

What's New:

The World Of Hepatitis C

It is anticipated the next decade will bring further advances and improvements in the management of people chronically infected with hepatitis C. Meanwhile, primary prevention of infection and slowing the rate of progression of fibrosis in those already infected remain important goals.

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Presented at Bug Day 2001, held in conjunction between the Winnipeg Health Sciences Centre and the University of Manitoba, Winnipeg, Manitoba, October 2001.



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Hepatitis C

Hepatitis C remains a major public health problem. It is estimated that 3% of the world population has been infected with hepatitis C virus (HCV), meaning there are more than 170 million people chronically infected.¹ In Canada, it has been estimated the prevalence of HCV antibody (anti-HCV) positivity is approximately 0.8%, reflecting between 210,000 and 275,000 people.² Between 1992 and 1998, there were almost 80,000 new cases reported in Canada.³

Hepatitis C infection is a leading cause of liver disease requiring transplantation and has risen significantly as an indication for transplant over the past several years.⁴ Modeling used to estimate the increased burden of sequelae related to HCV in Canada between 1998 and 2008

shows the number of prevalent cirrhosis cases will almost double, cases of liver failure will increase by 126% and hepatocellular carcinoma cases by 102%. It is estimated the number of liver deaths will increase by 126% over the same period.⁵

What Is HCV?

HCV is a spheric, enveloped, positive strand ribonucleic acid (RNA) virus and is a member of the flaviviridae family. The single-stranded RNA genome is approximately 9.5 kb in length, with a single, large open reading frame of approximately 3,000 amino acids.⁶ There is marked heterogeneity of HCV sequences and phylogenetic evaluation of isolates from multiple geographic regions, suggesting there are at least six major

Summary

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- In Canada, it has been estimated the prevalence of hepatitis C virus (HCV) antibody (anti-HCV) positivity is approximately 0.8%, reflecting between 210,000 and 275,000 people.
- HCV is a spheric, enveloped, positive strand ribonucleic acid (RNA) virus and is a member of the flaviviridae family.
- Following acute HCV infection, the virus will spontaneously clear in between 15% and 30% of people. The majority, however, will become chronically infected with hepatitis C.
- The most common symptom in patients with hepatitis C infection is the nonspecific complaint of fatigue.
- In Canada, the most important risk factor for acquisition of HCV is injection drug use (IDU).
- Initial screening for hepatitis C infection should be performed by obtaining anti-HCV status, in addition to baseline liver enzymes.
- The primary indication for therapy is having a positive HCV-RNA in addition to a serum alanine aminotransferase (ALT) greater than 1.5 times the upper limit of normal over at least six months.
- Recently, randomized controlled trials have demonstrated the efficacy of pegylated interferons in the treatment of chronic hepatitis C infection.
- Currently, there is no vaccine available for the primary prevention of hepatitis C infection. Those with chronic hepatitis C infection, however, should be vaccinated against hepatitis B virus (HBV) if they are at increased risk (*i.e.*, IDU) or if they are serologically negative.

