
Chronic Viral Hepatitis and Chronic Liver Disease

With chronic viral hepatitis acting as a precursor to chronic liver disease, it is crucial for family physicians to be able to recognize hepatitis B and C so appropriate treatment can be administered.

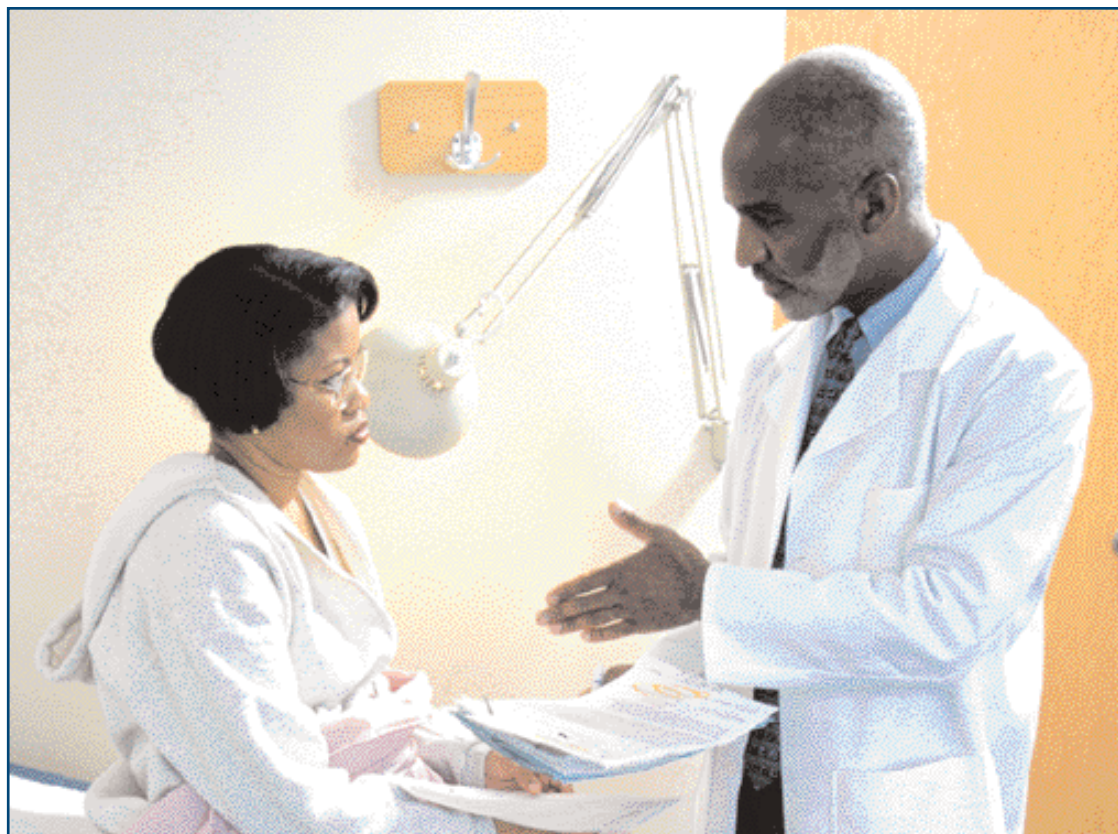
By Morris Sherman, MB, BCh, PhD, FRCPC

Over the next 20 to 30 years the Canadian health-care system will be faced with a sharp increase in the incidence of cirrhosis, liver failure and hepatocellular carcinoma (HCC). This will be due to the large pool of patients currently living with chronic viral hepatitis—both hepatitis B and hepatitis C—who, after many years of relatively mild liver disease, develop the later stages of their disease. The demographics of the patient population infected with each of these viruses is different, but in both cases the demographics and epidemiology of the diseases will function to infect patients with end-stage disease over the next two to three decades.

In this article, the author will examine the reasons behind this prediction, and will highlight how chronic viral hepatitis can be better addressed. The preparedness of Canada's health-care system to deal with this problem also will be examined.

