

# Overview of Epidemiology, Diagnosis, and Disease Progression Associated With Hepatitis C

Tram T. Tran, MD

**H**epatitis C virus (HCV) infects about 3% of the world's population and has been declared a global health problem by the World Health Organization due to its impact on morbidity and mortality.<sup>1</sup> Only a small percentage (about 3%) of patients in the United States receive treatment with antiviral therapy, and up to half of infected patients are unaware of their infection.<sup>2</sup> A recent report from the Institute of Medicine (IOM) noted that lack of knowledge and awareness of HCV among healthcare providers, at-risk patients, health policy makers, and the general public contributes to poor diagnosis and missed opportunities for diagnosis, prevention, and treatment.<sup>3</sup> In response to the IOM report, the US Department of Health and Human Services created a road map which calls for an increase in the proportion of persons who are aware of their HCV infection, from 45% to 66%, and a 25% reduction in the number of new cases of HCV infection.<sup>4</sup> It was recently proposed that the rate-limiting factor in the achievement of better treatment outcomes is a lack of access to diagnosis and treatment.<sup>2</sup>

The commonality and health consequences of HCV, along with the lack of awareness among healthcare providers and at-risk patients, highlight the importance of bringing attention to HCV. The articles in this supplement will provide an overview of HCV and its diagnosis and treatment; managed care considerations will also be discussed.

## Prevalence and Epidemiology

The estimated global prevalence of HCV was 3%, or 170 million individuals, in 1999.<sup>1,5</sup> Peak prevalence occurs in the eastern Mediterranean region (4.6%), specifically in Egypt (about 20%), and the lowest prevalence is in the United Kingdom and Scandinavia (0.01 to 0.1%).<sup>5</sup> In North and South America, the prevalence is about 1.7%.<sup>5</sup> Approximately 2.7 to 3.9 million people are living with chronic hepatitis C in the United States.<sup>3</sup> The predicted annual incidence in the United States is about 76,000 cases per year, approximately the same as the incidence of human immunodeficiency virus (HIV), which is estimated at 79,000 cases per year. However, the peak incidence of HIV in 1989 was 142,000, and the peak incidence of HCV in 1984 was 350,000.<sup>1</sup> Approximately 80% of new infections with HCV

## Abstract

Hepatitis C virus (HCV) infects approximately 3% of the world's population and has a significant impact on morbidity and mortality. Unfortunately, there is currently a lack of knowledge and awareness of HCV among healthcare providers and patients. The rate-limiting factor in the achievement of better treatment outcomes is a lack of access to diagnosis and treatment. Clinicians and patients need better education on the risk factors for HCV to obtain the correct diagnosis and treatment. Once the diagnosis is made, there are a number of factors associated with disease progression, which clinicians must understand to guide appropriate treatment.

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## Reports

progress to chronic infections.<sup>5</sup> The majority of patients with HCV are in their fourth or fifth decade of life.<sup>6</sup>

### HCV Risk Factors

The association between patient age and HCV infection is important because a majority of transmissions occurred before universal screening of blood donors was implemented in 1992. Exposure to infected blood or blood products has been the predominant mode of transmission. Currently, most cases arise from illicit intravenous (IV) drug use (with shared, unsterilized, or poorly sterilized needles and syringes) and/or high-risk sexual contact.<sup>5,6</sup> Other much less common causes of transmission include transplantation of infected tissues or organs, mucosal exposure through non-high-risk (stable monogamous) sexual or perinatal routes, and needle-stick injuries in healthcare workers.<sup>5,6</sup> At-risk populations include hemophiliacs, dialysis patients, IV drug users, the homeless, and individuals who are incarcerated.<sup>6,7</sup> It is important to note that the homeless, prisoners, and IV drug users are generally excluded from epidemiological surveys, suggesting that the prevalence of HCV may be higher than reported.<sup>6</sup> Although the exact prevalence is unknown, the incidence of HIV/HCV coinfection and hepatitis B virus (HBV)/HCV coinfection may be up to 88% in HIV-infected and 7% in HBV-infected populations, respectively.<sup>8</sup>

