBV also applies to patients with HCV.

There have been no studies to determine whether screening for HCC decreases the disease-specific mortality. Thus, the most important piece of information about whether the potential effectiveness of screening is missing. The decision to screen or not screen therefore must rest on other factors.

One of the reasons why screening may not be effective is the poor sensitivity of our screening tests. The currently employed screening tests, which include alpha-fetoprotein and ultrasound, have sensitivities of 50% and 70% respectively (107). Furthermore, HCC tends to occur in patients with cirrhosis, many of whom cannot tolerate a curative surgical resection. Thus, the other treatment options left are liver transplantation or alcohol injection of the lesions. The former is only limited to patients who are HBV DNA negative either spontaneously or induced by therapy. The lack of suitable organ donors makes this option available to a limited few. Alcohol injection can be an effective treatment for HCC, but its efficacy is markedly reduced in patients with large tumours (>5cm). It is technically difficult to perform in patients with ascites and coagulopathy.

Screening should only be performed when effective curative therapy is possible, and in patient groups where the relative risk of HCC development is high. Screening is also appropriate in patients who have undergone a curative resection for HCC.

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]).

HEPATITIS B VACCINATION

At present hepatitis 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. Recent data indicate that in endemic countries horizontal transmission is more common than previously recognized. Horizontal transmission has also been shown to occur at a high rate in South East Asian and other immigrant communities in North America (110-112). The objectives of a universal hepatitis B vaccination policy should be to eliminate vertical (mother to child) transmission, as well as horizontal transmission

in early childhood. The policies 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. There should be a standardized national policy, so that vaccination is assured for all children when their families move between provinces.

The seroconversion rate after hepatitis B vaccination in healthy young adults is >90% and children >98%. Therefore, **serologic testing post-immunization is not recommended routinely**. It is recommended, however, for those with continual or repeated exposures. This would apply to 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 (113).

HEPATITIS A VACCINATION

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. In addition, some studies have suggested that acute hepatitis A infection in patients with chronic liver disease may also cause severe disease, including death (114). However, it is not clear whether the risk of severe hepatitis A is related to the severity of the underlying liver disease or to other factors.

Hepatitis A vaccines are safe and effective. Patients with compensated cirrhosis appear to respond adequately to the hepatitis A vaccine (115).

Current recommendations by NACI with regard to populations in whom vaccination is appropriate remain pertinent (116). These are listed in table 7.

Table 7 Recommended usage for pre-exposure prophylaxis against hepatitis A.

Potential candidates for the vaccine are
1. Travelers to countries where hepatitis A is endemic, especially when travel involves rural or primitive conditions
2. Residents of communities with high endemic rates or recurrent outbreaks of HAV
3. 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
4. Residents and staff of institutions for the developmentally challenged where there is an ongoing problem with HAV transmission
5. Inmates of correctional facilities in which there is an ongoing problem with HAV infection
6. People with life-style determined risks of infection, including those engaging in oral or intravenous illicit drug use in unsanitary conditions
7. Men who have sex with men
8. People with chronic liver disease who may not be at increased risk of infection but are at increased risk of fulminant hepatitis A
9. 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 cost effectiveness of a universal strategy of hepatitis A vaccination in Canada is not known. There is limited information on the long-term benefit of hepatitis A vaccination in patients with chronic liver disease. Although universal vaccination for hepatitis A is a worthy goal its role in any unified strategy for disease prevention remains to be determined.

HEPATITIS G VIRUS

Hepatitis G (HGV) is a flavivirus, which shares about 27 – 40% sequence homology with HCV (117). HGV is identical to the "GB-C" agent, originally found in a surgeon with hepatitis and later identified in animals to be different from hepatitis viruses A, B, C, D and E, respectively. Studies on post transfusion hepatitis in HGV RNA-positive blood donors, and in community acquired acute hepatitis have suggested that HGV is not an important cause of chronic liver disease (118,119). Some patients who acquired hepatitis G from transfusion have developed a mild transient aminotransferase elevation that resolves spontaneously (120). Although the virus may persist, it appears that chronic liver disease does not ensue. Further, the liver is not the primary site of HGV replication (121). There is a high prevalence of HGV in blood donors, perhaps in the order of 1-2%. Fulminant hepatitis is rare. HGV is transmitted by intravenous and sexual routes and perhaps also via perinatal transmission. Its presence in liver transplant recipients does not affect the outcome of the disease (122). **Routine screening of blood donors or wide spread testing for HGV is not recommended**. Diagnosis requires virologic methods based on PCR or serologic assays using the E2 antibody. Neither of these is readily available.

TRANSFUSION TRANSMITTED VIRUS

Transfusion transmitted virus is a recently described virus (123,124). Its epidemiology and disease associations are unknown. Viremia is common (125), but there is no known association with liver disease. There are no commercially available kits to assay for this virus. Therefore**, no active attempt at diagnosing this infection is required.**

THE CANADIAN ASSOCIATION FOR STUDY OF THE LIVER CONSENSUS CONFERENCE ON VIRAL HEPATITIS

This report was written by a committee consisting of:-

Chairman – Eldon Shaffer, University of Calgary
Florence Wong, Susan King, Morris Sherman, University of Toronto
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Jutta Preiksaitis, University of Alberta

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Linda Scully - University of Ottawa
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SUMMARY OF RECOMMENDATIONS

CHRONIC HEPATITIS B

- 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 6 months with or without continuing liver enzyme abnormalities accounts for the greatest burden of disease.