Chronic Hepatitis B

Hepatitis B in Canada is a disease largely prevalent among immigrant groups. This has been clearly documented in several studies. In a series of about 1,000 hepatitis B carriers, 80% were born outside of Canada.¹ There also exists a seroepidemiologic survey in university students in



Toronto, of whom, about 2.3% were infected with hepatitis B.² All of those infected had been born outside of Canada. In a survey of patients with HCC, 50% of the cases were related to hepatitis B, and all patients were from an immigrant background.³

There are other series of carriers in Canada in which the relationship between immigration and hepatitis B infection is not so concrete.⁴ It is common experience in hepatology practices, however, that the majority of patients with chronic hepatitis B are in the former group.

How does this information predict an increase in the incidence of hepatitis B-related end-stage liver disease (ESLD)? To answer this question one must consider the ages at which hepatitis B carriers develop liver disease complications, and the average age among the affected populations. We also need to consider the countries of origin. Table 1 shows estimates of hepatitis B carriers in various populations. This data was derived by considering the numbers of immigrants from the different areas, and



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Table 1

HEPATITIS B IN VARIOUS IMMIGRANT POPULATIONS

Country of origin	Population in Canada	Estimate hepatitis B prevalence rates	Total
Low-risk immigrants and Canadian-born	27x10 ⁶	0.56	151,200
China	360,590	7	25,222
Italy	705,590	3	21,288
South Asia	266,800	7	18,676
Aboriginals	746,410	2	14,928
Africa	174,790	7	12,235
Portugal	199,595	3	5,988
Philippines	93,280	5	4,664
Greece	143,780	3	4,313
Vietnam	53,015	7	3,711
Middle East	101,665	3	3,050
Korea	26,855	7	1,880
South America	80,715	2	1,614
Total			268,769

estimating the prevalence of hepatitis B in each area. Estimates of the hepatitis B carrier state in home countries were taken from the literature. A conservative estimate was then applied to the local population from that country.

For example, the prevalence of hepatitis B in Hong Kong is about 10% to 15%, and the author applied an estimate of 7% prevalence of hepatitis B in the Hong Kong immigrant population in Canada. According to StatsCan, the average age of Hong Kong immigrants is 29 years.

Massive immigration to Canada from Hong Kong started in the 1970s. Now, 30 years later, the hepatitis B carriers in the immigrant population are reaching the age where the usual complications of hepatitis

B start to appear, the most frequent of which is HCC.

The incidence of HCC increases with age.⁵ In our population, the author has shown the average age of patients with HCC to be 69 years.³

The risk of HCC is not equal in all hepatitis B carriers, and is highest among African and Asian carriers. About 3,000 hepatitis B carriers have been admitted into Canada each year from these areas since the 1970s. This cohort is now about 90,000 strong, which means approximately 11,000 members of this cohort of hepatitis B carriers will develop HCC over the next 20 to 30 years. According to Health Canada data, about 900 cases of HCC occur in Canada each year.⁶

Table 2

HEPATITIS C IN IMMIGRANTS

Country	Hepatitis C Prevalence (%)
Italy	0.5
Greece	1.5
Egypt	18.1
Somalia	0.9
Hong Kong	0.5
Romania	4.5
Korea	1.7
India	1.8
Pakistan	2.4
Phillipines	3.6
Rwanda	17.0
Vietnam	6.1
Russia	2.0
Poland	1.4

Hepatitis C

The epidemiology of hepatitis C in Canada encompasses at least three distinct groups: transfusion-related hepatitis C accounts for

about 10% of all cases;⁷ cases associated with intravenous drug use probably account for 50% of cases; and hepatitis C is common in certain immigrant populations.

Transfusion-related hepatitis C

Transfusion-related hepatitis C will probably not contribute significantly to the pool of patients who will

develop chronic liver disease complications, because this group is relatively small, and many will succumb to the disease, which creates the need for transfusion in the first place.

Hepatitis C in country of origin

Population groups in which hepatitis C is common include those from Italy, Eastern Europe, Vietnam, Somalia, Egypt and Pakistan (Table 2). In Italy and Eastern Europe, most infected patients are more than 50 years old.^{8,9} These individuals were likely infected as children, during mass vaccination campaigns, or by the use of improperly sterilized non-disposable needles and syringes.¹⁰ In Somalia, the author has observed that the routes of transmission are not as well defined, but probably include ritual scarification with poorly sterilized instruments, as well as the factors described in the Italian population. Hepatitis C in the Somali immigrant population is seen at all ages. In Vietnam and Eastern Europe, there is no ritual scarification, but infection is seen at all ages. It is likely that, in these areas, the use of risky injections given for legitimate health reasons has persisted much longer than in Italy. In Egypt, parenteral treatment of schistosomiasis seems to have been associated with high levels of hepatitis C transmission.¹¹