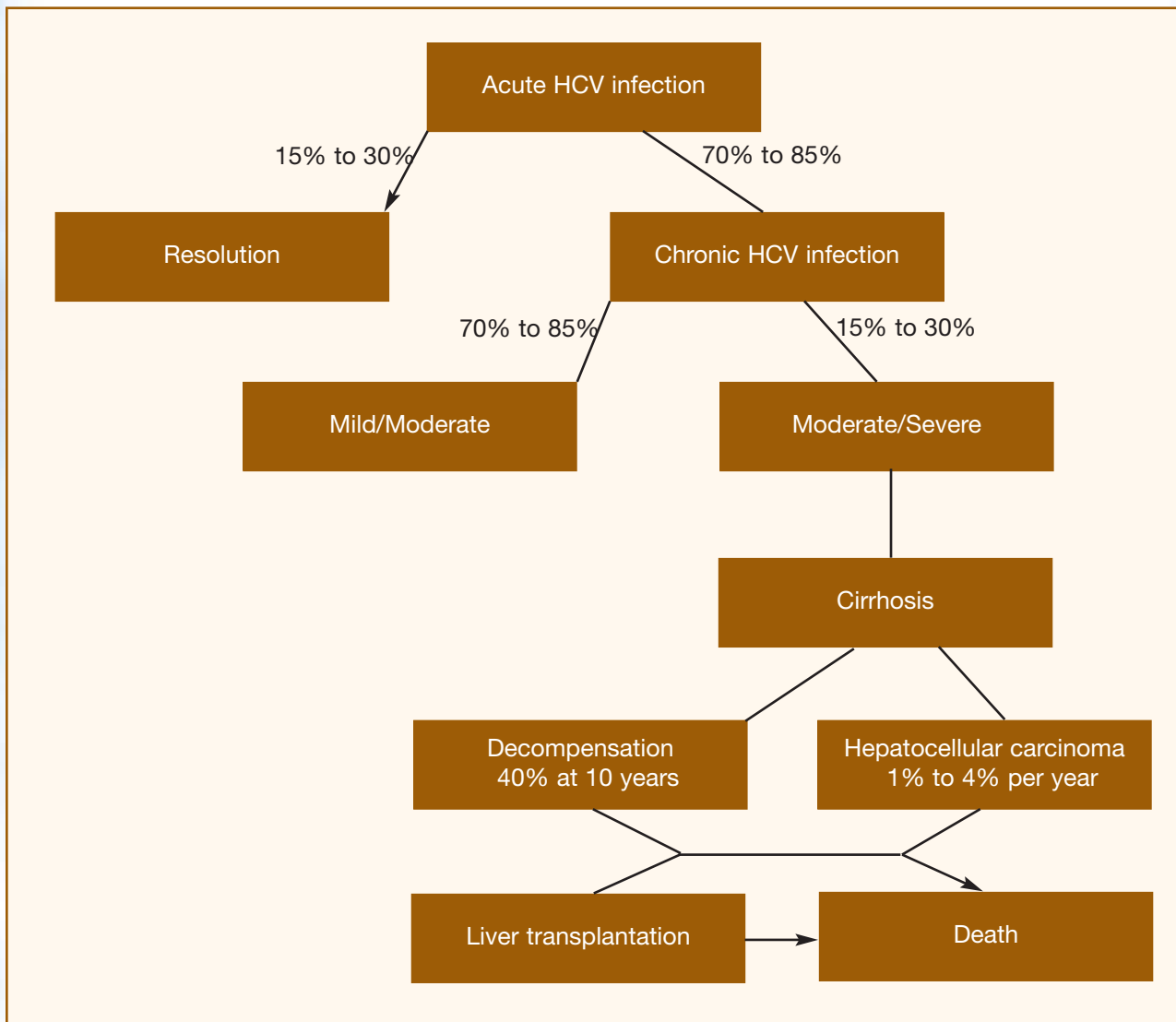


Figure 1. Spectrum of hepatitis C disease.

genotypes and several subtypes within these regions.⁷

In Canada, genotypes 1, 2 and 3 are commonly found, although genotype 1 predominates.⁸ In addition to this genetic diversity, due to the rapid level of virion turnover and the absence of proof reading by the RNA polymerase, there is a rapid accumulation of mutations within the viral

genome. This results in sequence variability, known as quasispecies, within an individually infected host.⁹

Spectrum Of Disease

The natural history of HCV infection is outlined in Figure 1. Following acute HCV infection, the virus will spontaneously clear in between 15%

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Table 1

Risk Factors

- Injection drug use (IDU)
- Recipient of blood, blood components or solid organs before 1992
- Needle stick injury
- Hemodialysis
- High-risk sexual activity
 - IDU in sexual partner
 - Multiple sexual partners
 - Anal intercourse
 - Partner with sexually transmitted disease
- Unlicensed tattoos or body piercing
- Prisoner in correctional institution
- Snorting cocaine with/without shared equipment
- Childhood vaccinations in endemic areas
- Mother with hepatitis C virus (HCV) (rare)
- Sharing personal hygiene items with an HCV-infected person (*i.e.*, razor, scissors, nail clippers, toothbrush)

Table 2

Symptoms and Signs

Symptoms

- Fatigue
- Nausea
- Weight loss
- Anorexia
- Weakness
- Abdominal discomfort
- Arthralgias

Signs

- Hepatomegaly
- Splenomegaly
- Ascites/edema
- Palmar erythema
- Spider angiomas
- Muscle wasting
- Jaundice/scleral icterus
- Gynecomastia
- Asterixis

and 30% of people. The majority, however, will become chronically infected with hepatitis C. Of those chronically infected, 70% to 85% will have mild-to-moderate disease, but no apparent long-term sequelae. The other 15% to 30% of people will go on to develop moderate-to-severe disease, resulting in cirrhosis.¹⁰ In those who develop cirrhosis, there is a risk of decompensation with jaundice, ascites, variceal hemorrhage or hepatic encephalopathy. In addition, there is a risk of 1% to 4% per year for the development of hepatocellular carcinoma.^{11,12} Once cirrhosis has developed, the 10-year survival rate is 80%.

