



## *Hepatitis C*

*Pedro Jose Greer, MD*

**T**he hepatitis C virus (HCV) was identified in 1989 and found to account for the majority of those patients with “non-A, non-B hepatitis”. HCV is now the most common blood-borne infection in the USA and a leading cause of chronic liver disease. Almost 4 million Americans have been infected with HCV, and 2.7 million are chronically infected. Many of those who are chronically infected are unaware because they have no signs or symptoms. By conservative estimates, 35,000 new hepatitis C infections occur each year in the USA. The world wide burden of chronic hepatitis C infection is estimated to range from 140-170 million individuals.

Hepatitis C is a small enveloped RNA virus belonging to the Flaviviridae family and the genus hepacivirus. HCV replicates rapidly in the liver and has marked sequence heterogeneity with 6 genotypes and over 90 subtypes. In the USA, 75% of individuals infected with HCV have genotypes 1a and 1b, 15% have genotypes 2a and 2b, and 7% have genotype 3. Genotype 1a is common in Europe, while 1b is found frequently in southern Europe and around the world. Genotypes 2a and 2b are common in Italy, North Africa, and Spain. Genotype 3 is common in Northern Europe.

After infection with HCV, 55-85% of individuals fail to clear the virus and develop chronic hepatitis C infection. This infection is usually asymptomatic, although persistent or fluctuating elevations in the liver enzyme ALT are common. However, 30-40% of persons with chronic HCV infection will have normal ALT levels. The consequential hepatic

sequelae of hepatitis C include progressive hepatic fibrosis, cirrhosis, and hepatocellular carcinoma. The extra-hepatic manifestations include sicca syndrome, cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda, as well as all the extra-hepatic manifestations of chronic liver disease.

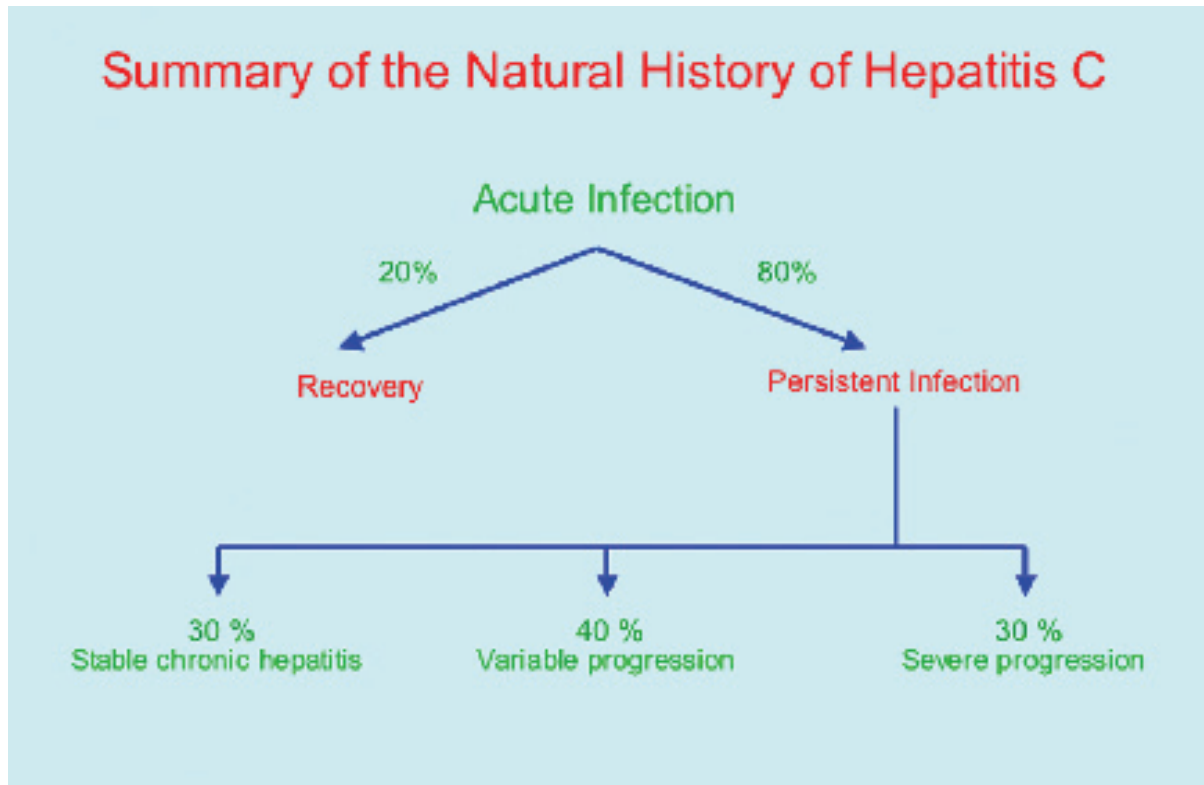
### **Transmission**

The known risk factors for infection with HCV have evolved as understanding of the pathogenesis has progressed. Blood transfusions received before 1991 accounted for a substantial portion of those infected prior to that time. Improved testing of blood supplies has resulted in a dramatic decline in the number of new HCV infections due to transfusions. Rather, intravenous drug use (IVDU) now accounts for 60% and sexual exposure for 20% of new HCV infections. Occupational exposure, hemodialysis, household contacts, and perinatal