Emigration from Italy to Canada has been considerable. In fact, Italians are the largest single immigrant group in Canada. The current age distribution of this population is unknown, but a significant number are over 50 years old. These people were first-generation immigrants, and brought with them the high prevalence of chronic hepatitis C. In hepatology practices

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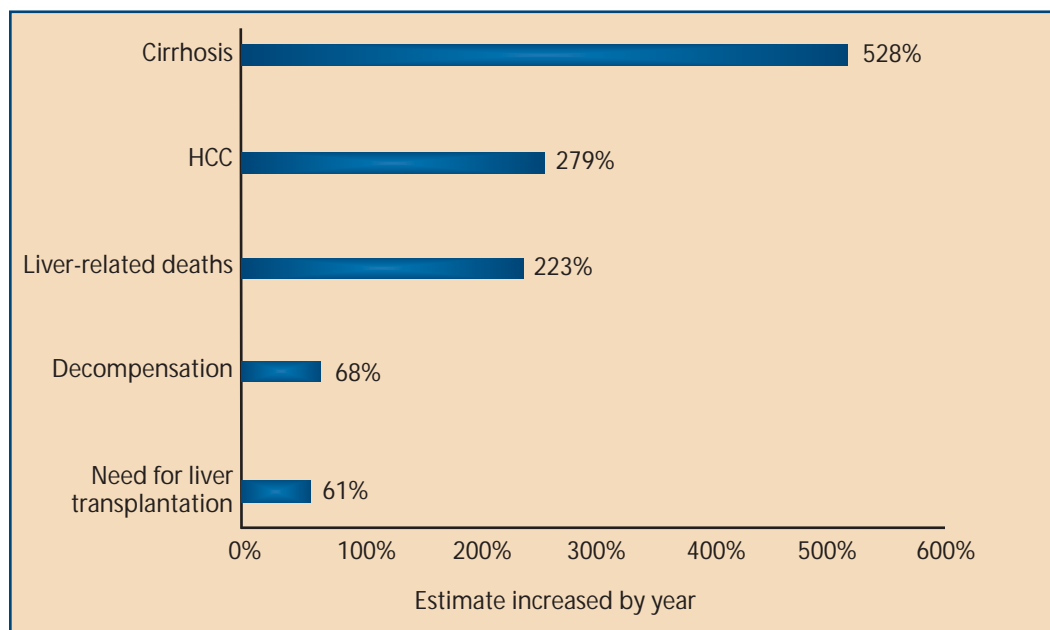


Figure 1. Future disease burden due to hepatitis C in the United States.

middle-aged and elderly Italian immigrants comprise a significant proportion of the hepatitis C patient population.

Hepatitis C acquired in childhood is an indolent disease, often taking 40 to 60 years to cause significant liver disease. Thus, the Italian immigrant population with hepatitis C and other immigrants of similar age from other areas are now reaching the age where we can expect them to show evidence of liver complications.

Hepatitis C in injection drug users

Intravenous drug use has always been present in Canada, but really became a serious problem in the 1960s, during the hippie era. Since that time, intravenous drug use has declined, but is still common, with an estimated 10,000 registered users in Ontario alone. In the 1960s, needle-sharing was common, and this practice was only changed with the spread of human immunodeficiency virus (HIV) infection in the early

1980s and the need for more precautions.

One of the remarkable features of hepatitis C and intravenous drug use is that infection occurs early in the course of drug use. It is very common, therefore, that occasional use or even single casual use of intravenous drugs with sharing of needles can result in disease. This was common practice in the 1960s and 1970s.

Hepatitis C acquired as an adult is a more rapidly progressive disease than childhood-acquired disease. In this population, patients start to develop hepatitis C-related complications after 30 to 40 years. Thus, intravenous drug users, who likely became infected when they were in their teens and 20s during the hippie era, will develop liver disease complications at about age 40 to 60, or over the next 10 to 20 years.

Estimates of the burden of disease in Canada for hepatitis C are currently being undertaken, however, there are estimates available for the U.S. and France. In



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France, it is estimated that it will take 20 years before the rising incidence of HCC and cirrhosis starts to fall. Increases in the consequences of chronic liver disease due to hepatitis C in the U.S. are shown in Figure 1. It is estimated the costs associated with these diseases will be about \$10 billion per decade.

