

[Hepatitis C Expert Column](#)

Burden of Hepatitis C Infection: Realities and Challenges

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Burden of Disease

"Burden of disease" is a term that captures the frequency of the disease (such as the incidence and prevalence) as well as how it affects other aspects of the health of a population. This may include the negative impact of disease on longevity (such as premature death and years of lost life), morbidity (pain and impaired health-related quality of life), and economic consequences of the disease (such as direct healthcare expenditures in caring for the disease and indirect costs related to lost income from premature death or disability). Therefore, one needs to take all of these aspects into account in order to understand the true magnitude of a disease's burden. Such understanding is also essential in formulating healthcare policies to prioritize health interventions and to allocate scarce resources across a range of medical diseases. For example, expensive interventions (eg, new treatments for hepatitis C virus [HCV] infection) will add cost and therefore may increase the disease burden; however, these interventions may actually reduce the overall disease burden by prolonging life and improving quality of life.

Chronic infection with HCV is a major cause of liver-related morbidity and mortality. An estimated 180 million people worldwide, including 4 million in the United States, are infected with the virus.^[1] In the United States, end-stage liver disease due to chronic hepatitis C is the most common indication for liver transplantation,^[2] and markers for the virus have been found in at least half of all cases of hepatocellular carcinoma (HCC).^[3,4] HCV infection is postulated to result in an 8- to 12-year reduction in overall life expectancy in infected individuals, as well as in reduced health-related quality of life.^[5]

As the screening, diagnosis, and treatment of HCV infection continues to evolve with the availability of more effective yet more costly treatments, the cost of care will continue to rise. However, this increasing cost of care may still be acceptable and justifiable if it results in an accompanying improvement in quality-adjusted life years (ie, if it is cost-effective).

HCV Prevalence

Data from the most recent 1999-2002 National Health and Nutrition Examination Survey (NHANES) have found the prevalence of HCV to be 1.6% in the United States, equating to an estimated 4.1 million individuals.^[6] Of these, 3.2 million are chronically infected with HCV.

Although the number of new cases of infection has declined from a high of 240,000 per year in the 1980s (primarily due to injection-drug use and transfusion with unscreened blood and blood products) to 26,000 per year in 2004,^[7,8] the prevalence of individuals infected with HCV for longer than 20 years is expected to continue to increase.^[9]

HCV infection remains largely underdiagnosed, presenting a barrier to patients receiving appropriate treatment. A survey of 1412 primary care physicians in the United States revealed that only 59% had asked all of their patients about hepatitis C risk factors and that 25% did not know what treatment to recommend for hepatitis C patients.^[10] At an urban community health

center in Massachusetts, just 27% of 208 HCV-infected patients under primary care were found to have undergone treatment for hepatitis C.^[11]

Life Expectancy and HCV Infection

The prevalence of antibodies to HCV (anti-HCV) in 40- to 49-year-olds is 4.3%, the highest among all age categories.^[6] Most individuals with HCV infection are thus now in their fourth to fifth decade of life and are expected to live well into their seventies. This means that a greater proportion of HCV-infected individuals in the United States could live long enough to progress to cirrhosis, HCC, and death than in the past. After 30 years of infection, 15% to 35% of those infected will have cirrhosis, with a 5-year survival rate of 75% to 80%.^[5] Indeed, US projections show that without effective treatment, the numbers of patients per year with cirrhosis, hepatic decompensation, or HCC are expected to roughly double by 2020, and liver-related deaths will almost triple.^[12]

Fibrosis and Cirrhosis

Progressive hepatic fibrosis leading to cirrhosis is the major complication of chronic HCV infection and accounts for most of the disease's morbidity and mortality.^[12] Duration of infection is a major risk factor for more severe hepatic fibrosis. There seems to be little, if any, progression of fibrosis during the first decade of infection, followed by a slow, regular progression in the next 15 years, increasing to an intermediate rate over a period of another 10 years (Figure 1).^[13,14] Among plasma donors infected in the early 1970s, 34% were found to have bridging fibrosis, cirrhosis, or HCC after 31 years; the 35-year cumulative survival in these patients was 84% vs 91% to 95% for the general population.^[15]

