

# Hepatitis C infection: Its sequelae and outcomes – State-of-the-Art Workshop, September 24 to 25, 1998

Canadian Association for Study of the Liver (CASL)

Canadian Association for Study of the Liver (CASL). Hepatitis C infection: Its sequelae and outcomes, State-of-the-Art Workshop, September 24 to 25, 1998. *Can J Gastroenterol* 2000;14(Suppl B):49B-58B. This report summarizes a state-of-the-art workshop held in September 1998 on the "Natural History and Outcome of Hepatitis C Infection". Sixteen Canadian and two internationally renowned hepatologists were invited. A practical classification of HCV infection served as a framework for the meeting. The concepts of modelling of chronic disease, the epidemiology of HCV infection before the introduction of anti-HCV testing, and the outcome of various forms of chronic hepatitis C in adults and children were presented. Lectures on the outcome of HCV cirrhosis, hepatocellular carcinoma, the role of liver transplantation, the influence of host factors on outcome, iron overload in chronic hepatitis C and possible modification of the natural history by antiviral therapy were followed by discussion and consensus statements pertaining to each presentation. "The European Experience in Assessing Chronic Hepatitis C" was presented by Prof G Dusheiko from the United Kingdom, and Prof Leonard Seeff from the National Institutes of Health (United States) presented "The Epidemiology and Outcome of Hepatitis C Infection in the United States and the World".

**Key Words:** *Chronic hepatitis C; Consensus statement; Hepatitis C virus; Hepatocellular carcinoma; Liver transplantation*

## L'hépatite C, ses séquelles et son aboutissement : Atelier des 24 et 25 septembre 1998 pour faire le point

**RÉSUMÉ :** Ce rapport présente les points saillants d'un atelier tenu en septembre 1998 pour faire le point sur les plus récentes découvertes sur l'histoire naturelle et l'issue de l'hépatite C. Seize hépatologues canadiens et deux hépatologues de renommée internationale y avaient été conviés. La classification standard de l'infection par le HCV a servi de cadre à la réunion. Les médecins ont abordé la notion de modélisation appliquée aux maladies chroniques, l'épidémiologie de l'infection par le HCV avant l'introduction des tests de dépistage de l'anticorps anti-HCV et l'issue des diverses formes d'hépatite C chronique chez l'adulte et chez l'enfant. Des présentations sur l'issue de la cirrhose liée à l'HCV, l'hépatocarcinome, le rôle de la transplantation hépatique, l'influence des facteurs liés à l'hôte sur l'évolution de la maladie, la surcharge ferrique dans l'hépatite C et la modification possible de l'évolution naturelle de la maladie au moyen des antiviraux ont été suivies de discussions et d'énoncés consensuels relatifs à chacune. « *L'European Experience in Assessing Chronic Hepatitis C* » a été présentée par le Professeur G. Dusheiko, du Royaume-Uni, et le professeur Leonard Seef, des *National Institutes of Health* des États-Unis, a pour sa part abordé le thème « *Epidemiology and Outcome of Hepatitis C Infection in the United States and the World* ».

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This report summarizes the presentations made during an important meeting sponsored by Health Canada held in Toronto on September 24 and 25, 1998, to discuss the sequelae and outcomes of hepatitis C infection. Key points raised during interactive discussion and in response to questions submitted by interested parties are included. During the course of the meeting, a number of consensus statements were developed, with broad agreement from participants. A brief synopsis of each presentation is provided, along with the consensus statements pertaining to each discussion.

### POST-TRANSFUSION HEPATITIS C VIRUS (HCV) – IMPLICATIONS AND CLASSIFICATION OF THE ANTI-HCV-POSITIVE INDIVIDUAL

*Dr S Victor Feinman*

Over the past 110 years, clinicians have known that hepatitis could result from infection of human plasma, but only thanks to progress in basic science did the various causes of chronic hepatitis become apparent. Important contributions from basic science included advances in enzymology (testing for serum alanine aminotransferase [ALT] levels was only developed in 1956 [1]), liver biopsy (introduced in 1884 but only clinically used since 1957), antigen-antibody detection systems, electron microscopy and immunoelectron microscopy, all the way to recombinant technology in the late 1980s. At each step, advances in technology and basic science have enriched clinical knowledge and treatment. Whereas Blumberg et al (2) required immunodiffusion to describe the hepatitis B virus antigen, 33 years later Houghten (and colleagues Choo et al [3]) had the help of recombinant technology to characterize the HCV genome.

Now, at the end of the 20th century, the same process continues. Designer HCV-like particles, genomic manipulation and drugs (such as nucleoside analogues, protease inhibitors and helicase inhibitors) are all recent examples of basic science advances that have direct clinical applications.

