Diagnosis and Management of Hepatitis C Infection in Primary Care Settings

Debra Guss, MS, APRN, ANP-C[1], *Jagannath Sherigar, MD*[1], *Paul Rosen, MD*[2], *and Smruti R. Mohanty, MD, MS FACP*[1]

[1]Division of Gastroenterology and Hepatobiliary Diseases , New York-Presbyterian Brooklyn Methodist Hospital, Brooklyn, USA; [2]Department of Family Medicine, Brooklyn Hospital, Brooklyn, USA.

Hepatitis C virus (HCV) infection is a significant health problem worldwide, and is the leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation in the United States. The management of HCV has changed significantly over the last 5 years, as treatments have become simpler and more efficacious. Medication efficacy is now greater than 90%, with a high barrier to resistance and few side effects. This review is a collaboration between primary care and hepatology providers to explore all aspects of HCV management: acute versus chronic HCV infection, transmission and testing, and diagnosis and treatment. Specific medications for the treatment of HCV infection are considered, and patient and medication factors including genotype, liver disease status, and comorbidities affecting medication choice are discussed. This is a new era for the management of HCV infection, and interested primary care physicians, family doctors, and general internists can be at the forefront of diagnosis, management, and treatment of HCV.

KEY WORDS: hepatitis C; primary care management; direct-acting antivirals (DAA).

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Hepatitis C virus (HCV) infection is a significant worldwide health problem, representing an economic burden of over $6.5 billion in the United States alone,[1] and a leading cause of cirrhosis, hepatocellular carcinoma (HCC), and liver transplantation. While the prevalence of HCV infection peaked in 1994, the Centers for Disease Control and Prevention (CDC) estimates that there are currently 2.7–3.9 million persons in the United States with chronic HCV infection.[2] A disturbing trend of increased infections was observed from 2006 to 2012 among those less than 30 years of age, mostly due to increased injection drug use.[3] A significant number of these patients with HCV are seen in the primary care setting, but have not been adequately tested, and therefore not diagnosed. A larger number of patients have been identified as having HCV and were referred to a gastroenterologist or hepatologist but lost to follow-up, had treatment deferred at the time of referral, or failed prior treatments and have not re-engaged in care. With the development of simpler and more efficacious drug regimens, a greater opportunity exists to successfully manage chronically infected HCV patients at the primary care level and to cure patients of HCV infection. The door has opened for primary care physicians, family doctors, and general internists to diagnose, treat, and cure HCV.

Treatment of HCV infection has changed dramatically since 1991 when the U.S. Food and Drug Administration (FDA) approved the first treatment for HCV infection. The standard of care at the time, interferon-alpha (subsequently pegylated interferon) and ribavirin, had poor cure rates of less than 50%, with treatment requiring self-injection and risk of several severe adverse reactions[4]. The first oral medications, boceprevir and telaprevir (NS3/4a protease inhibitors), were approved in 2011 and were the first direct-acting antivirals (DAAs) to target HCV viral replication and clearance of infection.[5] These NS3/4a protease inhibitors demonstrated 70–80% efficacy in curing HCV infections.[6,7] However, while the duration, efficacy, and side effects of these early oral medications were better than previous regimens, they still required the concomitant use of pegylated interferon injections and had significant side effects. Treatments continued to be improved and simplified, and in 2013, the first all-oral regimen sofosbuvir plus ribavirin was approved by the FDA.[5] This combination of medications changed the face of HCV treatment, with easy dosing, few side effects, and high efficacy. More recently, DAAs with greater potency have been introduced, and HCV treatments continue to evolve. The new DAAs have efficacy rates greater than 90%, a higher barrier to resistance, and fewer side effects.[8,9] A new era in HCV treatment has arrived, and for treatment-naïve patients without severe liver damage or significant comorbidities, treatment of HCV has been dramatically simplified, thus enabling

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primary care providers (PCPs) to diagnose, treat, and cure HCV without referral to specialists.

ACUTE HCV INFECTION

A complete understanding of the natural history of HCV infection is difficult, as acute HCV infection is not always recognized. Indeed, it is asymptomatic in most patients, though many present with vague flu-like symptoms. Acute hepatitis can occur 2–12 weeks after exposure (mean 7 weeks) and can last 2–12 weeks, with a range of symptoms, from complete absence of symptoms, to fatigue, myalgia, low-grade fever, dark urine, clay-colored stools, or jaundice. Elevation of serum alanine aminotransferase (ALT) levels more than 10 times the upper limit of normal (ULN) is unusual.