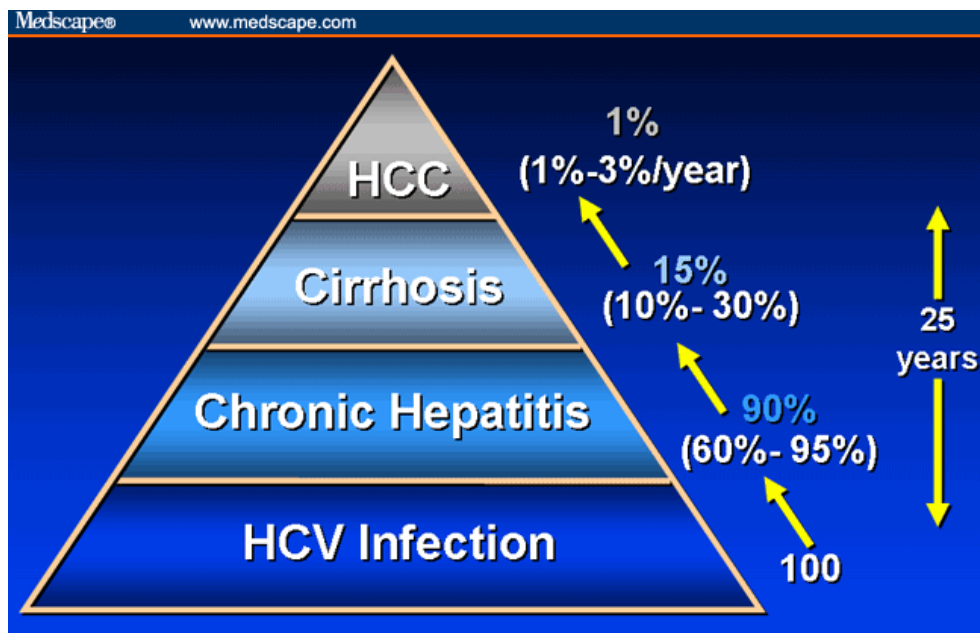


Figure 1.

HCV to HCC pyramid: a schematic representation of the progression of HCV over time.

Several other factors, including male sex, the presence of baseline fibrosis, HIV or hepatitis B virus (HBV) coinfection status, and alcohol consumption affect the rate of histologic progression of fibrosis.^[14,16-26] Insulin resistance is associated with the presence of fibrosis^[27,28] as well as

with a greater severity of fibrosis.^[20,29] Identification of these factors can thus be useful in determining prognosis and in advising patients on minimizing liver damage.

HCC

A comparison of the number of deaths in the United States occurring secondary to malignancies in 1995 vs those occurring in 2004 showed that the greatest increase was in cancers of the liver and bile duct, of which HCC comprised about 76%.^[30] Studies examining changes in HCC risk factors over time in the United States have found the greatest proportional increases occurring in cases of HCV-related HCC (Figure 2), whereas rates for HBV- and alcohol-related HCC have remained stable.^[31,32] Over the past decade, Hispanics and whites have seen the greatest increases in HCC incidence.^[33]