Before the introduction of universal testing of blood donors in May 1990, anti-HCV prevalence ranged from 0.2% to 0.3% in Canadian donors, 0.4% to 1.0% in American donors, and 0.9% to 1.7% in South American donors. A key point from these studies is that before testing of blood donors, anti-HCV positivity was approximately twice as high in the United States as it was in Canada.

Rates of post-transfusion hepatitis in Canada were 3.1% in 1984 to 1985, dropping to 0.6% from 1988 to mid-1990, and then falling further to 0.2% with the advent of anti-HCV testing after May 1990 (4). In the United States, the rate of post-transfusion hepatitis C was 3.84% in 1984-85, 1.59% with the use of surrogate testing in 1986 to 1990 and then 0.57% with surrogate plus anti-HCV testing after June 1990. Again, it is interesting to note that the rates in the United States were higher than those in Canada at each stage of testing. The decline in rates of post-transfusion hepatitis in Canada in the late 1980s can be explained by more stringent selection of donors.

Further analysis of anti-HCV-positive donors detected

**TABLE 1**  
**Classification of hepatitis C virus (HCV) infection**

Patient group	Description
I	<b>Anti-HCV-positive, normal ALT, HCV RNA-negative</b> False positive (RIBA-negative) Remote HCV infection Chronic hepatitis with complete response to antiviral therapy Transient absence of HCV RNA in chronic infection
II	<b>Anti-HCV-positive, normal ALT, HCV RNA-positive</b> Subgroup of chronic hepatitis C with good prognosis? Need frequent reviews "Tolerant" state of hepatitis C? Occasional case of compensated cirrhosis
III	<b>Anti-HCV-positive, elevated ALT, HCV RNA-positive</b> Chronic hepatitis C mild, no cirrhosis Chronic hepatitis C moderate to severe, no cirrhosis Chronic hepatitis C with cirrhosis (compensated) Chronic hepatitis C with cirrhosis (decompensated) Hepatocellular carcinoma
IV	<b>Anti-HCV-negative, elevated ALT, HCV RNA-positive</b> Early two to three weeks of acute hepatitis C Chronic hepatitis C in immunosuppressed patients

*ALT Alanine aminotransferase; RIBA Recombinant immunoblot assays*

between 1990 and the end of 1993 found that many were false-positives (only 176 were confirmed of 340 detected). In turn, of those 176 donors confirmed to be anti-HCV-positive, only 107 (61%) were viremic when tested by polymerase chain reaction (PCR). Almost half (47%) of these confirmed positive donors admitted to intravenous drug use in the past. This underscores the crucial point that one of the most important screening procedures for the prevention of post-transfusion hepatitis C is still thorough questioning of donors about risk factors, especially intravenous drug use.

During a study of post-transfusion hepatitis between 1988 and 1992, 3842 blood product recipients were tested for anti-HCV before and 24 weeks after receipt of blood products. Whereas 56 of the 3842 study subjects were anti-HCV positive 24 weeks after transfusion, 41 (1%) of these 56 were positive before transfusion (unpublished data). In other words, many blood recipients were infected with HCV before receiving blood products.

A proposed classification of HCV infection is shown in Table 1. This classification served as a framework for the remainder of the meeting.

Several implications of this classification scheme were discussed. The participants debated whether improved testing (possibly PCR assessment of liver tissue) would find minute amounts of HCV RNA in the first group (group I in Table 1), which would lead to the conclusion that successful treatment of hepatitis C leads to resolution of disease, but not eradication of the virus. With the present state of knowledge, it was agreed that patients in the first group (group I in Table 1) simply require follow-up with ALT testing. Most of these patients have recovered from a remote HCV infection.

**Consensus statement 1:** The natural history and outcomes of hepatitis C infection are very difficult to study. Most information comes from studies of patients who are ill, and may overrepresent patients who have more severe disease. Hepatitis C infection has an acute stage that is often asymptomatic, so the date of onset of infection is often unknown. Infections in some patients completely resolve after the acute stage but most go on to chronic infection. There is no way to predict who will clear the acute infection. After 20 or 30 years of infection, a minority of patients develop serious liver disease, although, rarely, overt liver disease can occur in the first decade of infection. Again, there is no way to predict the rate of progression for any individual. Many exogenous factors influence the rate of progression, among which alcohol use is one of the most powerful.

### FUNDAMENTALS OF MODELLING CHRONIC DISEASE

*Dr Murray Krahn*

Theoretical modelling of chronic disease has become a powerful tool for examining outcomes, especially in conditions that have a clinical course measured in decades. Modelling is based on decision analysis, which is a systematic approach to decision-making under conditions of uncertainty. Decision analysis is explicit, quantitative and proscriptive; it gives an explicit solution that is rational. First developed in World War II, decision analysis is used in business and increasingly in medicine, both at a policy level and for looking at cost effectiveness.