It is not always easy to determine whether a patient has an acute or chronic infection. Support for the diagnosis of acute infection includes a positive HCV RNA with negative antibody test (window period), or a positive HCV antibody test after prior negative antibody tests.[10] For patients with no known exposure, HCV RNA should be monitored every 4–6 weeks for 6–12 months to determine spontaneous clearance versus persistence of HCV infection.[11] The presence of acute infection warrants expedited linkage to care with a specialist engaged in the management of hepatitis patients, and patients should be counseled extensively in how to prevent transmission to others. Any sign of acute liver failure, such as hepatic encephalopathy or elevation in the international normalized ratio (INR) greater than 1.5, should prompt referral to a liver transplant center.[11]

Spontaneous clearance of HCV infection occurs in some patients, generally within 6 months of infection, but it is unclear which patients will experience spontaneous clearance of acute HCV infection. A systemic review of 675 patients predicted a 25% rate of spontaneous viral clearance after infection,[12] though other sources cite a rate of 20–50%.[13] Thus, deferral of treatment for 6 months is recommended to see whether spontaneous clearance will occur. Treatment regimens for acute HCV infection are the same as for chronic infection.[11]

Treatment is indicated in patients who maintain HCV RNA for more than 6 months after initial infection. Those patients with spontaneous clearance, indicated by an undetectable HCV RNA, do not need HCV treatment. However, such patients should be counseled on the risk of reinfection, as HCV antibody positivity does not protect against future infection.[11]

CHRONIC INFECTION

Chronic HCV infection is characterized by a chronic inflammatory state, with liver injury that leads to the development of cirrhosis in 10–20% of patients over 20–30 years of infection.[14] The risk for progression to cirrhosis in patients with chronic HCV is multifactorial, including alcohol consumption and coinfection with hepatitis B virus (HBV) or HIV. Once a patient has cirrhosis, there is a 1–5% annual risk of HCC, and a 5% risk per year of decompensation, including ascites, variceal hemorrhage, or hepatic encephalopathy.[15]

TRANSMISSION AND TESTING

Transmission of HCV occurs primarily through percutaneous means, including blood transfusions (before screening of the blood supply in 1992), intravenous drug use with needle sharing, needle-stick injuries, mother-to-child exposure to infected blood, or less frequently through unprotected sex with blood-to-blood contact.[2]

Testing for HCV infection is based on previous or current exposure to risk factors, along with cohort testing. The CDC recommends one-time HCV testing for persons in the 1945–1965 birth cohort, without prior ascertainment of risk. This population has a sixfold higher prevalence of HCV than adults of other age groups, representing 81% of patients with chronic HCV.[16] Other persons should be screened for HCV infection based on the presence of risk factors for HCV exposure. Patients with prior or current injection or intranasal drug use should be tested. If exposure was in the past, one-time testing should be performed. Persons who continue to inject drugs should receive annual blood testing for HCV infection. Others considered to have prior risk exposure are patients who have been on long-term hemodialysis; those who had a blood transfusion prior to 1992, when testing of the blood supply for HCV began; health care, emergency medical, and public safety workers; children born to HCV-infected women; persons who were ever incarcerated; and patients with a history of parenteral injections.[11]

There is also evidence that these screening recommendations should be broadened to include more of the general population, as HCV is now believed to be more ubiquitous than originally thought. Studies have reported that universal testing for HCV would be cost-efficient and would reduce liver-related morbidity and mortality.[17] Although guidelines do not yet reflect this thinking, there is likely to be further discussion of this broadening of screening guidelines.

ACCURATE DIAGNOSIS OF HCV

Diagnostic evaluation for HCV begins with a serum antibody test. A non-reactive result means that there has been no exposure to HCV, but a reactive antibody cannot distinguish between current and past infection. Approximately 15–25% of persons who are exposed to HCV spontaneously clear the virus from their bodies without treatment and do not develop chronic infection[2]; these patients will have a positive HCV antibody test although they do not have an active infection. Patients who were previously treated and cured will also show

a positive antibody test. In those patients with a reactive or indeterminate/equivocal antibody test, a qualitative or quantitative HCV RNA test should be ordered, which is specific for active infection. If HCV RNA is detected, diagnosis of HCV infection is confirmed. Failure to detect HCV RNA indicates a past HCV infection that was subsequently cleared or a false-positive result. Patients with a reactive antibody test and an HCV RNA viral load number greater than the level of detection have an active HCV infection and are eligible for treatment[11] (Fig. 1).

