At least 3 million people in the United States are infected with hepatitis C virus (HCV) infection. Unfortunately, 75% of infected individuals remain undiagnosed and untreated, putting them at risk of advanced liver disease. Because the majority of infected individuals are baby boomers, many societies and organizations recommend HCV screening of persons born between 1945 and 1965.

The Centers for Disease Control and Prevention (CDC) has estimated that about 3 million individuals are infected with hepatitis C virus (HCV) in the United States; this exceeds the combined prevalence of both HIV (1.1 million people) and hepatitis B virus (HBV; 0.8-1.4 million people) [1-3]. However, the accuracy of this HCV prevalence estimate may be affected by the lack of data for several cohorts: incarcerated individuals, homeless persons, and veterans. Chak and colleagues [1] have argued that the true prevalence of HCV infection in the United States is 5-7 million individuals.

The overall prevalence of HCV antibodies in the United States is about 2%, but this figure depends on factors such as race, age, geographic area, and sex. For instance, the prevalence of HCV antibodies is 1.3% among Mexican Americans and 3% among non-Hispanic blacks [1]. Among African Americans, the highest prevalence is seen in those aged 40-49 years, with rates of 14% and 6% in men and women, respectively.

Natural History

The majority of patients with HCV are infected through blood contact. Most patients with acute HCV infection remain asymptomatic, with about 15%-20% of these patients clearing the infection spontaneously, but 20%-90% of infected individuals will progress to chronic HCV infection. The course of chronic HCV infection plays out over decades and varies among individuals based on factors such as age at infection, sex, race, alcohol consumption, co-infection with HIV or HBV, diabetes, body mass index, hepatic steatosis, and HCV genotype. Over the first 20 years of infection, most patients develop only hepatic inflammation and moderate fibrosis. A percentage of these patients then progress to cirrhosis, decompensated cirrhosis, and ultimately hepatocellular carcinoma [4, 5]. In addition to the late complications of untreated infection, HCV is associated with an increase in all-cause mortality even after accounting for other factors (older age, HCV genotype, higher Ishak fibrosis score, diabetes, and alcohol abuse) [6].

HCV Screening

Due to HCV’s devastating impact, it is imperative that all infected patients be screened and offered therapy. Unfortunately, about 70%-80% of all infected individuals are unaware of their HCV status. This is due in part to the fact that most patients with chronic HCV infection are asymptomatic. Furthermore, transaminase levels are normal in approximately one-third of HCV-infected patients, and these levels fluctuate in another one-third of patients. In contrast to the large percentage of HCV-infected patients who have not been diagnosed, only 12% of those infected with HIV are unaware of their status [7].

In order to raise awareness about the prevalence of HCV and to improve the rate of disease detection, the CDC has released updated and revised national guidelines for HCV screening (see Table 1). The risks of exposure to HCV is highest in several groups: individuals who received clotting factors prior to 1987 and/or blood transfusions or organ transplantation prior to 1992; illicit drug users, including intravenous drug users and nasal drug users; chronic hemodialysis patients; patients infected with HIV; and individuals born from 1945 through 1965 (baby boomers).

With respect to the CDC guidelines of 2011, 3 different age cohorts—individuals born in the period 1945-1965, those born 1950-1970, and those born 1945-1970—were evaluated and stratified based on race, ethnicity, and sex. The cohort born in 1945-1965 was ultimately chosen for inclusion in the guidelines, as this sample of patients encompassed the greatest diversity of race and ethnicities. The prevalence of HCV was found to be 5 times higher in this cohort than in the other cohorts; according to the CDC, this “reflects the substantial number of incident infections throughout the 1970s and 1980s and the persistence of HCV as a chronicกวิอาชีกที่มีความต้องการที่สูง”
TABLE 1
Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Diseases

| Recommendations for the identification of chronic HCV infection among persons born during the period 1945–1965* |
|-------------------------------------------------|
| • Adults born during the period 1945–1965 should receive 1-time testing for HCV without prior ascertainment of HCV risk. |
| • All persons with identified HCV infection should receive brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment for HCV infection and related conditions. |

Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents*

• HIV-infected patients should be routinely tested for evidence of chronic HCV infection. Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV in blood.