Undertaking a decision analysis involves four steps: creating a tree of all outcomes, with assigned probabilities and estimated values; calculating the expected value of each alternative; performing a sensitivity analysis; and interpreting the results. Modelling is difficult. It is time-consuming and can take months to years. Because it is a mathematical approach that is nonintuitive, it may be threatening to clinicians. Further, it is always an oversimplification of clinical reality, and methods for assessment of quality of life remain difficult.

However, in cost effectiveness and policy decisions, theoretical modelling can be a valuable way to arrive at objective data.

**Consensus statement 2:** Decision analysis modelling for outcomes in hepatitis C is difficult because of the uncertainties described. Nonetheless, models have been published (5) and can form a basis for estimating outcomes, with appropriate caveats.

### ASSESSMENT OF THE PATIENT WHO IS ANTI-HCV-POSITIVE AND HCV RNA-POSITIVE, WITH A NORMAL ALT

*Dr Urs Steinbrecher*

The assessment of a large group of patients who were anti-HCV positive and HCV RNA-positive, but with normal ALT levels was discussed. A number of small studies have examined liver histology in these patients, with wide ranging results. About 70% of such patients have high fibrosis scores or frank cirrhosis, whereas 20% have normal or minimally abnormal liver histology on biopsy. Treatment in patients with normal ALT levels has been studied, but just in small trials, with inconclusive results. Because treatment is expensive, can have unpleasant side effects and may lead to deleterious changes in quasispecies, the value of treatment in these patients must be questioned.

The value of liver biopsy as part of the assessment is not clear. Although liver histology is the most accurate predictor of prognosis, liver biopsy has measurable risks. Recent guidelines from the Canadian Association for Study of the Liver (CASL) (6) and from the National Institutes of Health (NIH) (7) suggest that the choice of biopsy be up to the individual patient and doctor. Treatment is not routinely recommended.

**Consensus statement 3:** In patients with no apparent active disease (anti-HCV positive, HCV RNA-positive, persistently normal ALT), liver biopsies can reveal mild inflammation in up to 80%. Recommendations from NIH and CASL should be followed with respect to investigation and treatment for this group, who generally have a very favourable prognosis.

### PROGNOSIS FOR PATIENTS WITH MILD CHRONIC HEPATITIS C

*Dr Averell Sherker*

The majority of data on the outlook for patients with mild chronic hepatitis C (CHC) come from Japan, with only a few studies examining sequential biopsies. The most important influencing outcome is duration of infection (a difficult variable to consider in CHC because the time of infectious exposure is often unknown). Cross-sectional studies have attempted to estimate prognosis by comparing results of biopsy in patients with normal ALT levels with biopsy results in matched patients with abnormal ALT levels. One such study found an estimated rate of progression of fibrosis scores of 0.05 U/year for patients with normal ALT levels, compared with 0.13 U/year for patients with elevated ALT levels (8).

For individual patients, the most accurate tool for assessment and prognosis is liver biopsy. Although there are minor variations in staging and grading criteria in different centres, the most frequently used criteria for grading and staging of liver biopsies are shown in Table 2.

**TABLE 2**  
**Staging and grading in chronic hepatitis**

Grade of inflammation/ necrosis	Description
Grade 0	No inflammation
Grade 1	Portal inflammation, minimal lobular activity
Grade 2	Changes of grade 1 plus some piecemeal necrosis (interface hepatitis) and more lobular activity
Grade 3	Changes of grade 2 plus more piecemeal necrosis and more lobular activity
Grade 4	Changes of grade 3 plus bridging necrosis
Staging of fibrosis	Description
Stage 0	No fibrosis
Stage 1	Mild portal fibrosis
Stage 2	Portal and periportal fibrosis
Stage 3	Changes of stage 2 plus bridging fibrosis
Stage 4	Cirrhosis

Whether mild CHC can persist without progression to cirrhosis or whether complete recovery can occur is unclear.

**Consensus statement 4:** For patients with mild CHC (anti-HCV positive, HCV RNA positive, ALT level more than 1.5 times normal, and liver histology showing mild inflammation and no or minimal fibrosis), outcomes can be projected in general terms:

10-year projection – significant histological progression unlikely, morbidity highly unlikely, mortality very highly unlikely;

20-year projection – significant histological progression possible, morbidity unlikely, mortality highly unlikely.

**Consensus statement 5:** Does natural history of transfusion-associated hepatitis (TAH) differ from the natural history of hepatitis C acquired in any other way? Few studies have examined this issue; while the majority of work suggests a worse prognosis for TAH, conflicting information also exists, and other factors (such as age, previous transfusion, alcohol use, being male, co-infections and immunosuppression) are confounders. Patients who have had a transfusion may have acquired hepatitis C in some other manner, either before or after the transfusion.