### Classification and Genotype Distribution

HCV is a single-stranded ribonucleic acid (RNA) virus from the *Flaviviridae* family and the genus *Hepacivirus*, which preferentially infects liver cells. The structural proteins that form the virus particle include the core protein and the envelope glycoproteins, E1 and E2. Non-structural proteins play key roles in the life cycle of HCV, and include the NS2-3 protease, the NS3 helicase serine protease, the RNA helicase, the NS4A polypeptide, the NS4B and NS5A proteins, the NS5B RNA-dependent RNA polymerase (RdRp), and the p7 ion channel. The structure and life cycle of the HCV particle have been reviewed in detail elsewhere.<sup>9</sup> Briefly, based on what is currently known, P7 and the NS2-3 proteases are essential for in vivo HCV replication, the NS3-4A complex appears to be involved in unwinding RNA and immune sensing, the NS4B serves as a scaffold for HCV replication complex, the NS5A may provide protection for the RNA strand, and the NS5B synthesizes complementary negative strand RNA. All of the structures and functions have yet to be completely determined.<sup>9</sup>

HCV has a propensity for frequent mutations, and consequently, there are more than 50 subtypes classified into 6 genotypes, with nucleotide sequences differing by as much

as 30% to 35%.<sup>6,9,10</sup> The geographic distribution varies by genotype. Genotypes 1a and 1b account for approximately 75% of cases in the United States, and genotypes 2 and 3 are present in 10% to 20% of patients. Genotype 4 is found most commonly in the Middle East, Egypt, and central Africa.<sup>5</sup> Genotype 1 has a lower response to interferon-based therapies than genotypes 2 and 3.<sup>6,11</sup>

### Diagnosis

The diagnosis of HCV infection is based on screening individuals with known or suspected exposure. Guidelines for HCV diagnosis, management, and treatment have been recently endorsed by the American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the American College of Gastroenterology.<sup>12</sup> More recently, the Centers for Disease Control and Prevention issued recommendations urging patients at risk for HCV, based on previously discussed behaviors or exposure, or patients born between 1945 and 1965 ("birth cohort" screening), to undergo laboratory testing using qualitative serologic assays that determine the presence of antibody to HCV (anti-HCV).<sup>12,13</sup> The anti-HCV tests have high sensitivity and a specificity greater than 99%. Tests are also available for quantification of HCV in serum plasma. These tests provide a value for the levels of HCV RNA in blood or serum in the form of a viral load, and these tests also have high sensitivity and specificity (in the range of 98% to 99%). A detailed review of these tests is available elsewhere.<sup>12</sup> Typically, the anti-HCV test should be performed first, with HCV RNA testing performed when the anti-HCV test is positive, when antiviral treatment is being considered, or in patients with a negative anti-HCV test if the clinician suspects that the patient may be immunocompromised or that the patient may have HCV infection despite a negative anti-HCV test result. When the anti-HCV and HCV RNA tests are negative, this is interpreted as absence of HCV infection. If the anti-HCV test is positive and the HCV RNA test is positive, it may be suggestive of acute or chronic HCV, depending on the clinical context. A positive anti-HCV with a negative HCV RNA constitutes resolution of HCV or acute HCV during a period of low-level viremia. A negative anti-HCV test with a positive HCV RNA test indicates early acute infection, chronic infection in an immunocompromised host, or a false positive HCV RNA test.<sup>12</sup> False positive anti-HCV tests may occur when testing is done in a population where the prevalence of HCV is extremely low. All tested patients should be counseled on avoidance of HCV transmission.<sup>12</sup>

When interferon-based treatment is being considered, HCV genotyping should be performed prior to treatment to

■ **Table. Pretreatment Assessments in Patients With Chronic HCV Infection**<sup>14</sup>