The rate of development of decompensation over that same time period, however, is about 40%. Furthermore, once decompensation occurs, survival decreases to 50% at five years.¹¹

In an individual patient, it is very difficult to clinically determine who will go on to develop cirrhosis. Several factors have been strongly associated with fibrosis progression, including age at infection of more than 40 years, daily alcohol consumption of 50 g or more and male sex.¹³

Table 3

Investigations and Interpretation Of Results

Screening

- Anti-hepatitis C virus (HCV)
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT)
- HCV-RNA (if anti-HCV positive or immunocompromised)

Results

Interpretation

Negative Anti-HCV

- | Results | Interpretation |
|--------------------------------------|--|
| • HCV-RNA positive | - HCV infection or false-positive |
| • HCV-RNA negative | - No HCV infection |
| Positive Anti-HCV | |
| • HCV-RNA positive with normal ALT | - HCV infection, no biochemically detectable liver disease |
| • HCV-RNA positive with elevated ALT | - HCV infection with active liver disease |
| • HCV-RNA negative with normal ALT | - False-positive anti-HCV |
| | - Spontaneous viral clearance |
| | - False-negative HCV-RNA |
| | - Low level viremia with no or minimal liver disease |
| • HCV RNA negative with elevated ALT | - False-positive anti-HCV |
| | - Spontaneous viral clearance |
| | - False-negative HCV-RNA |
| | - Low level viremia, but alternate cause of liver disease |

Positive Anti-HCV

Investigations to rule out other causes of elevated aminotransferases

- Drugs (careful history)
- Alcohol (AST/ALT > 1; history)
- Hepatitis B (HBsAg)
- Fatty liver (abdominal ultrasound)

If clinically indicated

- Autoimmune hepatitis (antinuclear antibody)
- Hemochromatosis (iron, total iron binding capacity, ferritin)
- Wilson's disease (ceruloplasmin)

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Table 4

Indications and Contraindications To Therapy For Hepatitis C

Indications

- HCV-RNA positive
- ALT > 1.5 x ULN for > six months
(Liver histology showing \geq Grade 2 inflammation/Stage 2 fibrosis)

Contraindications

Interferon

- Neutrophils < $1.0 \times 10^9/L$
- Platelets < $80 \times 10^9/L$
- Decompensated liver disease (*i.e.*, jaundice, ascites, variceal hemorrhage, encephalopathy)
- Active drug abuse
- Active autoimmune disease
- Major psychiatric disorder
- Non-hepatic solid organ transplant
- Significant cardiac disease
- Unstable diabetes mellitus
- Hyperthyroidism
- Uncontrolled seizure disorder

Ribavirin

- Anemia (< 120 g/L in women; < 130 g/L in men)
- History of ischemic heart disease or any other serious disorder not likely to tolerate rapid decline in hemoglobin
- Renal failure
- Pregnancy
- Active alcohol abuse
- Inadequate birth control in women and men

HCV-RNA = hepatitis C virus ribonucleic acid;
ALT = alanine aminotransferase; ULN = upper limit of normal

Risk Factors: Who Should Be Tested?

Any person with risk factors for hepatitis C infection, as outlined in Table 1, in addition to anyone with signs or symptoms of liver disease, as outlined in Table 2, should undergo screening. Keep in mind the most common symptom in patients with hepatitis C infection is the nonspecific complaint of fatigue.¹² Any person with unexplained elevation in their liver enzymes — in particular the alanine aminotransferase (ALT) or aspartate aminotransferase (AST) — also should be tested.