#### PROGNOSIS OF SEVERE CHC – NO CIRRHOSIS

*Dr Bernard Willems*

In patients with severe hepatitis C, but no cirrhosis, the mean time from infection to cirrhosis is 20 years, ranging from three years to 50 years or longer. The disease pro-

gression in an individual patient is extremely difficult to predict.

The rate of fibrosis progression varies widely between individuals; some develop fibrosis slowly, some quickly. Hence, the fibrosis score, calculated as: 4 years to cirrhosis, and expressed in fibrosis unit/year (or FU/yr), can vary from nearly 1 to 0.04 fibrosis units/year (9).

Histological stage (fibrosis) and grade (inflammation) on the initial liver biopsy are the most important tools in evaluating prognosis. Septal fibrosis (stage 3) is associated with the worst prognosis – 50% to 100% of these patients develop cirrhosis after 10 years. Patients with moderate to severe inflammation progress twice as rapidly as those with mild inflammation.

The existence of histopathological heterogeneity of liver biopsy in CHC is problematic. In one study (10) comparing the interpretation of two biopsy samples (taken at the same time), the diagnosis of cirrhosis was missed on the first sample in 31% of the cases. Hence, there is a risk of underdiagnosis of the actual liver disease severity. Further studies are necessary to address these problems.

Other parameters identified as determinants of progression to cirrhosis include the following.

Age at infection – those infected after 50 years of age progress more quickly.

Sex – males progress more rapidly than females.

Alcohol consumption – the odds ratio of becoming cirrhotic is approximately 3 in alcoholics versus nonalcoholics.

Route of transmission – in Western countries, the disease in those infected by intravenous drug use progresses more slowly than that in those infected by transfusion, irrespective of the age at infection.

HCV genotype – an important determinant of the response to treatment, but does not seem to play a role in disease progression.

Effective therapy – sustained response to available (or future) treatment with a long term loss of HCV-RNA stops the progression of the disease; on the other hand, the disease continues to progress in patients with relapse after treatment, or in nonresponders.

**Consensus statement 6:** Biopsy is the most accurate prognostic tool in evaluating prognosis. A patient with marked fibrosis (stage 3 of 4) is very likely to progress to cirrhosis in one or two decades. A patient with no fibrosis and only mild inflammation is unlikely to develop cirrhosis, and extremely unlikely to die of liver disease for at least 20 years.

**Consensus statement 7:** Liver biopsy can provide very useful information. The risks of percutaneous biopsy can be estimated as one in 10,000 to one in 17,000 for death, and one in 600 to one in 1000 for major complications (primarily bleeding needing transfusion or biliary puncture requiring laparotomy). Use of the Menghini-type needle is thought to give fewer complications than use of the Tru-Cut needle. Alternative biopsy methods such as transjugular biopsies may be preferred in some patients.

**Comments on liver biopsy:** The following comments were offered by Dr S Victor Feinman, Professor of Medicine at the University of Toronto, and meeting organizer. In patients with clinical evidence of CHC (abnormal liver enzymes, HCV RNA-positive, and clinical suspicion of liver disease), a liver biopsy is necessary. The test is valuable to assess the severity of the disease, grade of inflammation and necrosis, stage of fibrosis, and presence or absence of cirrhosis, and to rule out conditions other than hepatitis C. Assessment of the patient before biopsy should include an abdominal ultrasound and measurement of clotting factors. Biopsies carried out under ultrasound control have the advantage of localizing the gallbladder, but postbiopsy bleeding rates are unaffected. To be of diagnostic value, the biopsy core should be at least 1.0 cm in length; preferably two biopsies should be taken from different parts of the liver in order to reduce the possibility of sample error in diagnosing cirrhosis. Biopsy should only be performed by qualified personnel.

Indications for biopsy are to be decided by the clinician, and risks must be explained to the patient. After the procedure, the patient must be monitored as an outpatient because bleeding can be delayed.

The decision to perform sequential biopsies to determine the fibrosis progression rate or to discern the impact of antiviral therapy should be made by the clinician after informed discussion with the patient.

#### INFLUENCE OF HOST FACTORS ON OUTCOME OF HEPATITIS C

*Dr Gerald Minuk*

The influence of certain host factors on outcomes has been clearly proven (Table 3). The effects of other factors that have so far been examined only in small studies are still debatable. In most studies, the outcome measured was rate of progression to cirrhosis.