Necessary
• Medical history, including complications of liver disease, presence of significant extrahepatic disease, and symptoms of chronic HCV that may diminish quality of life
• Psychiatric history, including past or ongoing psychiatric and substance use disorders
• Screening for depression and alcohol use
• Biochemical markers of liver injury and assessment of hepatic function, including serum ALT, serum albumin, serum bilirubin (including direct bilirubin), and prothrombin time
• Hemoglobin, hematocrit, WBC with differential, and platelet count
• TSH
• Serum creatinine
• Serum glucose
• Uric acid (while receiving TVR)
• Serum ferritin, iron saturation, and serum ANA
• Pregnancy test (in women of childbearing age)
• HIV serology
• Serum HBsAg, antiHBc, antiHBs, antiHAV (total)
• Quantitative HCV RNA measurement
• HCV genotype
• Previous antiviral therapies and response
• ECG in patients with preexisting cardiac disease
Recommended
• Liver biopsy (if results will influence management)
• IL28B genotype (if results will influence management)
• Eye exam for retinopathy in patients with diabetes or hypertension
• Urine toxicology screen for opiates, cocaine, and amphetamines
<small>ALT indicates alanine transaminase; ANA, antinuclear antibody; antiHAV, antibody to hepatitis A virus; antiHBc, antibody to hepatitis B core antigen; antiHBs, antibody to hepatitis B surface antigen; ECG, electrocardiogram; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; TSH, thyroid-stimulating hormone; TVR, telaprevir; WBC, white blood cell.                      Reprinted with permission from Yee HS, Chang MF, Pocha C, et al. <i>Am J Gastroenterol</i>. 2012;107:669-689.</small>

plan the dose and duration of therapy and to estimate the likelihood of response.<sup>12</sup> A liver biopsy can also be considered in patients with chronic HCV infection in order to obtain more information about fibrosis stage to help determine prognosis or inform treatment decisions. Noninvasive tests have also been developed to evaluate fibrosis, but those require further validation studies before they may be recommended in lieu of liver biopsy.<sup>12</sup> In addition, interleukin (IL)-28B testing can be performed (eg, to predict response to pegylated interferon and ribavirin in HCV genotype 1) in cases where the results may influence treatment decisions.<sup>13</sup> A single-nucleotide polymorphism in chromosome 19 in the region of the IL28B gene strongly predicts response to treatment in genotype 1–infected patients treated with peginterferon and ribavirin. Individuals with a CC genotype at rs12979860 have a 2-fold increase in sustained virological response (SVR) compared with those with CT or TT genotype.<sup>14</sup> A comprehensive workup, as

outlined in a position paper from the Department of Veterans Affairs, should be conducted prior to treatment (**Table 1**).<sup>14</sup>

### Disease Progression

Most patients are asymptomatic after initial exposure to HCV. When symptoms occur with initial viremia, they often present several weeks after the incident and are mild, nonspecific, or intermittent. Symptoms may include jaundice, fatigue, anorexia, weakness, abdominal pain, and dark urine.<sup>6</sup> As evidenced in published literature, 50% to 85% of infected individuals progress to chronic infection and then subsequent liver disease–related complications.<sup>6,15</sup> Chronic hepatitis leads to cirrhosis in 10% to 20% of patients, depending on the rate of fibrosis (the hallmark feature of hepatic cirrhosis).<sup>16</sup> In a study conducted at the National Institutes of Health, untreated patients with chronic hepatitis C with 2 liver biopsies at 4 to 212 months apart (mean 44 months) were

## Reports

analyzed for progression of fibrosis. Liver biopsy specimens were graded using histology activity index and Ishak fibrosis score (range 0-6 [0, no fibrosis; 1-2, portal fibrotic expansion; 3-4, bridging fibrosis; 5-6, cirrhosis]). Among 123 patients, 48 (39%) showed progression of fibrosis score, 46 (37%) showed no change, and 29 (24%) showed improvement. Of those with a worsening of fibrosis, 75% had a 1-point increase in Ishak score and 25% had a 2-point increase in Ishak score. The overall rate of progression was 0.12 fibrosis units per year, suggesting progression to cirrhosis in about 50 years, if linear. However, several factors were shown to accelerate the progression of fibrosis. Fibrosis was higher in older patients, patients with extensive periportal necrosis on initial liver biopsy, and those with higher serum alanine and aspartate aminotransferase.<sup>16</sup> High levels of alcohol consumption (4 or 5 drinks or more per day) have also been shown to increase the rate of progression of liver fibrosis.<sup>8</sup>