Recommendations for prevention and control of HCV infection and HCV-related chronic disease¹

Routine HCV testing is recommended for the following groups:

• Persons who ever injected illegal drugs, including those who injected once or a few times many years ago and do not consider themselves as drug users.
• Persons with selected medical conditions, including:
  • Persons who received clotting factor concentrates produced before 1987;
  • Persons who were ever on chronic (long-term) hemodialysis;
  • Persons with persistently abnormal alanine aminotransferase levels.
• Recipients of transfusions or organ transplants, including:
  • Persons who were notified that they received blood from a donor who later tested positive for HCV infection;
  • Persons who received a transfusion of blood or blood components before July 1992;
  • Persons who received an organ transplant before July 1992.

Routine HCV testing is recommended for persons with recognized exposures, including:

• Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood.
• Children born to HCV-positive women.

Note. CDC, Centers for Disease Control and Prevention.

¹This recommendation is from the CDC publication “Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965” [8]
²This recommendation is from the CDC publication “Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents” [9]
³This recommendation is from the CDC publication “Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease” [10]

While individuals born in 1945–1965 only account for 27% of the US population, this birth cohort accounts for 75% of all HCV infections in the United States and 73% of HCV-related mortality; this group also has the highest risk of developing complications such as cirrhosis and hepatocellular carcinoma. Therefore, proactively screening individuals born during this time period—independent of other possible risk factors—yields early identification, diagnosis, and access to treatment. Adherence to the CDC’s HCV screening guidelines would also alleviate the burden of questioning all patients regarding their history of having used illicit drugs or having received blood products. Based on birth cohort screening, some investigators predict that up to 1,162,323 new patients would be diagnosed with previously unknown chronic HCV infection [12].

While the CDC guidelines have identified the age group with the highest prevalence of HCV-related mortality, it is important to also continue to screen those with known risk factors, regardless of their age. Recently, a soaring epidemic of HCV related to prescription drug use has been reported in Kentucky, West Virginia, Tennessee, and Virginia, with the highest rates occurring among individuals 30 years of age or younger. In Kentucky alone, it has been reported that the incidence of HCV increased from 1.25 cases per 100,000 population to 4 cases per 100,000 in the period 2006–2012, reaching a peak incidence of 5.1 cases per 100,000 in 2013. This new cohort of HCV-infected patients is twice as likely to live in rural areas and often includes opioid abusers, mainly persons who inject drugs.

Costs and Benefits of HCV Treatment

A computer simulation that compared 4 strategies for screening and treatment of HCV infection (plus the option of no screening or treatment) found that birth cohort screening and treatment of all HCV-infected patients would save more than 4 million life-years at an incremental cost of $36,585 per quality-adjusted life-year (QALY) [13], which is well below the widely accepted threshold of $50,000 per QALY used to define cost effectiveness in health care. For example, the risk of hepatocellular carcinoma was 4% with birth cohort screening followed by treatment of all HCV-positive patients, 5% with birth cohort screening and HCV treatment based on staging, 15% with a risk-based screening strategy, and 20% with no screening.

Current HCV Treatment Strategies and Implications

Unlike HIV (where the genome undergoes reverse transcription to DNA and is permanently stored in the host...
nucleus) and HBV (where the genome is converted to covalently closed circular DNA and incorporated into the host genome), HCV RNA is located in the cytoplasm, which makes it possible to clear the virus. Thus, the goal of HCV therapy is to cure the infection in order to prevent or mitigate the potential complications of HCV-related liver diseases and extrahepatic diseases, which can include hepatic fibrosis, cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, severe extrahepatic manifestations, and death. Given this goal, the target endpoint of therapy is sustained virologic response, which is achieved if the patient has undetectable levels of HCV RNA 12 or 24 weeks after the end of treatment. Thus, all treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease related to HCV should be considered for therapy if they are willing to undergo treatment and have no contraindications to treatment.