---

*Cheryl Kane, a nurse on BHCHP's Street Team, brings medication to a man living under a bridge near the Charles River. Photo by Stan Grossfeld*

Figure 1:



The Natural History of Hepatitis C. Courtesy of UpToDate (www.uptodate.com)

exposure account for another 10%. The remaining 10% of HCV infections have no recognized source, although low socio-economic status appears to be common in this group. Other risk factors include: intranasal cocaine use; tattooing with contaminated needles or ink; extensive body piercing; and a history of military service, especially during the Vietnam era. Certain occupations have a higher risk of hepatitis C, including health care providers, emergency medical personnel, and public safety workers (firefighters, law enforcement officials, and correctional facility personnel).

Using a computer cohort simulation model, Wong and his colleagues estimate that HCV will cause the loss of 1.83 million years of life in individuals younger than 65 and cost society \$54.2 billion during the decade 2010-2019. Their model predicts 165,900 deaths from chronic liver disease and 27,200 deaths from hepatocellular carcinoma during that period.

#### Prevalence of HCV among Homeless Populations

Given our understanding of the risk factors for HCV and the silent and aggressive nature of this infection, one should not be surprised that studies have found the prevalence of HCV to be 10-20 times higher in some sub-groups of the homeless population than in the general population. The

USA population has a prevalence of 1.8%, while one study of homeless veterans showed an overall prevalence of 44%. The prevalence increases with age among homeless populations that have been studied. A study of homeless adolescents published in 2003 found that 12% tested positive for HCV. Rates among sub-groups of homeless adults have ranged from 22% to 80%, with the latter number found among those with a history of IVDU. Studies have shown higher HCV prevalence rates among recent daily users of intravenous drugs than those who were non-users or less frequent users. Co-infection with the human immunodeficiency virus (HIV) increases the risk of mortality from HCV.

With such high prevalence rates among homeless populations, clinicians caring for homeless individuals should maintain a high index of suspicion for HCV infection. Because this disease is indolent and often asymptomatic yet can have dire consequences, we feel strongly that all patients in homeless clinics should be offered HCV testing whenever treatment is a viable and accessible option.

#### Diagnosis and Evaluation of HCV Infection

The initial test in the evaluation of at-risk individuals and those with clinical liver disease should be an antibody against the HCV. An initial

enzyme immunoassay (EIA) can detect the presence of anti-HCV antibody, which is present from 6-16 weeks after the acute infection. The positive predictive value of this test is low in populations with low incidences of HCV infection, and therefore the CDC recommends a confirmatory test with a higher specificity, such as recombinant immunoblot assay (RIBA). This test can be performed on the same sample of blood used for the EIA. HCV antigens from the core and non-structural genes are utilized in both techniques. The newer third generation EIAs have a sensitivity of greater than 99% and specificity of 99% in immunocompetent patients. The use of these tests will eliminate the need for a confirmatory immunoblot assay except in certain situations, such as individuals who are immunocompromised or undergoing hemodialysis. These patients rarely have false-negative results. Conversely, false positives can occur in patients with autoimmune disorders.

The diagnosis of HCV may also be made by the detection of HCV RNA using gene amplification techniques such as polymerase chain reaction (PCR) or transcription mediated amplification (TMA). These tests are expensive but allow the diagnosis of HCV to be made within 1-2 weeks of HCV infection. Many clinicians advocate the early treatment of acute HCV in order to prevent chronic disease, and many studies are underway to evaluate this approach. These tests are qualitative and detect the presence of HCV RNA but do not measure the amount or level of the virus in the blood. These tests can detect viral levels as low as 50-100 IU/ml, and the latest generation TMA can now detect levels as low as 5-10 IU/ml. This type of qualitative testing is very helpful in establishing the diagnosis of HCV infection but is not useful in the management of patients who are being treated for HCV.

The HCV RNA level (or viral load) can be measured with quantitative assays that utilize PCR or branched DNA signal amplification. The viral load provides important information on the likelihood of response to antiviral treatment, although it should be noted that disease severity is not correlated with the level of the viral load. The viral load is measured regularly during and after treatment to determine success or failure. The goal is to maintain a sustained viral response (SVR) after treatment.