TREATMENT CONSIDERATIONS

HCV genotype, prior HCV treatment experience, comorbidities, and degree of liver fibrosis will influence treatment decisions and follow-up care. The goal of treatment for HCV is clearance of infection, thus reducing the progression of liver disease to cirrhosis and its related complications such as end-stage liver disease and HCC, and a reduction in liver-related morbidity and mortality and all-cause mortality. Treatment is recommended for all patients with HCV except those with short life expectancy (less than 12 months).[11]

Genotype and HCV Treatment Regimens

There are six common genotypes of HCV, which vary in geographical distribution, progression of liver disease, and treatment response to medications. Approximately 75% of persons in the United States with HCV have genotype 1 (subtypes 1a or 1b), and 20–25% have genotype 2 or 3, with small numbers of patients infected with genotypes 4, 5, or 6. Genotype 3 is more frequently associated with intravenous drug use and with increased rates of steatosis, faster progression of the disease to cirrhosis, and increased rates of HCC. It is also associated with lower rates of response to DAAs, though this difference may be overcome with most newer regimens.[18,19]

Patients with all genotypes can be treated for 8–16 weeks with a daily, all-oral medication regimen of 1–3 pills. Treatment duration is determined by many factors, including HCV genotype, prior treatment with HCV medications, and the presence of cirrhosis. There are currently ten FDA-approved DAA treatment regimens. Medication regimens comprise DAAs used in combination to inhibit different steps in the HCV life cycle at the NS3/4A, NS5A, and NS5B receptors. Genotype has historically played a major role in determining appropriate medication regimens for individual patients. Currently, however, three

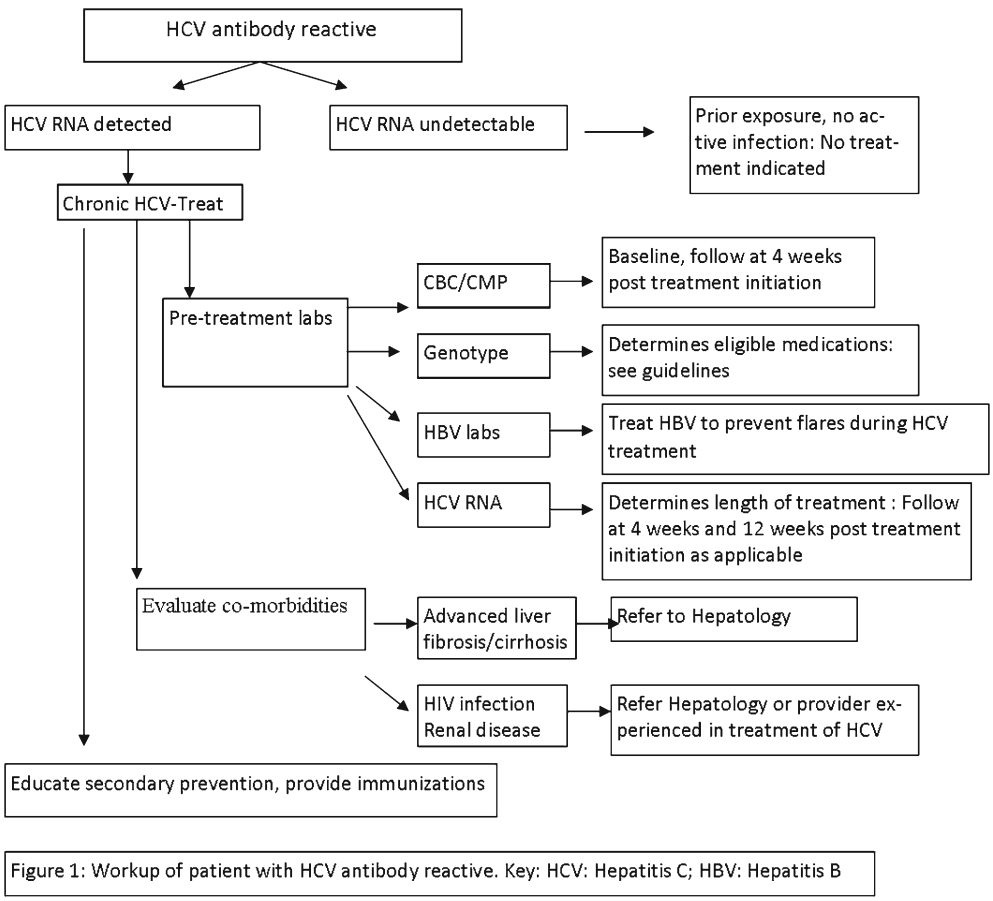

Figure 1 Workup of patient with HCV antibody reactive result. HCV, hepatitis C; HBV, hepatitis B.