Until 2011, the approved treatment for HCV infection was a combination of pegylated interferon and ribavirin for 24-48 weeks, but this regimen had significant side effects and abysmally low rates of sustained virologic response. More recently, rapid breakthroughs in the treatment of HCV infection have dramatically altered the treatment landscape for this chronic disease. Specifically, direct-acting antiviral (DAA) drugs have been developed based on our knowledge of the HCV lifecycle; these drugs target every step of this cycle with specific inhibitory approaches that act through various mechanisms. The available DAA drugs include those that inhibit HCV polyprotein maturation (NS3-4A protease inhibitors), those that inhibit HCV RNA synthesis (nucleo-
tide analogue inhibitors of the HCV RNA-dependent RNA polymerase), and those that inhibit HCV particle assembly and release (NS5A inhibitors).

Currently, the strategy for HCV therapy is to combine 2 or 3 oral drugs to create regimens that have superior virologic efficacy, ease of use and tolerability, and in some instances pangenotypic capabilities (with rare relapses mainly due to resistance-associated variants). In view of the effectiveness of available drug regimens, even populations that were previously hard to treat are now able to achieve desirable sustained virologic response; these special populations include HCV-HIV co-infected patients, HCV-infected patients with chronic liver disease (Child-Pugh scores of B or C), African American patients with the interleukin-28B TT genotype, patients with end-stage renal disease and/or those on hemodialysis, and transplant recipients with HCV. If properly used, these new generations of DAA drugs could yield cure rates of 90%-100% [14, 15].

Based on the availability of newly approved DAA drugs, there are 3 different treatment strategies now in use: nucleotide analogue–based combinations, nucleotide-free triple combinations of drugs with low barriers to resistance, and nucleotide-free double combinations that include at least 1 drug with a high barrier to resistance [16].

**Nucleotide analogue–based combinations**

Given its high barrier to resistance, a nucleotide analogue can be used as the backbone of therapy in combina-
tion with ribavirin and/or a DAA that has a low barrier to resistance. Examples of such treatment combinations are sofosbuvir plus ribavirin, which can be used in the treatment of patients with HCV genotype 2 (and to some extent those with genotype 3); sofosbuvir and simeprevir, which can be used in the treatment of patients with HCV genotypes 1 or 4; sofosbuvir plus ledipasvir (available together in a single pill) for patients infected with HCV genotypes 1, 4, 5, or 6; and sofosbuvir and daclatasvir (where available), which can be used for treatment of all HCV genotypes.

Nucleotide analogue-free triple combinations

In this strategy, there is no backbone drug with a high barrier to resistance; instead, clinicians combine 2 or 3 drugs that individually have low barriers to resistance but that collectively achieve a high barrier to drug resistance. One such regimen is ritonavir-boosted paritaprevir and ombitasvir, which is available in a single pill. This treatment option is indicated for patients with HCV genotype 4; it can also be used with the addition of dasabuvir for treatment of patients with HCV genotype 1.

Nucleotide analogue-free double combination with at least 1 drug with a higher barrier to resistance

A third treatment strategy is a combination of 2 drugs that are not nucleotide analogues, 1 of which has a high barrier
to resistance. An example of such a regimen is grazoprevir and elbasvir, which can be used to treat patients with HCV genotypes 1 or 4 (and possibly 5 or 6), HCV-HIV co-infected patients, and those with end-stage renal disease.