In Canada, the most important risk factor for acquisition of HCV is injection drug use (IDU). It currently accounts for at least 60% of all HCV transmissions.¹⁴ The risk associated with blood or blood product transfusion is very low (less than 1/100,000). It must be noted, however, that having had a blood transfusion prior to 1990 (when the Canadian Red Cross instituted specific screening of blood products for HCV) is the second most important factor for acquisition. Other associated risks include tattoos, body piercing and intranasal cocaine use. There is circumstantial evidence that sexual transmission occurs, however, this has not been proven.

Follow-up of HCV-infected hemophilic patients has not demonstrated an increased risk in their seronegative sexual partners.¹⁵ Maternal-to-infant transmission also appears to be uncommon, with an average of 5% of infants born to anti-HCV-positive mothers becoming persistently anti-HCV positive.¹⁶ Although HCV-RNA is present in breast milk, there has been no documented increased risk of transmission in breast fed, as compared to bottle fed, babies of HCV-positive mothers.¹⁷

What Tests Should Be Ordered?

Initial screening for hepatitis C infection should be performed by obtaining anti-HCV status, in addition to baseline liver enzymes (*i.e.*, ALT, AST, alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT]). Table 3 outlines how to interpret the anti-HCV results and confirm active hepatitis C infection. If the anti-HCV is negative and suspicion remains high, this may be a false-negative (*i.e.*, an immunocompromised host with abnormal aminotransferases), then a HCV-RNA should be obtained. This will help determine whether or not there is evidence of viral replication.

All patients with a positive anti-HCV should have HCV-RNA testing performed to assess whether or not there is evidence of active infection. If the HCV-RNA is positive, the patient should be referred to a specialist with experience in the management of HCV infection. In addition, other causes of liver disease, such as drugs, alcohol, hepatitis B infection and fatty liver, should be ruled out. If clinically indicated, screening for autoimmune hepatitis, Wilson's disease and hemochromatosis also should be performed.

If the HCV-RNA is negative, this most likely represents clearance of the virus, particularly if the liver enzymes are normal. It can occasionally represent a decline in the level of the virus to below limits of detection of the assay. The HCV-RNA, therefore, should be repeated. If it remains negative on two occasions at least six months apart, no further follow-up is required unless there are ongoing risk factors or persistently unexplained abnormal liver enzymes.

Patients should be referred to a specialist with expertise in the management of hepatitis C infection if they are:

- HCV-RNA positive with abnormal liver

- enzymes;
- HCV-RNA positive with normal liver enzymes;
- HCV-RNA negative, but anti-HCV positive with unexplained abnormal liver enzymes;
- Co-infected with hepatitis B virus (HBV) or human immunodeficiency virus (HIV); or
- Suspected of having acute HCV infection.

Liver biopsy is generally recommended for grading and staging of the liver disease, however, is not considered mandatory.¹⁸

The primary indication for therapy is having a positive HCV-RNA in addition to a serum ALT greater than 1.5 times the upper limit of normal over a period of at least six months.

Who Should Be Treated And How?

When making decisions about therapy for HCV infection, it should be kept in mind the majority of patients have an excellent prognosis, the current standard therapy is only moderately effective and the therapy is both expensive and associated with numerous side effects. The indications and contraindications to therapy are outlined in Table 4.

The primary indication for therapy is having a positive HCV-RNA in addition to a serum ALT greater than 1.5 times the upper limit of normal over a period of at least six months. Those with ALT below 1.5 times the upper limit of normal usually have mild disease and an excellent prog-

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Table 5

Pegylated Interferons Compared To Standard Interferon For Treatment Of Chronic HCV

| | Sustained Virologic Response | |
|---|------------------------------|-----------------|
| | <u>Pegylated</u> | <u>Standard</u> |
| Peginterferon alpha-2A 180 µg Q week <i>versus</i> Interferon 3 mIU TIW x 48 wk† | 36% | 5% |
| Peginterferon alpha-2A µg Q week <i>versus</i> Interferon 6 mIU TIW x 12 wk <i>then</i> Interferon 3 mIU TIW x 36 wk†† | 39% | 19% |
| Peginterferon alpha-2B 1.0 µg/kg Q week <i>versus</i> Interferon 3 mIU TIW x 48 wk††† | 25% | 12% |

†Adapted from: Shiffman M, Pockros P, Reddy R, et al: A controlled, randomized multicenter, descending dose phase II trial of pegylated interferon alfa-2a vs standard interferon alfa-2a for treatment of chronic hepatitis. *Gastroenterology* 1999; 116(4, Part 2):A1275.