Approximately 10% to 20% of individuals who develop chronic hepatitis C will develop chronic liver disease complications, such as cirrhosis and hepatocellular carcinoma (HCC).<sup>7</sup> In a small portion of patients, HCC may develop before cirrhosis, but more frequently, HCC develops as a result of cirrhosis.<sup>15,17</sup> Cirrhosis often develops within 20 to 30 years, and HCC occurs in 1% to 5% of individuals with advanced fibrosis/cirrhosis.<sup>7</sup> HCV is estimated to cause 27% of cirrhosis and 22% to 25% of HCC cases worldwide.<sup>5,7</sup> Once cirrhosis develops, outcomes typical of advanced liver disease are expected, including ascites, variceal bleeding, hepatic encephalopathy (requiring transplantation), and death from cirrhosis. The current estimate for HCV-related mortality in the United States is 8000 to 10,000 deaths per year.<sup>5</sup> The mortality rate for HCV is expected to peak in 2030, with an estimated mortality rate of 4300 (confidence interval [CI], 3500-5100) women and 8600 (CI, 8300-9000) men, for a total of 12,900 deaths per year.<sup>1</sup> The presence of HCV RNA increases the risk of mortality, which is further increased as HCC, cirrhosis, and chronic liver disease develop. Mortality from HCV has surpassed mortality from HIV, although HIV increases the risk of death in coinfecting individuals.<sup>18,19</sup>

In an effort to characterize the progression of HCV-related liver disease, the HALT-C (Hepatitis C Antiviral Long-term Treatment against Cirrhosis) trial was conducted. This 3.5-year randomized trial evaluated the effect of maintenance peginterferon monotherapy versus no therapy on liver disease progression among patients who had not cleared the virus on peginterferon and ribavirin therapy.<sup>20</sup> Among 1050 subjects (60% with advanced fibrosis, 40% with cirrhosis), investigators determined the rate of progression to cirrhosis over 4 years and evaluated clinical outcomes for 8 years. As patients

progressed through fibrosis to cirrhosis, changes in laboratory values suggested biochemical progression of liver dysfunction. One of the main conclusions in this study was that maintenance therapy with interferon did not impact clinical outcomes. Observable changes in laboratory values included reductions in albumin and platelets, and increases in serum creatinine, bilirubin, prothrombin time/international normalized ratio, and MELD score (a liver transplantation priority score). These factors comprised the CTP score, which was used as an overall assessment of disease severity. Patients with fibrosis or cirrhosis were compared with respect to mortality. The mortality rate was 12.2% with advanced fibrosis and 31.5% with cirrhosis.<sup>20</sup> This study determined the incidence of cirrhosis among patients with fibrosis to be 9.9% per year.<sup>20</sup>

Disease progression is therefore impacted by many factors, but a recent meta-analysis demonstrated that patients who experienced SVR when treated for HCV had improvements in mortality (relative risk [RR], 0.23; 95% CI, 0.01-0.52), HCC (RR, 0.21; 95% CI, 0.16-0.27), or hepatic decompensation (RR, 0.16; 95% CI, 0.04-0.59) compared with patients who experienced treatment failure.<sup>21</sup> The next article in this supplement will discuss the treatment of HCV.

## Summary

HCV is an important public health concern because it is frequently underdiagnosed and undertreated. The prevalence of HCV infection is increasing, and increased awareness of the disease and its consequences is needed among both clinicians and patients. In addition to the development of cirrhosis and consequent liver disease manifestations, the risks of mortality and cancer are increased with HCV. The first step in improving outcomes in HCV is ensuring diagnosis and treatment. Effective treatment, the focus of the next article in this supplement, is associated with reductions in mortality, HCC, and hepatic decompensation.

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**Address correspondence to:** E-mail: TranT@cshs.org.

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