Expanding HCV Care Beyond The Specialty Setting:
A Series for Primary Care Clinicians

The Critical Role of Careful Evaluation of Liver Health

Chronic hepatitis C virus (HCV) infection and its complications kill more people in the United States (US) than human immunodeficiency virus (HIV), tuberculosis, and 58 other infections combined. Furthermore, HCV is one of the leading indications for liver transplantation and is a major cause of hepatocellular carcinoma (HCC) in the US.

Approximately 3.5 million persons in the US are infected with HCV, nearly one-half of whom are unaware of their infection. Unfortunately, the prevalence of HCV is believed to be increasing, with the current opioid crisis and its associated injection drug use adding approximately 30,000 new HCV cases annually (range, 24,200 to 104,200). In addition, HCV disproportionately affects marginalized populations for whom traveling to specialty clinics and/or attending appointments in an unfamiliar setting can be a substantial barrier.

Another challenge in the HCV treatment landscape is the insufficient specialist workforce in the US, which is unable to meet both the current and anticipated volume of patients with HCV; in 2013, fewer than 50% of 2,000 surveyed members of the American Association for the Study of Liver Diseases (AASLD) reported that they spend more than one-half of their time practicing hepatology. In addition, the development of tolerable, highly effective direct-acting antiviral therapies has increased the demand for HCV care and created a bottleneck effect in hepatology/gastroenterology clinics. Fortunately, as testing recommendations and treatment approaches for HCV have changed considerably in the past 5 years, patients are increasingly receiving successful HCV treatment in the primary care setting rather than the specialty setting. Indeed, for HCV elimination to be possible—a goal of both the World Health Organization and the National Academies of Science, Engineering, and Medicine—treatment must move beyond the walls of major academic medical centers.

Case Description

Fred, a 68-year-old veteran of the Vietnam War, sustained significant injuries during combat that required multiple blood transfusions. After returning home, he obtained several tattoos memorializing his experiences from those hard years. For years, Fred has also had joint pain, believed to be related to rheumatoid arthritis. His doctor prescribed methotrexate, which Fred has been taking without any clear side effects.

Recently, Fred began complaining of nausea and lost a substantial amount of weight over the course of a few months. The primary care physician (PCP) thought that Fred was at a healthier weight than before and prescribed an antiemetic. This medication seemed to help with the nausea, but the unintended weight loss continued. In 2016, after hearing some public service announcements about the prevalence of HCV in the baby boomer cohort, Fred asked his PCP to test him for HCV. Fred's HCV antibody test was reactive, and a confirmatory RNA test was positive. Fred, having never used injection drugs and only experimenting a "tiny amount" with intranasal cocaine in the distant past, was stunned by the diagnosis. His PCP told him that he had HCV genotype 1b, and at the time of diagnosis, his viral load was 8.4 million IU.

After a review of Fred's liver enzyme levels, his PCP—believing that Fred had **compensated** cirrhosis—prescribed 12 weeks of treatment with

ombitasvir/paritaprevir/ritonavir plus dasabuvir. Two weeks after beginning treatment, Fred presented to the emergency department with complaints of shortness of breath, increased abdominal girth, abdominal pain, nausea, vomiting, confusion, and itching. The emergency department physician noted hyperbilirubinemia, diagnosed Fred with ascites, and began diuretics.

A consultation with hepatology revealed that Fred had **decompensated** cirrhosis, for which Fred's HCV regimen was not recommended and which, in fact, might have facilitated rapidly progressive liver failure.

Devastated by the news of his illness and angry and frustrated over what he saw as the physician's gross negligence and malpractice, Fred considered a lawsuit against his PCP for medical malpractice. Fred met with a plaintiff's attorney, explained his story, and asked if he had a "good" case. After months of reviewing the details, the attorney decided that Fred had a very good case against the physician. He explained that Fred's complaint against the PCP would be for medical malpractice based on negligence in his care and treatment.

Case Discussion and Lessons for the Future

Recommendations for HCV testing in baby boomers were published in late 2012; however, Fred's screening (and subsequent diagnosis) occurred more than 3 years later and only after he requested it. He had symptoms consistent with extrahepatic manifestations of HCV—confusion, tiredness, lack of appetite, and joint pain—over the course of 18 months, but his PCP did not understand their significance. "The doctor never mentioned getting tested for HCV," said Fred's wife. "It was only when Fred saw a television commercial recommending that baby boomers get screened that it even occurred to us."

Meanwhile, Fred's significant and unexpected weight loss—another potential symptom of HCV—was instead seen by his PCP as a positive development. The physician also did not take into consideration that Fred had HCV risk factors, specifically blood transfusions, tattoos that may have been obtained in an unregulated setting, and intranasal cocaine use.