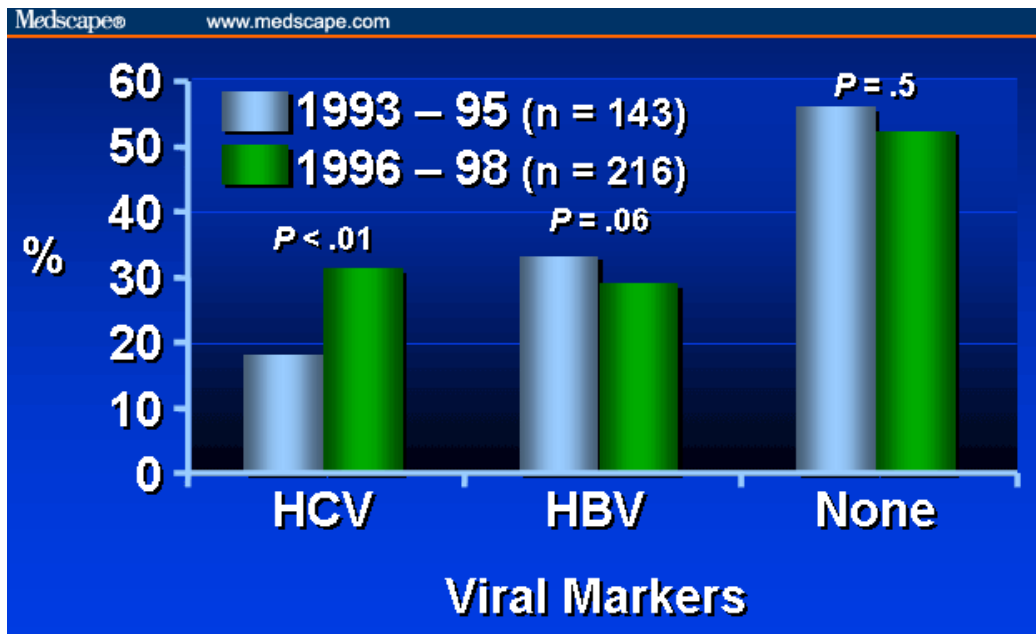


Figure 2.

Proportion of US-born patients with HCC related to viral hepatitis.

Comparisons of US and Japanese HCV strains, based on molecular evolutionary analysis, suggest that the US HCV epidemic began about 2-3 decades after the epidemic in Japan.^[34,35] This finding has led to speculation that the burden of HCC in the United States may eventually equal that currently being observed in Japan as HCV-infected individuals age and the duration of their infection increases. In Japan, HCV-related HCC accounts for 80% of all HCC cases,^[36] and the rate of HCC among HCV-infected men has increased from 17.4 per 100,000 in 1972-1976 (equivalent to 32,335 deaths) to 27.4 per 100,000 in 1992-1996 (equivalent to 109,365 deaths).^[37]

HCC generally develops only after hepatic cirrhosis is established, signifying the likely importance of long-standing necrosis and regeneration in the pathogenesis of malignant transformation. Data from a recent study of 214 HCV-infected patients in Italy with Child-Pugh A cirrhosis show that HCC developed at a rate of up to 4% per year.^[38] HCC was the first complication to occur in 58 (27%) patients over an average of 9.5 years; by the end of the study, HCC had developed in 68 (32%) patients.^[38] Seventy-five (35%) patients in the study died, 33 (44%) of whom died due to HCC progression over a total follow-up of 17 years.^[38]

Several factors affect the risk of developing HCC in patients with HCV-related cirrhosis. In general, increased HCC risk is reported in patients older than 50 years of age, men, those who are overweight or have diabetes, and patients with advanced cirrhosis or high alpha-fetoprotein levels.^[39] Other possible risk factors include the presence of hepatic steatosis,^[40] Asian or black race,^[41] and occult hepatitis B infection.^[42]

Strategies to Reduce the Impact of HCV Infection

Diagnosis and Screening

Those at high risk for hepatitis C should be tested, including persons transfused before 1992 or those who have ever injected drugs or are HIV-positive.^[43,44] Once diagnosed, patients can then be evaluated and referred for appropriate care. Lifestyle modifications such as weight loss and changes in diet reduce insulin resistance and may subsequently slow the rate of fibrosis. All patients with chronic hepatitis C should be assessed for immunity against hepatitis A and B by assessment of markers for hepatitis A virus and HBV and should be vaccinated if seronegative. Counseling should be offered regarding alcohol consumption, with abstinence advised as appropriate, depending on level of consumption and degree of liver disease. About 85% of HCV-positive persons in the United States general population can be identified on the basis of 1 of 2 risk factors (history of injection-drug use or receipt of a blood transfusion before 1992) or 1 laboratory result showing an abnormal serum alanine aminotransferase level.^[6] However, a retrospective chart review involving urban primary care sites in Philadelphia showed that HCV risk factor histories were rarely documented and that patients in ethnic minorities with a known HCV risk factor were less likely to be tested for HCV.^[45] Those who tested positive for HCV were also less likely to be referred for subspecialty care and treatment.^[45]

Treatment of Chronic HCV Infection

The lack of effective, widely available, well-tolerated therapeutic options to treat HCV infection has serious clinical implications for both the current and the future burden of hepatitis C for patients and societies alike. Less than half of the patient population infected with genotype 1 HCV, which accounts for approximately 75% of HCV infection in the United States,^[46,47] achieves a sustained virologic response (SVR; defined as undetectable HCV RNA for 6 months after completion of therapy) with the current standard of care, combination pegylated interferon + ribavirin.