### **The Treatment of HCV Infection**

The current standard treatment for chronic HCV infection is interferon alfa in combination with ribavirin. The length of treatment is from

24-48 weeks. Interferon alfa is given subcutaneously three times a week; pegylated interferon alfa is now available, which is given once a week. The side effects of interferon alfa include flu-like symptoms (which usually occur early in therapy and then improve), fatigue, bone marrow suppression, and psychiatric problems. Ribavirin can cause hemolytic anemia (in persons with a pre-existing anemia), bone marrow suppression, and renal failure. Ribavirin is teratogenic and contraindicated during pregnancy.

All individuals with HCV infection should be vaccinated against hepatitis A, which is more virulent in persons who have HCV. HCV patients who are seronegative for hepatitis B virus (HBV) should be vaccinated against HBV.

### *The Importance of Genotype to Treatment Response*

Persons with known HCV who are candidates for treatment should be tested for genotype. The most common genotypes in the USA are 1a and 1b, followed by 2a and 2b, and then genotype 3. The genotype is a major factor in determining the length of treatment and amount of ribavirin needed. The standard treatment regimen of genotype 1a and 1b lasts 48 weeks, with SVRs from 47-54%; genotypes 2 and 3 require only 24 weeks of treatment, with SVRs of 73% and 82% respectively.

### *Liver Biopsy*

Individuals with HCV who are candidates for antiviral therapy should have a liver biopsy performed in order to establish the degree of injury to the liver. Treatment can be deferred for those with stage 0-1 fibrosis. The necessity and the timing of a follow-up biopsy remain controversial and must be determined on an individual basis.

### *Who is a Candidate for Treatment?*

A past history of alcohol abuse is not a contraindication to treatment. Alcohol accelerates the progression of HCV liver disease to cirrhosis and hepatocellular carcinoma, and continued alcohol use during therapy adversely affects response to treatment.

HIV infection is not a contraindication to treatment. Treatment for HCV does not appear to compromise antiretroviral treatment for HIV/AIDS. This should be approached on a patient by patient basis and requires specialty referral.

Homeless populations and substance abusers have higher rates of depression than the general population. The prevalence of depression is also

more common in persons with HCV. Depression is also a very common complication of our current therapies for HCV and occurs in 12-44% of persons who are treated with interferon and combination therapy with interferon and ribavirin. Therefore the identification of homeless patients with HCV and a history of depression is very important prior to the initiation of treatment. The potential neuropsychiatric side effects of HCV treatment should be carefully explained to each patient and are an important consideration in each patient's decision to undergo treatment. Several years ago, when the treatment response (SVR) was less than 15%, moderate to severe depression was a relative contraindication to treatment. With overall SVR rates now in excess of 50%, and as high as 80% in selected populations, depression is no longer considered a reason to withhold treatment. The SSRIs have proven effective for pre-existing depression as well as treatment-induced depression. Most patients have been able to tolerate and finish treatment. Whenever the antidepressant therapy is not successful, the interferon dose is reduced. If the depression persists, then the HCV treatment is terminated.

Active injection drug use is not a contraindication for the treatment of HCV. Since IVUD is the most common risk behavior for new HCV infection in the USA, any successful treatment modality will help to reduce transmission of the virus within this population. Management is enhanced by linking these patients to drug treatment programs, including methadone maintenance programs. All patients with drug and alcohol abuse should be offered these programs.

Several individuals are **not** good candidates for treatment with interferon and ribavirin:

- pregnant or nursing mothers, because of the teratogenicity of these medications;
- unmonitored psychiatric disease or untreated depression;
- active substance abuse;
- decompensated liver disease, since HCV treatment can cause thrombocytopenia, neutropenia, and progression of liver disease;
- severe co-morbid illnesses, which can be exacerbated by HCV treatment.

#### *Who Should Start and Monitor Treatment?*

Ideally, all patients with HCV who are potential candidates for treatment should be referred to a hepatologist. In today's world, the waiting times in academic and public hospital settings are often

unacceptably prolonged. Homeless patients face enormous obstacles to specialty and other health care clinics, including language barriers and a lack of insurance, transportation, and housing. Health care professionals trained in the monitoring and treatment of HCV should ideally be available at health care for the homeless clinics. While the management of HCV treatment is not difficult, the time commitment is significant, particularly in monitoring the side effects of antiviral therapy.

#### *Complications of Treatment*

(1) Depression is the principal side effect and cause of termination of therapy. Thus, optimal treatment for depression in patients with a prior history of depression is essential before and during therapy. Identification of mood disturbances in treated patients is of utmost importance.