#### PROGNOSIS IN CHC WITH CIRRHOSIS

*Dr Mang Ma*

Many patients with hepatitis C die from causes other than that disease. The long interval between infection and decompensated cirrhosis means that a proportion of patients die of other unrelated causes. A generally accepted estimate

**TABLE 3**  
**Factors affecting outcome of chronic hepatitis C virus (HCV) infection**

Factor	Influence on outcome
Duration of infection	Longer duration may increase rate of progression
Age at infection	Older patients at time of infection have poorer prognosis
Sex	Women recover more often than men, ALT levels are higher in men
Route of infection	Transfusion-related infections have poorer prognosis than IVDU
HLA type	Some HLA types clear HCV more readily than others
Hemophilia	Less fibrosis and active liver disease in hemophiliacs, but limited data
Diabetes	Increased risk of disease
Iron overload	Increased progression
Alcohol	Increased progression (dose-related)
Alpha-1-antitrypsin phenotype	No association
HBV co-infection	Does not increase progression to cirrhosis, but does increase chance of HCC
HIV co-infection	Faster progression to cirrhosis, higher rate of cirrhosis
Smoking	Increased risk of HCC

*ALT Alanine aminotransferase; HBV Hepatitis B virus; HCC Hepatocellular carcinoma; HIV Human immunodeficiency virus; HLA Human leukocyte antigen; IVDU Intravenous drug users*

is that time from infection to cirrhosis is 30–15 years. Once cirrhosis develops, time to decompensation is 10–5 years. In this context, decompensation can mean portal hypertension with varices and bleeding, encephalopathy, ascites, spontaneous bacterial peritonitis or hepatorenal syndrome. Even in patients with decompensated cirrhosis, the five-year survival rate is approximately 50%. One retrospective study of patients with compensated cirrhosis found that, each year, 3.9% of patients decompensated, 1.4% developed hepatocellular carcinoma (HCC) and 1.9% died (11).

**Consensus statement 8:** After 20 years of infection, 3% to 20% of patients show cirrhosis on liver biopsy. Most of the patients with cirrhosis have compensated or asymptomatic disease. This means that after 20 years of infection, at least 80% of patients are free from cirrhosis. When cirrhosis has been diagnosed, the probability of decompensation is 25% after 10 years. Once a patient develops decompensated cirrhosis, the death rate (without transplantation) is 50% after five years. With cirrhosis, the risk of developing HCC is approximately 1.4%/year. Factors shown to increase the rate or probability of progression are being male, age older than 40 years at time of infection and excessive alcohol use (more than three standard drinks/day).

**TABLE 4**  
**Extrahepatic manifestations of hepatitis C**

Proven association	Probable but unproven association
Cryoglobulinemia, with or without vasculitis	Autoimmune thyroid disease
Membranoproliferative glomerulonephritis	Diabetes
Non-Hodgkin's lymphoma	Mooren's corneal ulcer
Porphyria cutanea tarda	Sialadenitis Idiopathic thrombocytopenia Lichen planus

#### EXTRAHEPATIC MANIFESTATIONS OF HEPATITIS C

*Dr Linda Scully*

The extrahepatic manifestations of hepatitis C are rare and seldom have an impact on outcome or prognosis. The associations, both proven and probable, are listed in Table 4. The occurrence of non-Hodgkin's lymphoma in patients with CHC is especially strong in Italy. The common pathogenic link may involve cryoglobulinemia developing first, with immune stimulation leading to the development of a specific clone of T lymphocytes.

#### HCC ASSOCIATED WITH HEPATITIS C

*Dr Morris Sherman*

HCC often is associated with hepatitis C cirrhosis and appears to be more prevalent recently in Canada. This increase and the state of demographic factors suggest that the prevalence of HCC will rise. The natural history of HCC is clearly dependent on size; larger symptomatic tumours have a poor prognosis, with one-year survival of 30% to 40%, and five-year survival is less than 10%. Small tumours have a mean doubling time of 5.7 months, although that is quite variable.

Screening for HCC confers no proven mortality benefit and is expensive. Treatment for HCC, with either resection or ethanol injection, provides significantly better results than no treatment. For small tumours, liver transplantation offers excellent results.

An exciting possibility with HCC is prevention. Chemo-prevention using retinoids has shown benefit in preventing recurrences, and may be useful in primary prevention. Successful treatment for hepatitis C, using interferon (IFN)-based therapy, also appears to reduce the rate of HCC, although this has yet to be conclusively demonstrated.

**Consensus statement 9:** Screening for HCC has no proven benefit. The decision whether to screen is an individual decision of doctor and patient, and partly depends on local resources.

#### HOW TO ASSESS SEVERITY AND OUTCOME OF CHC – THE EUROPEAN EXPERIENCE

*Dr Geoffrey Dusheiko*

The huge variability of outcome in CHC makes prognosis very difficult to determine for an individual patient. The mechanism of progression in CHC is still unknown, despite many studies. Progression might be a straight line from mild to moderate to severe involvement, proceeding at a uniform rate for each patient. Progression may alternatively be an iterative process with episodes of inflammation, each causing a further degree of fibrosis.