Diagnosis of Viral Hepatitis

The test to diagnose active hepatitis B infection is the hepatitis B surface antigen (HBsAg). The antibody to HBsAg is called anti-HBs, and indicates recovery and immunity. Patients who are anti-HBs-positive should not be considered to be infected. They are, in fact, cured. In contrast, hepatitis C is diagnosed by finding the antibody, not the antigen. The test is anti-hepatitis C virus. Most laboratories also do confirmatory tests. A test called a recombinant immunoblot assay (RIBA) used to be done, but this is now rare. The hepatitis C ribonucleic acid (RNA) test measures the concentration of the virus in serum. This does not indicate severity of liver disease, however, nor does it give any indication of prognosis. Higher viral loads are associated with a poorer response to therapy, and therefore, the only reason to do hepatitis C viral load testing is prior to treatment. Even then, it should only be done if the result will alter whether a patient gets treated or not.

Improving The Outcome

All the above estimates assume that patients are untreated. Clearly, if treatment has the potential to decrease the risk of developing HCC or cirrhosis, then these estimates are unlikely to become reality. It seems likely that successful treatment for chronic hepatitis C does indeed improve prognosis and decrease the risk of a liver-related death. Treatment of hepatitis B, however, may not be associated with a similar improvement in outcome. The second variable determining whether the estimates will be accurate or not is whether patients who need treatment are getting the appropriate therapy.

Treatment of chronic hepatitis B

There are two licensed drugs available to treat chronic hepatitis B: interferon alpha and lamivudine. The standard end point of therapy in this disease is a composite end point, consisting of loss of hepatitis B e (HBe) antigen, development of antibodies to the e antigen, loss of hepatitis B virus deoxyribonucleic acid (DNA) from serum (using a relatively insensitive test) and normalization of transaminases. Interferon alpha is given in a time-limited fashion, usually for four to six months.¹⁰ The composite end point is achieved in about 20% to 30% of patients. There are data suggesting that successful interferon treatment is associated with a decrease in the incidence of HCC and cirrhosis complications.¹² Interferon is not usually used in patients who are anti-HBe-positive at the start of treatment.

The second drug is lamivudine, a nucleoside analogue, which efficiently suppresses viral replication. Use of lamivudine also can be associated with development of the composite end point. After one year, this occurs in about 20% of patients,¹³ rising to about 30% after three years. Initially, lamivudine was used in a time-limited fashion, but more recently it is being used on a long-term basis to achieve suppression of viral replication in a manner similar to the use of HIV drugs.

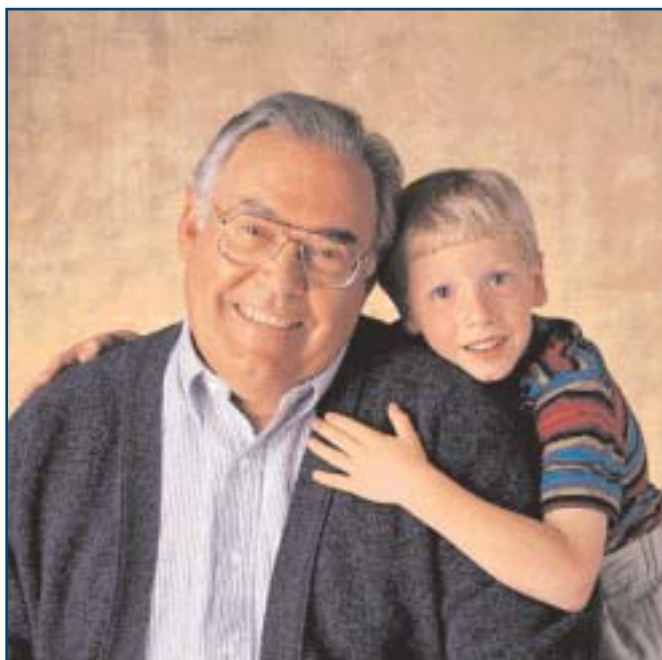
It is too soon to tell whether the use of lamivudine will result in a decrease in liver disease complications, however, early results are encouraging. In the absence of the development of viral resistance, viral suppression is associated with an improvement in liver histology and function, and even in a decrease in the level of fibrosis.¹⁴



Newer antivirals will be used in combination therapy, so the problem of viral resistance to therapy will be reduced. Long-term suppression of hepatitis B virus replication has the potential to decrease both the incidence of HCC and the complications of cirrhosis. Once more, however, the other side of the equation is whether patients requiring treatment are being identified and appropriately treated.