regimens can be used across all genotypes, including two drug regimens just approved in July and August 2017 (Table 1). The main adverse effects of DAA medications are fatigue, GI side effects, and headache, with some variation among regimens. See Table 1 for a complete, updated list of FDA-approved medications and dosing considerations for treatment-naïve patients with and without cirrhosis.[20–27]

The newest DAA, glecaprevir and pibrentasvir, is the first 8-week treatment approved by the FDA for all genotypes in the treatment-naïve patients without cirrhosis.[26,27] Alternatively, ledipasvir/sofosbuvir can be used for 8 weeks in patients with genotype 1 with low levels of viremia (less than 6 million copies) and no cirrhosis.[21] Most other FDA treatment regimens are used for 12 weeks in treatment-naïve patients without cirrhosis (Table 1). Treatment-naïve patients with genotype 1a and NS5a mutations will require 16 weeks of treatment with elbasvir/grazoprevir, though this mutation is rare.[11] Therefore, NS5a testing should be performed at baseline in genotype 1a patient if the provider intends to treat with elbasvir/grazoprevir therapy.

Treatment-experienced patients and patients with cirrhosis will require 12–24 weeks of treatment. Two new DAAs have specific indications for treatment-experienced patients who have failed prior DAA regimens. Sofosbuvir/velpatasvir/voxilaprevir was approved in July 2017, and is indicated for 12 weeks in all genotypes for patients who have been previously treated.[28] Glecaprevir/pibrentasvir has been approved for patients with genotype 1 who were treated with either an NS5A inhibitor or an NS3/4A protease inhibitor (but not both) for 12 weeks, patients with genotype 1, 2, 4, 5, or 6 previously treated with other non-NS5A or NS3/4A medications for 8 weeks, and genotype 3 treatment-experienced patients for 16 weeks.

Liver Disease Status

Evaluation of the degree of liver fibrosis is essential in this patient population. Many patients with cirrhosis are not diagnosed until they are late in the disease process, which leads to worse outcomes, including complications of portal hypertension (ascites, variceal hemorrhage, hepatic encephalopathy, and HCC).[29] Baseline blood work and ultrasound of the abdomen should be performed, along with non-invasive tests for liver fibrosis. Biomarkers for evaluating liver fibrosis such as FibroSure or FibroTest are readily available and can be used to estimate the extent of liver fibrosis. Other non-invasive tests for fibrosis, including transient elastography (commonly

Table 1 Hepatitis C Medications

Generic	Brand	Genotype(s)	Drug class	Considerations
Sofosbuvir/velpatasvir	Epclusa	1–6	Sofosbuvir: NS5B polymerase inhibitor Velpatasvir: NS5A inhibitor	Cannot be used in renal disease
Elbasvir/grazoprevir	Zepatier	1, 4	Elbasvir: NS5A inhibitor Grazoprevir: NS3/4A protease inhibitor	Can be used with renal disease Not to be used in decompensated (Child B/C) cirrhosis
Daclatasvir	Daklinza	1, 3	Daclatasvir: NS5A inhibitor Used with sofosbuvir: NS5B polymerase inhibitor	Efficacy reduced in cirrhosis Different dosage pills available for concomitant use of some drugs, including HIV medications
Glecaprevir/pibrentasvir	Mavyret	1–6	Glecaprevir: NS3/4A protease inhibitor Pibrentasvir: NS5A inhibitor	Not recommended in patients with Child B, contraindicated in Child C Can be used in renal patients DAA treatment failures with NS5A or NS3/4A failures
Ombitasvir, paritaprevir, ritonavir	Technivie	4	Ombitasvir: NS5A inhibitor Paritaprevir: NS3/4A protease inhibitor Ritonavir: CYP3A inhibitor	Contraindicated in patients with decompensated (Child B/C) cirrhosis With ribavirin
Ombitasvir, paritaprevir, ritonavir, dasabuvir	Viekira Pak (XR)	1	Ombitasvir: NS5A inhibitor Paritaprevir: NS3/4A protease inhibitor Ritonavir: CYP3A inhibitor Dasabuvir: NS5B polymerase inhibitor	Contraindicated in patients with decompensated (Child B/C) cirrhosis With ribavirin in 1a patients
Ledipasvir/sofosbuvir	Harvoni	1, 4,5, 6	Sofosbuvir: NS5B polymerase inhibitor Ledipasvir: NS5A inhibitor	Cannot be used in renal disease
Simeprevir	Olysio	1	Simeprevir: NS3/4A protease inhibitor	Used in combination with sofosbuvir Contraindicated in patients with decompensated (Child B/C) cirrhosis
Sofosbuvir	Sovaldi	1–6	Sofosbuvir: NS5B polymerase inhibitor	Used in combination with other medications
Sofosbuvir/velpatasvir/voxilaprevir	Vosevi	1–6 Prior treatment experience	Sofosbuvir: NS5B polymerase inhibitor Velpatasvir: NS5A inhibitor Voxilaprevir: NS3/4A protease inhibitor	Genotypes 1–6 previously treated with NS5A Genotypes 1, 3 previously treated with sofosbuvir without NS5A