Access to HCV Therapy

Given the prohibitively high cost of DAA drugs and the large number of infected patients, the American Association for the Study of Liver Diseases initially recommended that patients should be prioritized so that the sickest are treated first. The prioritized patient populations include those with advanced fibrosis (METAVIR score F3 to F4), including patients with Child-Pugh scores of B or C; HCV-HIV or HCV-HBV co-infected individuals; pre- or post-liver transplant patients; patients with extreme fatigue or other extrahepatic manifestations of HCV, regardless of the stage of hepatic fibrosis; and individuals at risk of transmitting HCV, including active injection drug abusers, men who have sex with men and engage in high-risk sexual practices, women of childbearing age who wish to get pregnant, hemodialysis patients, and incarcerated individuals.

Given this situation, many insurers, including North Carolina Medicaid, have implemented coverage restrictions and prior authorization requirements, which limit coverage to those with advanced hepatic fibrosis who have at least 6 months of abstinence from alcohol or illicit drug use and are receiving treatment from a specialist [17]. These restrictions on access are being challenged by the Centers for Medicare & Medicaid Services through a notice issued to all the state Medicaid programs.

Conclusion

We are in the midst of the peak burden of liver disease attributed to HCV infection, but screening of all baby boomers should identify over 800,000 new cases of infection. Over the next several years, DAA therapy will continue to evolve—possibly to the point of having a once-daily pill capable of treating and curing all genotypes, hopefully at a price that is affordable for all infected patients in our communities. NCMJ

Mitchell A. Mah’moud, MD, FAASLD consulting faculty, Division of Gastroenterology, Duke University School of Medicine, Durham, North Carolina; director, Hepatology Clinic, Boice-Willis Clinic, Rocky Mount, North Carolina.

Acknowledgments

I would like to thank Dr. Sammy Saab of the UCLA Pfieger Liver Institute and Dr. Paul Kwo of the Indiana University Liver Transplant Program for their insightful comments. I am also indebted to Dr. Andrew Muir, the chief of Duke’s division of gastroenterology, for his support and to all the patients who have taught me about liver disorders. Finally, I am grateful to my wife, Nana, and to my daughters—Mattia, Mia, and Mirelle—for their love and encouragement in getting this article written.

Potential conflicts of interest. M.A.M. has no relevant conflicts of interest.

References

1. Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in the USA: an estimate of true prevalence. Liver Int. 2011;31(8):1090-1101.
2. Colvin HM, Mitchell AE, eds. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. Washington DC: National Academies Press; 2010.
3. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006;144(10):705-714.
4. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007;147(10):677-684.
5. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med. 1999;340(10):745-750.
6. van der Meer AJ, Veldt BJ, Wedemeyer H, et al. Association between sustained virologic response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308(24):2584-2593.
7. Centers for Disease Control and Prevention (CDC). HIV in the United States: At A Glance. CDC website. http://www.cdc.gov/hiv/statistics/overview/ataglance.html. Updated September 29, 2015. Accessed April 26, 2016.
8. CDC. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. MMWR 2012; 61(No. RR–4).
9. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR 2009; 58(No. RR–4).
10. CDC. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR 1998; 47(No. RR–19).
11. Smith BD, Morgan RL, Beckett GA, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. MMWR Recomm Rep. 2012;61(RR–4):1-32.
12. Boschert S. Screen baby boomers, treat all hepatitis C. GI & Hepatology News. 2015;9(1):1,24,25.
13. McGarry LJ, Pawar VS, Panchmatia HR, et al. Economic model of a birth cohort screening program for hepatitis C virus. Hepatology. 2012;55(5):1344-1355.
14. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C. HCV Guidelines website. http://www.hcvguidelines.org/. Accessed March 3, 2016.
15. European Association for Study of the Liver. EASL recommendations on treatment of hepatitis C 2015. J Hepatol. 2015;63(1):199-236.
16. American Association for the Study of Liver Diseases. Managing Liver Disease—From the Clinic to the Community. San Francisco, CA: American Association for the Study of Liver Diseases; 2015.
17. NC Tracks. Prior approval. NC Tracks website. https://www.nctracks.nc.gov/content/public/providers/prior-approval.html. Accessed March 3, 2016.