Unlike hepatitis C, we have no idea of the number of patients with hepatitis B who require therapy, nor an idea of how many have been identified and treated. It is likely that recognition of chronic hepatitis B is better among family practitioners than hepatitis C. This may be due, in part, to the fact that hepatitis B is a disease seen largely in immigrant populations, and these patient populations tend to see physicians from their own backgrounds. For example, in the

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Asian community, physicians are acutely aware of hepatitis B and its consequences. Many routinely screen their patients from high-risk countries. One of the problems with hepatitis B is that the medical community

has not yet accurately defined who needs therapy for this disease. Currently, we only treat patients with active viral replication and active hepatic inflammation. However, inflammation in these patients is frequently intermittent, so periodic testing of the transaminases may miss periods of active disease, or may identify only mild disease when, on average, more active disease is present.

Treatment of chronic hepatitis C

Successful therapy of hepatitis C is tantamount to a cure. Once patients have achieved a sustained response to a course

of therapy, relapse is rare. Liver disease does not progress, and although there are inadequate long-term data so far, it is likely that the incidence of HCC and complications of cirrhosis are substantially reduced. This is particularly true in patients who were not cirrhotic at the time of therapy. Even in patients with established, but compensated, cirrhosis there is likely an improved outcome after successful therapy. A sustained response is defined as absent hepatitis C virus RNA in serum six months after completion of therapy, using a sensitive test, such as polymerase chain reaction.

The current standard of therapy is a combination of interferon alpha and ribavirin.¹⁵ This combination can achieve a 40% or better overall sustained response rate. The next generation of treatment will be a long-acting form of interferon, still given with ribavirin. This is expected to achieve a sustained response for somewhere between 50% and 60% of treated patients.¹³

Obviously, if 50% to 60% of hepatitis C carriers are successfully treated, the dire circumstances described above will not happen. Unfortunately, it is by no means clear that all patients requiring treatment will actually be treated. So far, only about one-third of all hepatitis C carriers in Canada have been identified (about 100,000 individuals). Far fewer have been treated. Currently, about 3,000 patients per year are being treated, and this volume has only been maintained for about three years, since the introduction of interferon and ribavirin. Thus, the majority of patients with chronic hepatitis C remain at risk for progressive liver disease.

Awareness of Viral Hepatitis

One of the major limiting factors in the treatment of viral hepatitis is the rate at which patients can be treated. This, in turn, is limited by the number of physicians available. There are only about 40 hepatologists in Canada. Many gastroenterologists and some infectious disease physicians treat viral hepatitis, but 75% of all treatment is performed by 25% of all treating physicians.

In this author's opinion, there is a need for additional physicians who are prepared to treat patients with viral hepatitis. Since evaluation and treatment decisions are not straightforward, physicians will need some form of training or mentoring, similar to what has been set up for HIV-treating physicians. With viral hepatitis, however, the size of the pool of patients requiring evaluation for therapy is larger. It is doubtful that physicians alone will be able to pro-

vide all the necessary care. Thus, it will fall to non-physicians, such as nurses, to undertake some of the care of these patients.

In the author's opinion, liver transplant demand will be met by a shortage of donors. Living-related transplants will be available for some patients, but this will still leave a large number of transplant candidates who will require cadaveric grafts. This also means that it will become necessary to look after a progressively increasing number of patients with ESLD, who are awaiting transplant.

There is a dearth of dedicated inpatient beds for these patients, and a dearth of hepatologists to look after these patients. In the author's opinion, this will translate into an unacceptable death rate for those waiting for transplantation.

Despite these dire predictions, there is really no well-developed attempt to deal





with the issues. In the author's opinion, a number of programs will have to be developed, which will require a commitment of money and dedicated staff from ministries of health, both federal and provincial. Health Canada, mainly in the form of the hepatitis C division and the Center for Infectious Disease Prevention and Control, has already committed money to the development of such programs. With the federal/provincial divide in Canada, however, Health Canada does not have the mandate to implement such programs. Some provin-

cial governments (*i.e.*, British Columbia) are working toward developing such programs, however, it will be some time before such programs are up and running. **Dx**

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