Successful HCV treatment has the potential to eradicate the virus, thereby preventing, reducing, or even reversing its deleterious hepatic effects and serious complications.^[48-50] Many patients with fibrosis who have an SVR achieve improvement in necroinflammatory activity and even, in some cases, fibrosis regression^[49-51] A reduced risk of developing HCC has been noted in patients who achieve SVR; however, recent reports on the occurrence of HCC after SVR was achieved in cirrhotic patients indicate a need for continued surveillance and reinforce the importance of attempting to eradicate infection before cirrhosis develops.^[52] Results from the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial revealed that 3.5 years of maintenance therapy with pegylated interferon alfa-2a 90 µg per week did not affect the incidence of fibrosis progression, HCC, hepatic decompensation, or death.^[53]

The future of hepatitis C treatment is likely to involve the use of combination therapy regimens, with the standard of care still as the backbone of treatment. An exciting advance in hepatitis C therapy is the development of agents that target and inhibit specific steps in the replication cycle of the virus (such as the protease and polymerase enzymes), the STAT-C (specifically-targeted

antiviral therapy for HCV) therapies. The STAT-C agents furthest along include the protease inhibitors telaprevir* (an inhibitor of the NS3-4A serine protease) and boceprevir* (an inhibitor of the HCV-NS3 protease). Other agents are being developed that target various stages of the HCV life cycle, including viral attachment, entry and fusion, translation, posttranslational processing, replication, and virus assembly and release. The STAT-C class of therapies is highly anticipated, but agents targeting the replication cycle of HCV will lead to concerns regarding resistance mutations that will need to be studied carefully.

Recently, Zeuzem and colleagues^[54] reported the final results of PROVE 2, a phase 2 study of telaprevir in combination with pegylated interferon ± ribavirin in treatment-naïve patients with chronic hepatitis C genotype 1, conducted mainly at European sites. Patients were randomized to 1 of 4 treatment arms:

standard of care (pegylated interferon + ribavirin) for 48 weeks;

pegylated interferon + ribavirin + telaprevir (triple-combination therapy) for 12 weeks only;

pegylated interferon + ribavirin + telaprevir for 12 weeks followed by 12 weeks of pegylated interferon + ribavirin; or

pegylated interferon + telaprevir for 12 weeks.

The rapid virologic response (RVR; defined as undetectable HCV RNA < 50 IU/mL at week 4 of therapy) rate was best for those arms receiving triple-combination therapy (69% to 80%). Safety analysis showed an increased risk for severe rash in patients in the telaprevir-containing arms.

Kwo and colleagues^[55] recently presented the results of SPRINT-1 (Serine Protease Inhibitor Therapy-1), a study evaluating the safety and efficacy of boceprevir in combination with pegylated interferon and ribavirin in HCV genotype-1 previously untreated patients. Patients received either:

4-week lead in of pegylated interferon + ribavirin followed by the addition of boceprevir (800 mg thrice daily) for 24 or 44 weeks (total, 28 or 48 weeks);

boceprevir in combination with pegylated interferon + ribavirin for 28 or 48 weeks; or

boceprevir in combination with pegylated interferon + low-dose ribavirin for 48 weeks, compared with pegylated interferon + ribavirin alone for 48 weeks (control).

The investigators found that with 28 weeks of treatment, with or without the lead-in, SVR rates ranged from 55% to 56%. The 48-week lead-in group demonstrated the highest SVR rate, at 74% (vs 38% for the standard-of-care arm). They noted less viral breakthrough in the treatment arms with a lead-in phase; adverse events were similar between the boceprevir-containing arms and the control group, with the exception of anemia.

Conclusion

The impact of HCV infection on the burden of liver disease has become increasingly evident as individuals who were infected decades ago age and develop significant liver damage. In the United States, up to 1 million people are predicted to develop hepatic complications due to HCV in the next 2 decades.^[12]

Measures to tackle this challenge include improving screening of infected persons, identifying patients at highest risk for fibrosis progression, increasing the proportion of patients who receive treatment, and optimizing therapy for HCV-infected patients. New treatments for HCV infection are currently in development and aim to increase SVR rates, thereby potentially decreasing the overall burden of hepatic complications in patient populations with significant unmet need.

**The US Food and Drug Administration has not approved this medication for this use.*

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