††Adapted from: Zeuzem S, Feinman SV, Rasenack J, et al: Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000; 343:1666.

†††Adapted from: Lindsay KL, Trepo C, Hcintges T, et al: A randomized double-blind trial comparing pegylated interferon alfa-2b to interferon alfa 2b as initial treatment for chronic hepatitis C. *Hepatology* 2001; 34:395.

nosis. Treatment, therefore, may not be required.¹⁸ Many specialists also would add a third criteria of having evidence of active histology (greater than or equal to grade 2 inflammation, stage 2 fibrosis).

The current standard of therapy for chronic hepatitis C is a combination of interferon alfa-2b and ribavirin. Interferon is given at a dose of three million units three times a week, while ribavirin is given at 1,000 mg for patients weighing less than 75 kg and 1,200 mg daily for patients

weighing more than 75 kg. In randomized controlled trials, this has been demonstrated to result in a 40% sustained response rate. This represents a significant improvement of the previous standard therapy of interferon alone, which resulted in cure rates of 5% to 15%.^{19,20}

Absolute and relative contraindications for the use of interferon include the following: a neutrophil count less than $1.0 \times 10^9/L$; platelet count less than $80 \times 10^9/L$; a history of decompensated liver disease (*i.e.*, jaundice, ascites,

Table 6

Peginterferon Alfa-2b Plus Ribavirin Compared To Interferon Alfa-2b Plus Ribavirin For Treatment Of HCV

| | Pegylated interferon alfa-2b 1.5 µg/k Q week + ribavirin 800 mg od x 48 wk | Interferon alfa-2b 3 mIU TIW + ribavirin 1,000 mg to 1,200 mg od x 48 wk |
|--|---|---|
| Overall sustained virologic response (SVR) | 54% | 47% |
| Genotype 1 SVR | 42% | 33% |
| Genotype 2 or 3 SVR | 82% | 79% |

Adapted from: Manns MP, McHutchison JG, Gordon SC, et al: Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C. *Lancet* 2001; 358:958.

variceal hemorrhage, encephalopathy); active alcohol abuse (within the previous six months); active drug abuse; active autoimmune disorders; major psychiatric disorders (particularly severe depression, suicidal ideation and bipolar illness); non-hepatic solid organ transplant; significant cardiac disease, including congestive heart failure; ischemic heart disease; significant respiratory disease (especially poorly controlled asthma); arrhythmia; unstable diabetes; hyperthyroidism; poorly controlled seizure disorder; psoriasis; autoimmune deficiency syndrome (AIDS); and pregnancy or breastfeeding (Table 4).

Ribavirin causes hemolytic anemia and is cleared exclusively through the kidneys. Its use, therefore, is contraindicated in patients with anemia (less than 120 g/L for woman and less than 130 g/L for men) and in any patient with a history of ischemic heart disease or other serious disorders that may be exacerbated by a rapid decline in the hemoglobin. It also is contraindicated in patients with renal failure. Ribavirin is teratogenic and, therefore, contraindicated in

current or planned pregnancy. Effective birth control measures are required in both men and woman taking therapy.

Treatment duration with interferon and ribavirin is determined by the viral genotype. Patients with genotype 2 or 3 may be treated for 24 weeks, while patients infected with any other genotype should be treated for 48 weeks.¹⁸ Patients with genotype 1 have about a 20% to 30% response rate, as compared to those with genotype 2 or 3, who have about a 60% to 80% response rate. Other predictors of response include age less than 40 years, absent or minimal fibrosis on liver biopsy, female sex and a low serum HCV-RNA (less than 800,000 IU/mL).²⁰

Therapy with interferon plus ribavirin requires frequent monitoring of both symptoms and laboratory investigations due to the numerous side effects associated with the combination's use. Ribavirin predictably causes hemolysis, with a hemoglobin level generally falling an average of 30 g/L within the first two to four weeks, and then stabilizing in most patients.

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Routine monitoring for adverse effects include a weekly complete blood count (CBC) for the first month, and then a monthly CBC in addition to a thyroid-stimulating hormone (TSH) every three months. Symptoms should be monitored monthly during treatment.