Even after Fred's HCV infection was diagnosed, his PCP did not evaluate his liver health before prescribing medication. Although ombitasvir/paritaprevir/ritonavir plus dasabuvir is appropriate for patients with HCV genotype 1b without cirrhosis or with compensated cirrhosis, the potential risk of severe liver complications in those with moderate-to-severe hepatic impairment makes it critical to stage patients' liver disease before initiating treatment. In fact, in 2015, the US Food and Drug Administration issued a black-box warning for ombitasvir/paritaprevir/ritonavir, stating that it can cause hepatic decompensation and liver failure in patients with advanced cirrhosis, sometimes leading to liver transplantation or death. Notably, liver injury may occur within 1 to 4 weeks of starting treatment. Ultimately, Fred's liver was further damaged as a result of his PCP's omission, which is unfortunate given the availability of effective HCV therapies that could have been used in his case.

In patients with newly diagnosed HCV, baseline studies should include liver function tests including alanine aminotransferase levels, a complete blood cell count with differential, HCV genotyping to guide treatment, a quantitative HCV RNA assay, thyroid function studies, screening for coinfection with HIV or hepatitis B virus, and screening for alcohol/drug abuse and/or depression, with referral to preventive or treatment resources as appropriate. In addition, assessing fibrosis is essential in HCV and other liver diseases.

Although the complexity of HCV treatment has decreased substantially, it is still imperative that clinicians initiating treatment are adept at fully evaluating and monitoring liver health in their patients with HCV. There are many ways to assess liver health, some of which are outside of the usual scope of practice for primary care clinicians. However, the severity of liver disease in patients with chronic HCV infection is a key factor in determining the appropriate initial treatment and monitoring, as demonstrated in Fred's case. Historically, liver biopsy has been used to assess liver damage for both grade (level of inflammation) and stage (fibrosis) using several scoring systems, including the Batts and Ludwig, METAVIR, and

International Association for the Study of the Liver scoring systems. However, the procedure has fallen out of routine use because of its invasive nature, risk of sampling errors, and low but non-negligible risk of complications. In addition, there are now noninvasive methods to assess fibrosis, including elastography and serum markers, that can perform well in the majority of patients with HCV. Still, the liver biopsy remains an important option when indirect measures show discordant results, a second cause of liver disease is suspected, or other tests are not available.

Fred's case illustrates that it is vital for any provider treating a patient with HCV to be knowledgeable about methods for choosing the appropriate regimen. One of the key priorities in initial HCV management is identifying cirrhosis if it is present. If the physician is not confident about a patient's clinical management, the patient should be referred to a specialist, such as a gastroenterologist or hepatologist who is familiar with the appropriate course of care. Patients can also be treated by a nonspecialist in collaboration with a specialist in HCV management.

Suggested Readings

1. American Association for the Study of Liver Diseases and Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. www.hcvguidelines.org. Accessed December 20, 2018.
2. Bruggmann P, Litwin AH. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. *Clin Infect Dis*. 2013;57(Suppl 2):S56-S61.
3. Chhatwal J, Wang X, Ayer T, et al. Hepatitis C disease burden in the United States in the era of oral direct-acting antivirals. *Hepatology*. 2016;64(5):1442-1450.
4. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med*. 2014;160(5):293-300.
5. Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. *N Engl J Med*. 2013;368(20):1859-1861.
6. Kattakuzhy S, Gross C, Emmanuel B, et al. Expansion of treatment for hepatitis C virus infection by task shifting to community-based nonspecialist providers: a nonrandomized clinical trial. *Ann Intern Med*. 2017;167(5):311-318.
7. Ly KN, Hughes EM, Jiles RB, Holmberg SD. Rising mortality associated with hepatitis C virus in the United States, 2003-2013. *Clin Infect Dis*. 2016;62(10):1287-1288.
8. McGowan CE, Fried MW. Barriers to hepatitis C treatment. *Liver Int*. 2012;32(Suppl 1):151-156.
9. National Academies of Sciences, Engineering, and Medicine. *Eliminating the Public Health Problem of Hepatitis B and C in the United States: Phase One Report.* Washington, DC: The National Academies Press, 2016.
10. National Academies of Sciences, Engineering, and Medicine. *Eliminating the Public Health Problem of Hepatitis B and C in the United States: Phase Two Report.* Washington, DC: The National Academies Press, 2017.
11. Norton BL, Fleming J, Bachhuber MA, et al. High HCV cure rates for people who use drugs treated with direct acting antiviral therapy at an urban primary care clinic. *Int J Drug Pol*. 2017;47:196-201.
12. Rein DB, Wittenborn JS, Weinbaum CM, Sabin M, Smith BD, Lesesne SB. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. *Dig Liver Dis.* 2011;43(1):66-72.
13. Singer AW, Reddy KR, Telep LE, et al. Direct-acting antiviral treatment for hepatitis C virus infection and risk of incident liver cancer: a retrospective cohort study. *Aliment Pharmacol Ther*. 2018;47(9):1278-1287.
14. US Food and Drug Administration. FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. October 22, 2015. www.fda.gov/Drugs/DrugSafety/ucm468634.htm. Accessed December 20, 2018.
15. World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. June 2016. www.who.int/hepatitis/strategy2016-2021/ghss-hep/en. Accessed December 20, 2018.

Developed in Collaboration

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Med-IQ

Supported by educational grants from AbbVie Inc. and Gilead Sciences, Inc.