The rate of progression in CHC, when compared with that in most other infections, is very slow. In a recent follow-up of the cohort of 414 Irish women who received HCV-contaminated Rh immune globulin in 1977, 44% have some degree of fibrosis, but only 2.8% have cirrhosis (12). There has been only one death so far due to decompensated cirrhosis.

The selection of patients for treatment remains contentious because the prognosis for an individual patient cannot be predicted with certainty. Current guidelines suggest treatment only for patients at greatest risk of progression, and for those with moderate degrees of necrosis, fibrosis and inflammation.

**Consensus statement 10:** Is the prognosis worse in patients with hemophilia than in those with hepatitis C acquired in any other way? There are insufficient histological data to answer this question.

#### FATIGUE AS A RESULT OF HEPATITIS C INFECTION

*Dr Mark Swain*

Fatigue is a common complaint among the general population, reported by 5% to 10% in surveys, but can fatigue be caused by CHC infection? An ambivalent answer is found in the literature. While some studies have found higher rates of chronic fatigue in patients with hepatitis C (similar to patients with diabetes or depression), others have not. There is no link between level of fatigue and any marker of hepatitis C activity, such as HCV viremia level, ALT levels or histology. Similarly, in the Irish women's cohort (12), there was no link between level of fatigue and HCV RNA positivity. Finally, although IFN appears to improve quality of life in treated patients, the subjective response is the same in responders as in nonresponders.

A major problem with this work is the subjectivity of measurement. Research studies use validated questionnaires to assess fatigue (one common scale is the Short Form-36), but there is no objective measurement available.

**Consensus statement 11:** While fatigue is thought to be a common problem in chronic HCV, the prevalence of severe fatigue (enough to interfere with daily activities, for at least six months) is roughly 10%. However, 5% to 10% of the general population also report severe fatigue. Fatigue appears to be more prominent in intravenous drug users. Degree of fatigue does not correlate with presence or level of viremia, with ALT levels, or with degree of inflammation or fibrosis on histology. Fatigue can be quantified only with subjective rating scales; there is no objective measurement of fatigue.

#### LIVER TRANSPLANTATION AND HEPATITIS C

*Dr Gary Levy*

Hepatitis C as an indication for liver transplantation is becoming much more common, accounting for 35% of liver transplants in Toronto, Ontario, and likely rising to account for over 50% in the year 2000. Although retransplantation for recurrent HCV is not routinely done in Toronto, in the United States, by 2005, a very high proportion of all transplants may be done for recurrent HCV.

Recurrent infections are a major concern after transplantation, and for patients undergoing transplantation for hepatitis C, the reinfection rate is 100%. Although 50% of patients develop biochemical or histological evidence of hepatitis, only half of these have clinically significant hepatitis. In one study, a five-year follow-up showed that 20% of patients had fibrosis or cirrhosis. Other studies have shown a range from 13% to 34%.

An active debate concerns treatment of recurrent hepatitis C in patients with liver transplants. Although these patients will likely develop recurrent progressive disease, IFN as a single agent does not work. The combination of IFN and ribavirin is much more promising.

**Consensus statement 12:** Liver transplantation is often used for patients with end-stage liver disease due to HCV. Viral reinfection is universal after transplantation. Short term survival, both of the patient and of the liver, is excellent. Immunosuppression increases viral replication. Sixty per cent to 70% of patients develop recurrent hepatitis, 20% to 30% go on to cirrhosis and a small number develop aggressive disease. Late graft loss and patient death are now being increasingly scrutinized. The value of antiviral therapy after transplantation is unclear.

#### HCV INFECTION IN CHILDREN – RESULTS OF A LOOK-BACK PROGRAM AT THE HOSPITAL FOR SICK CHILDREN, TORONTO, ONTARIO

*Dr Eve Roberts*

Little is known about long term HCV prognosis in adults, and even less is known about the disease in children. The look-back program at the Hospital for Sick Children followed all children (except those known to have died) who were transfused between December 1985 and May 1990. All of these children's parents were sent letters by priority mail suggesting screening for HCV. Extensive press coverage accompanied this initiative. A publicized telephone hot line received over 600 calls in the first week. In all, 6332 letters were mailed and 4496 delivered. A total of 153 anti-HCV-positive transfusion recipients were found, two-thirds of whom were under 18 years of age. This gives an apparent incidence of 3.4% (153 of 4496). More than half of these children were transfused for hemophilia or thalassemia; cardiac surgery accounted for 17% and premature babies another 8%.

Seventy patients were identified as having definitely acquired infection during transfusion. All of these patients are currently asymptomatic. ALT levels have been tested in 42 patients, with normal results in 22. Of 28 patients tested for HCV RNA, nine (32%) are negative. This suggests a lower rate of chronicity than is found in adults. Five patients had biopsies; fibrosis was not found.