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.

HBV DNA Assays

- It is important for the clinician to understand the type of assay methodology used, and its limitations, and that a consistent methodology be used 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.

Treatment of the Hepatitis B Carrier

- In the HBeAg-positive patient with abnormal ALT levels liver biopsy is strongly recommended, but not mandatory.
- 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.
- Lamivudine therapy for patients who are anti-HBe-positive and HBV DNA-positive is still considered experimental.
- The use of prednisone withdrawal prior to interferon therapy is contraindicated in the management of HBV-associated disease.
- There is insufficient information to recommend routine screening of immunosuppressed patients for HBV infection.
- There is also insufficient information to recommend lamivudine anti-viral prophylaxis for immunosuppressed patients who are known to be hepatitis B carriers.

Hepatitis D Virus

- Patients with active hepatitis D should be treated in expert centres.

Decompensated Hepatitis B Cirrhosis:

- Low dose interferon is not recommended in decompensated hepatitis B cirrhosis. Patients with decompensated chronic hepatitis B should be referred to a liver transplant center, and treatment with lamivudine coordinated with the transplant center.

Glomerulonephritis

- The indications for interferon therapy in patients with hepatitis B-induced membranproliferative glomerulonephritis are the same as for hepatitis B patients without glomerulonephritis. In membranous glomerulonephritis, the renal disease *per se* is an indication for interferon therapy. No recommendations for or against the use of lamivudine could be made.

Chronic Hepatitis B in Children

- Optimal treatment is between 3-6 Mu/m2 interferon thrice weekly for 6 months. The indications for treatment are similar to those in adults.

HEPATITIS C VIRUS

- 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.

- Factors that increase the risk of progression to cirrhosis include age over 40, consumption of even moderate amounts of alcohol, and increased age of acquisition of infection.
- The risk of progression to cirrhosis also appears related to the degree of liver inflammation and fibrosis seen at the time of a biopsy. Patients with persistently normal ALT have a lower likelihood of progression to cirrhosis.

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.
- Quantitative HCV RNA testing is not routinely required for all patients.

Sexual transmission of the hepatitis C virus

- HCV intra-spousal transmission appears to be rare in the absence of a parenteral risk in the partner.
- The infected person should inform sexual partners. 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. Couples should be given information about the risks of transmission, and about precautions which may reduce the risk of transmission in stable monogamous relationships. The com-mittee neither recommends nor recom-mends against the use of condoms. The choice belongs to the couple.

Mother-to-Infant Transmission of Hepatitis C Virus

- Rates of transmission of hepatitis C from mother to newborn infant vary between 0 and 3% according to different reports.
- Breast feeding is considered safe and is not contraindicated
- Testing for hepatitis C infection within the first 18 months of life should be by PCR assays.

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.
- A liver biopsy is recommended for grading and staging of the liver disease.
- It is recommended that response to treatment be defined in virologic terms.
- Successful treatment is indicated by clear-ance of hepatitis C virus RNA from serum (by sensitive PCR-based assays) 24 weeks after the completion of therapy (sustained response).

Dose and Duration of Treatment

- The recommended treatment for chronic hepatitis C is with a combination of inter-feron alpha 2b and ribavirin. The dose of interferon is 3 mu TIW, and the dose of ribavirin is 1000 mg for patients weighing less that 75 kg, and 1200 mg daily for patients weighing more than 75 kg
- Patients who carry genotypes 2 or 3 may be treated for 24 weeks. Patients carrying any other genotype should be treated for 48 weeks.
- 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

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.

- 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.

Treatment Failures

- Relapse after interferon monotherapy: - These patients should be offered treatment with interferon and ribavirin.
- Non-responder to interferon monotherapy: -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: - There are no proven treatment options for these patients at present

Hepatitis C Infection in Children

- Chronic hepatitis C in children should not be treated except in controlled trials.

Acute hepatitis C

- No recommendations can be made about the timing of therapy of acute hepatitis C
- Healthcare workers or others subjected to needle-stick injury or equivalent exposure should be tested by anti-HCV at the time of the injury at 12 weeks to detect infection. Treatment should be with standard combination therapy of interferon and ribavirin for the standard duration despite the lack of prospective 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.

COMBINED INFECTIONS

- In patients who are HBeAg-positive with detectable HBV DNA, undetectable HCV RNA and elevated aminotransferases, treatment is with interferon 27-36 mu weekly for 4 months.
- In patients who are HBeAg-positive with detectable HBV DNA, undetectable HCV RNA and elevated aminotransferases, treatment is with interferon 27-36 mu weekly for 4 months.
- Chronic hepatitis B in HIV-infected patients must not be treated with lamivudine monotherapy.
- There are no recommendations about therapy in patients co-infected with hepatitis C and HIV.

SCREENING FOR HEPATOCELLULAR CARCINOMA

- 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]).

HEPATITIS B VACCINATION

- The vaccination strategy for Canada should be universal vaccination of all neonates, combined with screening of all pregnant women. Newborns of infected mothers should 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. There should be a standardized national policy, so that vaccination is assured for all children when their families move between provinces.
- Serologic testing post-immunization is not routinely recommended.

HEPATITIS A VACCINATION

- Current recommendations by NACI with regard to populations in whom vaccination is appropriate remain pertinent.

HEPATITIS G VIRUS

- Routine screening of blood donors or wide spread testing for HGV is not recommended.

TRANSFUSION TRANSMITTED VIRUS

- No active attempt at diagnosing this infection is required.

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