known as FibroScan), acoustic radiation force impulse (ARFI) imaging, and magnetic resonance elastography (MRE), can also be used with good diagnostic accuracy.[30] These methods should be combined for use in conjunction with other clinical findings to increase the validity of results.[31] Any patient with advanced liver fibrosis or cirrhosis should be referred to a specialist with expertise in liver disease management. Liver biopsy is no longer indicated as a routine test unless there is a concern for other concomitant liver diseases or clinical ambiguity regarding cirrhosis of the liver despite other non-invasive tests.

In patients who are determined to have stage 3 liver fibrosis (pre-cirrhotic state) or cirrhosis, ultrasound of the abdomen is recommended every 6 months to screen for HCC, even post-HCV treatment.[32–34] However, it is known that these recommendations are not routinely followed, and every-6-month ultrasound surveillance rates are as low as 1.7–17.4%.[35] Patients diagnosed with cirrhosis should also be referred to a gastroenterologist to screen for esophageal varices, as at least two-thirds of patients with cirrhosis will develop varices in their lifetime. Bleeding from varices develops in 30–40% of these patients, with a high rate of mortality associated with first esophageal variceal hemorrhage (20–35%).[36]

The treatment of HCV differs among patients with liver cirrhosis. The NS3/4A protease inhibitors are contraindicated in patients with decompensated cirrhosis (Child B or C). Patients with cirrhosis require a longer course of treatment, and the addition of ribavirin in some regimens. It is recommended that these patients be referred to a specialist for treatment and management of cirrhosis.

Comorbidities. Comorbidities such as renal impairment, advanced liver disease including cirrhosis, HIV disease, and pregnancy[37] add a level of treatment complexity, and collaboration with a hepatologist or infectious disease specialist is recommended unless the health care provider has extensive experience and comfort in treating such patients.

Coinfection with HIV and HCV is common, as the two viruses share a common route of infection. Coinfection is found in 10–30% of all patients with HIV, and up to 90% of patients with HIV who inject drugs.[38] HIV is also known to accelerate liver fibrosis, so appropriate treatment of patients with HIV coinfection is critical.[11] The major issue in the treatment of such patients, however, is the risk of drug–drug interactions.[39] Adjustments in HIV medications are often needed, so close collaboration with infectious disease providers is recommended.

Treatment of patients with HCV and renal disease also requires specialized care. The prevalence of HCV in patients on hemodialysis is high, ranging from 7.8 to 44%,[40] and concomitant HCV and renal disease is associated with worse outcomes than either disease process alone.[41] Three medications are currently FDA-approved for the treatment of patients with HCV infection and renal disease. Glecaprevir and pibrentasvir attained a sustained viral response (SVR) of 98% across genotypes 1–6, including patients with severe chronic kidney disease (CKD) and on hemodialysis, regardless of previous treatment status or presence of compensated cirrhosis. Glecaprevir/pibrentasvir is the first medication approved for genotypes 2, 3, 5, and 6 in patients with renal disease.[42] For patients with genotypes 1 and 4, two older DAAs are also approved for the treatment of HCV in those with a glomerular filtration rate (GFR) of < 30 mL/min. The C-SURFER trial demonstrated a 94% SVR rate with grazoprevir and elbasvir, with few side effects.[40] The RUBY-1 trial reported an SVR rate of 90% in 20 patients treated with the combination of ombitasvir, paritaprevir, ritonavir, and dasabuvir, with the addition of ribavirin in patients with genotype 1a.[43]