Treatment response is monitored by the ALT and the HCV-RNA concentration. Because ALT is an imperfect marker of viral clearance, HCV-RNA testing is required.¹⁸ HCV-RNA should be determined at month six and, if it remains positive, treatment should be discontinued because this predicts nonresponse to therapy.¹⁸ Qualitative HCV-RNA also should be performed at 24 weeks after completion of therapy. Those who remain negative at 24 weeks post-treatment have what is termed a sustained virologic

Pegylated interferons are not licensed for use in chronic hepatitis C therapy in Canada. The combination of pegylated interferon plus ribavirin, however, will likely become the new standard of care within the next year.

response. This is highly predictable of long-term cure, with more than 95% of patients remaining HCV-RNA negative in long-term follow-up.²¹ Those who have a sustained virologic response require no specific follow-up, but should have liver enzymes obtained with their yearly routine assessments. They also should be warned their anti-HCV will likely remain positive indefinitely.

What's New In HCV Therapy?

A recent study examined the efficacy of interferon alfa-2b in the treatment of acute hepatitis C. A 98% efficacy rate was demonstrated in the prevention of developing chronic hepatitis C when interferon alfa-2b was given (five million units daily for four weeks, then three times per week for another 20 weeks) to those with acute infection.²² Given this newly available data, all patients suspected of having acute HCV infection should be referred to a specialist with expertise in the treatment of hepatitis C to determine if they are a candidate for therapy.

Recently, randomized controlled trials have demonstrated the efficacy of pegylated interferons in the treatment of chronic hepatitis C infection. Pegylated interferons have a polyethylene glycol (PEG) molecule conjugated to them which:²³

- Improves efficacy and therapeutic index;
- Maintains therapeutic concentrations by optimizing absorption, distribution, rate of clearance and rate of proteolysis; and
- Decreases immunogenicity.

As a result, pegylated interferons can be given once weekly with continuous interferon exposure throughout the dosing period. This helps avoid the large peaks and troughs that occur with standard interferon therapy.

Results comparing therapy with pegylated interferon alpha-2a and pegylated interferon alfa-2b with standard interferon monotherapy are summarized in Table 5. These results demonstrate a significant improvement in the sustained virologic response with pegylated interferon monotherapy, as compared to standard interferon monotherapy.²⁴⁻²⁶

Recent controlled trials also demonstrate an even greater response with the combination of pegylated interferon plus ribavirin. As outlined in Table 6, this combination results in a signifi-

cant improvement in response rates, to approximately 55% overall. The most benefit gained from this combination is achieved in those with genotype 1 infection.^{23,27} Currently, pegylated interferons are not licensed for use in the therapy of chronic hepatitis C infection in Canada. The combination of pegylated interferon plus ribavirin, however, will likely become the new standard of care within the next year.

Prevention

Currently, there is no vaccine available for the primary prevention of hepatitis C infection. Those with chronic hepatitis C infection, however, should be vaccinated against HBV if they are at increased risk (*i.e.*, IDU) or if they are serologically negative, as acute infection with HBV may cause severe disease or death in patients with pre-existing hepatitis C infection.

All patients with hepatitis C infection should be educated in terms of the mechanisms by which the virus is transmitted and how it can be avoided. This should include taking common sense precautions to avoid blood exposure of household contact and not sharing personal hygiene items, such as toothbrushes, razors, scissors or nail clippers.

Sexual partners should be informed of the infection by the infected partner and told their risk is low, but not absent. In short-term sexual relationships, the use of barrier precautions is advised. Unprotected sex during menstruation or in the presence of genital lesions should be avoided as well. In stable monogamous relationships, couples should be informed about the risk of transmission. There is no recommendation either for or against the use of condoms. Couples should be encouraged to make their own decision based on the information provided them.

Drug users should be educated about alternatives to injection and about safe injection prac-

tices.²⁸ All patients with chronic hepatitis C infection should be counseled with regard to the avoidance of alcohol consumption on a regular basis, as this has been associated with a more rapid progression of fibrosis.

Summary

Chronic hepatitis C infection is a significant public health problem, which is anticipated to increase over the years to come. Newer therapies under development for chronic HCV offer some hope, however, they remain imperfect. It is anticipated the next decade will bring further advances and improvements in the management of chronically infected people with HCV. Meanwhile, primary prevention of infection, and slowing the rate of progression of fibrosis in those already infected, remain important goals.

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