**Consensus statement 13:** Studies of hepatitis C infection in children are extremely limited. Most existing studies have been in the post-transfusion setting. Preliminary data from the Hospital for Sick Children suggest that children have a lower rate of progression to CHC following transfusion than adults. Children with chronic infection are rarely symptomatic. Antiviral treatment is not recommended for children, outside of clinical trials.

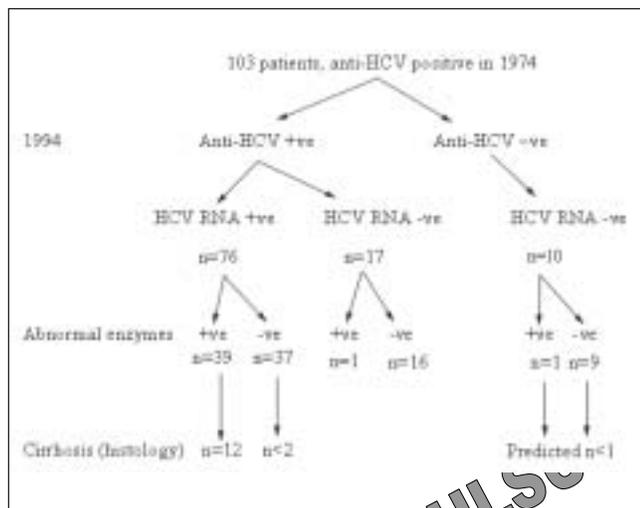


Figure 1) Long term follow-up of 103 patients with transfusion-associated hepatitis. HCV Hepatitis C virus; +ve Positive; -ve Negative

## EPIDEMIOLOGY AND OUTCOMES OF HEPATITIS C INFECTION IN THE UNITED STATES AND THE WORLD

Dr Leonard Seeff

Problems are inherent in studying the epidemiology of CHC. Although initially thought to be a mild and benign disease, hepatitis C was subsequently found to progress frequently. Most experts now agree that 85% of cases of acute hepatitis C progress to chronic disease, but thereafter the rate of resolution or rate of progression to cirrhosis, decompensation or HCC, is quite uncertain. Problems with studying CHC include that the acute onset is rarely identified, most cases are asymptomatic and the duration of the disease is much longer than the lifespan of research grants.

Prospective studies of TAH have found rates of biopsy-proven cirrhosis after eight to 14 years to range between 8% and 24%. Retrospective studies, with mean follow-up of four to 11 years, have found higher rates of progression to cirrhosis in 20% to 46% and HCC in 11% to 19%, with high mortality rates. Retrospective studies, however, may have a significant referral bias; these patients had established liver disease when they first were examined. Retrospective-prospective studies, including the Irish women's cohort (13), have provided long term follow-up that shows a benign course, with more than half of patients showing no fibrosis and only 2% with cirrhosis.

Long term follow-up of the five original TAH studies (13) has now shown no difference in total mortality (compared with matched controls who had transfusions but did not get hepatitis C), although liver-related mortality was higher (3.2%) in cases than in controls (1.5%) ( $P=0.033$ ). In older men, mortality is higher in cases than in controls.

From this series, 146 patients with acute TAH were further studied because they had sera available from the original

study and at follow-up. One hundred and three patients had hepatitis C, but 43 had non-A, non-E hepatitis (ie, 29% had acute hepatitis after transfusion but showed no sign of infection with any known hepatitis virus). Further description of the 103 patients followed 20 years after their acute hepatitis C is shown in Figure 1. Forty per cent of the 103 patients have abnormal enzymes, and roughly 15% have cirrhosis.

For many patients, hepatitis C is either self-limited or very benign. However, this disease affects millions of people, and even a low complication rate translates into thousands of cases of illness.

**Consensus statement 14:** In persons with more than one risk factor, it is not possible to specify the mode of acquisition of hepatitis C.

## IRON OVERLOAD IN HEPATITIS C – A FACTOR IN PROGNOSIS?

Dr Paul Adams

Many chronic liver diseases can cause elevated serum ferritin levels, including nonalcoholic steatohepatitis, alcoholic hepatitis and hemochromatosis. Although iron overload is capable of causing cirrhosis, cirrhosis often leads to iron overload, with liver iron levels usually rising in proportion to disease severity. The genetic testing for hemochromatosis is very accurate and eliminates much of the uncertainty in assessing a patient with elevated liver iron. Venesection as an adjunctive treatment for hepatitis C patients receiving IFN therapy is of no benefit.

## CAN CURRENT TREATMENT ALTER DISEASE OUTCOME?

Dr Jenny Heathcote

Reasons for treating patients with hepatitis C include to reduce symptoms, prevent progression, abolish extrahepatic manifestations and reduce the infectious pool. Because the main symptom of hepatitis C is fatigue, which does not respond to treatment, most attention is paid to preventing progression.