Treatment is indicated for elderly patients with HCV except in the case of short life expectancy. No significant increase in the side effects of HCV medications is seen in the elderly, and no dose adjustment is needed,[44] though there is an increased number of drug–drug interactions.[45] Women of childbearing age should be evaluated for pregnancy, as HCV medications have not been assessed for safety in pregnant women, and ribavirin is teratogenic (category X). New DAAs are pregnancy category B or C, but there are no medications for treatment of HCV that are currently recommended in pregnancy, and so women undergoing HCV treatment should avoid pregnancy.[11]

Prior Exposure to Hepatitis B. All DAAs for the treatment of HCV now have a black box warning to check the HBV infection status in patients who are to be treated for HCV. This is due to the risk of reactivation of HBV when patients with HCV infection are undergoing or have just completed treatment. This reactivation of HBV has led to liver failure or death in a small number of patients during treatment.[46,47] Patients who are not immune to hepatitis A and B should be immunized and should receive other maintenance immunizations as well, including yearly influenza vaccine, and pneumonia, tetanus, and zoster as applicable. Hepatitis A and B vaccinations can be given as a combined vaccine (Twinrix) at 0, 1, and 6 months or in single antigen injections. Any person with risk factors for hepatitis A or B, or anyone with chronic liver disease including HCV, cirrhosis, fatty liver, or other liver disease, should be given hepatitis A and B immunizations.[48]

Other Considerations. Evaluation of other medical history, medication and herbal use, and illicit drug and alcohol use should be completed per the standard of care. Interactions with antiarrhythmics can occur, particularly amiodarone, which is linked to severe cardiac issues and death when taken with sofosbuvir-containing regimens.[49] Other medications including anticonvulsants, HIV drugs, statins, and proton pump inhibitors (which may require dose adjustments) should be explored. There are no contraindications to the use of statins

with DAAs, though some medications require administration of lower-dose statins.

Some insurance carriers require documented evidence of abstinence from illicit drug use in order to approve medications, though treatment of patients with recent or active drug use is no longer seen as an absolute contraindication to treatment. However, it is recommended that patients who are active drug users be treated in a multidisciplinary care setting to reduce the risk of HCV reinfection.[11]

SUSTAINED VIROLOGIC RESPONSE

Quantitative HCV (HCV RNA) viral load testing is recommended 4 weeks into therapy and at 12, 24, and 48 weeks following completion of therapy.[11] SVR, also known as a virologic cure, is defined as an undetectable viral load at 12 weeks after the completion of therapy. SVR has traditionally been tested at 24 weeks after completion of treatment, and is commonly known as SVR_{24}. However, a 2015 study by Yoshida et al. showed that among 779 patients who achieved SVR at 12 weeks, 777 achieved SVR_{24}, demonstrating 99.7% concordance between these two results.[50] Predictably, many providers now check both SVR_{12} and SVR_{24} to assess for virologic cure. Recent recommendations are to confirm long-term SVR at 48 weeks, given a late relapse rate of ± 0.5%.[51] No further confirmation of SVR post-48 weeks is indicated.

ROLE OF THE PRIMARY CARE PROVIDER (PCP) IN TREATING HCV

In general, it is our belief that PCPs interested in the treatment of HCV can provide safe and effective treatment. This ability was demonstrated by PCPs and nurse practitioners (NPs) in the ASCEND study, where the outcomes for PCPs and NPs trained in the care of HCV-infected patients were similar to those for specialists in HCV treatment.[52] The use of specialty pharmacies can assist providers with medication authorizations and approval—the most difficult part of the treatment of HCV. Evaluation of patients for HCV treatment also provides PCPs an opportunity for contact with patients that may also have cirrhosis, enabling the evaluation and referral of these patients to specialist expertise in liver disease, including liver transplant evaluation. Furthermore, any PCPs who are comfortable managing complex HCV patients such as those with cirrhosis, HIV coinfection, HCV with CKD/end-stage renal disease (ESRD), or HCV with HCC should be able to treat chronic HCV in these patients. The HCV Guidance web aid (https://www.hcvguidelines.org/) is an important tool for guiding the management and treatment of hepatitis C patients, as it is a living document which will continue to provide updated information for clinicians. The time has arrived for PCPs to diagnose, treat, and cure patients with HCV, and interested PCPs should be able to add HCV as a disease that they can successfully manage in a primary care setting.

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Corresponding Author: *Debra Guss, MS, APRN, ANP-C; Division of Gastroenterology and Hepatobiliary Diseases New York-Presbyterian Brooklyn Methodist Hospital, Brooklyn, USA (e-mail: Dag9132@nyp.org).*

Compliance with Ethical Standards:

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