(2) Hematologic consequences of HCV therapy are significant and require careful monitoring. Anemia occurs in 9-23% of patients, neutropenia in 18-21%, thrombocytopenia in 1-4%, and any adverse hemodynamic event in 32-42% of treated patients. The anemia can be caused by bone marrow suppression from interferon alfa-2b (both pegulated and non-pegulated interferon), while ribavirin can cause hemolysis. The decline in hemoglobin can be 2-4 grams and occur in the first two weeks of therapy. Anemia can be treated by reducing the dose of both interferon and ribavirin and by using epoetin alfa. The hematological consequences can be life-threatening, and patients must be carefully monitored. When patients fail to appear for scheduled visits, this becomes a contraindication to either the initiation or the continuation of HCV treatment.

(3) Fatigue and viral like symptoms are the most frequently reported complications. These are treated symptomatically, usually with acetaminophen and hydration. Virtually all patients experience fatigue, but this generally lessens with time.

(4) Other possible side effects include dermatologic problems, hair loss, and thyroid dysfunction.

#### **Summary**

The key lessons from this chapter are the following:

- 1) homeless populations are at extremely high risk for infection with HCV;
- 2) the consequences of HCV infection are significant and long term;
- 3) all patients in a homeless clinic should be screened for exposure to HCV;

- 4) all HCV patients should be vaccinated against hepatitis A and B;
- 5) a careful and thorough medical and neuro-psychiatric evaluation is necessary for all potential candidates for anti-viral therapy, as many relative and absolute contraindications to treatment remain;
- 6) regular attendance at clinic visits and adherence to therapy are essential for treatment;
- 7) active IVU is not a contraindication to treatment, but compliance is;
- 8) active alcohol use is a strong contraindication to treatment;
- 9) side effects from HCV treatment are significant and appropriate management is essential;
- 10) much work remains to be done, especially in screening and in the development of appropriate systems to care for this disease in the homeless population. ■■

Hepatitis C Medication List		
Generic	Brand Name	Cost
interferon alfa-2a	Roferon - A	\$\$\$\$\$
interferon alfacon-1	Infergen	\$\$\$\$\$
peginterferon alfa-2a	Pegasys	\$\$\$\$\$
interferon alfa-2b	Intron A	\$\$\$\$\$
peginterferon alfa-2b	PEG-Intron	\$\$\$\$\$
ribavirin	Rebetol, Copegus	\$\$\$\$\$
interferon alfa-2a + ribavirin	Rebetron (each kit contains 2-week supply of each)	\$\$\$\$\$

## References

- Alter MJ. Epidemiology of hepatitis C. *Journal of Hepatology* 1997;26(Supplement 1):S62-S65.
- Beech BM, Myers L, Beech DJ. Hepatitis B and C infections among homeless adolescents. *Family and Community Health* 2002;25(2):28-36.
- Beech BM, Myers L, Beech DJ, et al. Human immunodeficiency syndrome and hepatitis B and C infections among homeless adolescents. *Seminars in Pediatric Infectious Diseases* 2003;14(1):12-29.
- Desai RA, Rosenheck RA, Agnello V. Prevalence of hepatitis C virus infection in a sample of homeless veterans. *Social Psychiatry and Psychiatric Epidemiology* 2003;38(7):396-401.
- Hoofnagle JH. Course and outcome of Hepatitis C. *Journal of Hepatology* 2002;36(5 Supplement 1):S21-29.
- Hunt CM, Dominitz JA, Bute BP, et al. Effect of interferon-alpha treatment of chronic hepatitis C on health-related quality of life. *Digestive Diseases and Sciences* 1997;42(12):2482-2486.
- Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *The Lancet* 2004;358(9286):958.
- Martins RM, Porto SO, Vanderborght BO, et al. Short report: prevalence of hepatitis C viral antibody among Brazilian children, adolescents, and street youths. *American Journal of Tropical Medicine and Hygiene* 1995;53(6):654-655.
- Miyaoka H, Otsubo T, Kamijima K, et al. Depression from interferon therapy in patients with hepatitis C. *American Journal of Psychiatry* 1999;156(7):1120.
- National Institutes of Health. NIH Consensus Statement on Management of Hepatitis C. *NIH Consensus and State-of-the-Science Statements*. June, 2002.
- Nyamathi AM, Dixon EL, Robbins W, et al. Risk factors for hepatitis C virus infection among homeless adults. *Journal of General Internal Medicine* 2002;17(2):134-143.

- Raoult D, Foucault C, Brouqui P. Infections in the homeless. *The Lancet Infectious Diseases* 2001;1(2):75.
- Renault PF, Hoofnagle JH, Park Y, et al. Psychiatric complications of long-term interferon alfa therapy. *Archives of Internal Medicine* 1987;147:1577-1580.
- Simmonds P. Viral heterogeneity of the hepatitis C virus. *Journal of Hepatology* 1999;31(Supplement 1):54-60.
- Thomas DL. Hepatitis C and human immunodeficiency virus infection. *Hepatology* 2003;36(5B):S201-S209.
- Wong JB, McQuillan GM, McHutchison JG, et al. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *American Journal of Public Health* 2000;90:1562-1569.