Because co-infection with hepatitis A and B may cause significant additional liver damage, vaccination against these diseases is a simple method of possibly reducing progression. Antiviral therapy with IFN reduces complications and can result in prolonged RNA negativity. The standard duration of therapy involves 12 months (rather than six months) of IFN treatment. Combination therapy using IFN and ribavirin gives better sustained response rates than monotherapy and is recommended. Therapy can be fine-tuned based on genotype; with genotype 1, response is better with 12 (versus six) months of combination therapy, whereas with genotypes 2 and 3, six months' therapy is as good as treatment for 12 months.

Numerous public health measures help to reduce the in-

fectious pool above the reduction achieved with effective use of antiviral therapy. Suggestions, such as provision of clean needles for intravenous drug users, drug rehabilitation programs, monitoring of tattoo and body piercing studios, and reducing tribal scarification, are all important.

**Consensus statement 15:** Several measures are proven to reduce progression of CHC. Minimal alcohol intake is recommended; abstinence is preferred. Antiviral therapy in those who show a sustained response reduces progression of cirrhosis and reduces the incidence of HCC. The most effective treatment is the combination of IFN and ribavirin for 12 months. For those who have not responded after four to six months, treatment can be stopped because

the chance of response after that is small. For patients with genotype 2 or 3, treatment can be stopped after six months because response is not improved after that. Further clarification of treatment regimens can be expected as ongoing trials are completed and published – this will include the use of induction regimens, higher doses of IFN or PEGylated IFN. Future treatments may include helicase and protease inhibitors.

Patients with CHC are at higher risk of decompensation if they acquire other viral hepatitis infections, so vaccination against hepatitis A should be considered. Patients without evidence of hepatitis B immunity may be considered for vaccination. To improve the efficacy and appropriate use of antiviral therapy, genotyping and assessment of viral load must become accessible.

#### CHAIRMAN'S SUMMARY

*Dr Sam Lee*

CHC is a common viral affliction, with previous estimates of 150 to 200 million infected worldwide, and 240,000 to 300,000 infected in Canada. The prevalence of hepatitis C in the Canadian blood donor population declined dramatically during the 1980s. At every time period, the prevalence was significantly lower than that of the American rates, even after introduction of the first-generation anti-HCV testing in 1990. Reviewing the natural history of different types of patients, including those with normal ALT levels, mild disease, active chronic necroinflammatory disease, compensated and decompensated cirrhosis, there is tremendous individual variability in rates of disease progression.

Hepatitis C is a benign condition for most people afflicted with this virus. It appears that the risk of dying from CHC, or of developing decompensated cirrhosis during the first

two decades of viral infection, is very low. Factors that increase the cirrhosis progression rate include chronic excessive alcohol consumption, being male and age older than 40 years at the time of viral acquisition. Of these, alcohol is probably the most important factor and the only one that a person can control. Liver biopsy, despite the limitations of possible sampling error, is an extremely useful prognostic indicator; absence of or scant fibrosis on the initial biopsy generally augurs a very favourable medium term (up to 20 years) prognosis.

Whether those with transfusion-acquired CHC or those with HCV and hemophilia have a different rate of progression than patients with intravenous drug use-acquired HCV is unclear. Although HCC is proven to have an increased frequency in patients with HCV cirrhosis, routine screening strategies in patients with hepatitis C is not recommended. Because the limited data suggest that HCV runs a more be-

#### SUGGESTED RESEARCH TOPICS

Throughout this Medical Experts Workshop, a recurring theme was the need for further research in many aspects of chronic hepatitis C. After the meeting, Dr Feinman (meeting organizer) suggested these specific topics as being especially worthy of consideration.

Establishing a national database for hepatitis C patients

Use of a standardized staging and grading system for liver biopsies.

Prospective multicentre study of sampling error in blind liver biopsies taken from two areas of the liver.

Prospective study of Child-Pugh's grade A cirrhosis.

Assessment of hepatic reserve in cirrhosis.

Double-blind study of retinoids in the primary prevention of hepatocellular carcinoma.

nign course in children, routine antiviral therapy in pediatric populations is also unwarranted at present.

In terms of treatment, available evidence suggests that a good response to antiviral therapy, with long term clearance of HCV-RNA, favourably affects the natural history. The progression to cirrhosis may be decreased, and the development of HCC appears to be lessened. Results from an Italian study of small numbers of HCV-afflicted patients developing severe acute hepatitis A superinfection suggest the useful-

ness of hepatitis A virus vaccination in patients with HCV. HBV vaccination may also be considered in patients with risk factors for acute hepatitis B.

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