

On the Front Lines: Hepatitis C Infection in Primary Care

George P. Kent, MD; Christopher McGowan, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Identify patients who should be screened for HCV infection
- Identify patients with HCV infection who may be considered for referral
- Initiate and modify pharmacologic therapy based on stage of infection and to meet individual needs
- Implement a follow-up care plan to improve long-term treatment and adherence

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of hepatitis C infection.

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Gregory Scott, PharmD, RPh, editorial support, discloses he has no real or apparent conflicts of interest to report.

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Release Date: 1 August 2018

Expiration Date: 31 July 2019

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SUPPORTER

This article is supported by an educational grant from Gilead Sciences, Inc.

George P. Kent, MD, Associate Director, Stanford Health Care-O'Connor Hospital Family Medicine Residency Program, Adjunct Clinical Professor, Division of Primary Care and Population Health, Department of Medicine, Stanford University School of Medicine, Stanford, California

Christopher McGowan, MD, Cary Gastroenterology Associates, Wake-Med Cary Hospital, Cary, North Carolina

DISCLOSURES

Dr. Kent discloses that he has no real or apparent conflicts of interest to report.

Dr. McGowan discloses that he has no real or apparent conflicts of interest to report.

ACKNOWLEDGEMENT

Editorial support was provided by Gregory Scott, PharmD, RPh. The authors were responsible for all content and editorial decisions.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from Gilead Sciences, Inc.

INTRODUCTION

Hepatitis C virus (HCV) infection is the most common blood-borne infection in the United States, with an estimated incidence of 33,900 acute cases in 2015—nearly a 100% increase from 2011 and a 250% increase from 2010.^{1,2} The largest increase has been among persons 20 to 39 years of age, with three quarters of cases occurring in persons who use illicit injection drugs.^{1,3} Other groups at increasingly high risk of acute HCV infection are men who have sex with men and newborns of infected mothers, as well as reproductive-age and pregnant women (the latter for unclear reasons).⁴⁻⁶

Approximately 75% to 85% of newly infected persons develop chronic HCV infection.^{7,8} An estimated 3.5 million persons are chronically infected in the United States; three quarters were born between 1945 and 1965.^{9,10} Among people with chronic HCV infection, approximately 20% develop cirrhosis and 10% develop end-stage liver disease or liver cancer; 3% to 4% will require a liver transplant or will die of an HCV-related cause.^{10,11} In 2014, 19,659 persons died of HCV infection, a 20% increase from 2010.¹⁰

There is, however, a real opportunity to change the story line for HCV, due to the advent of direct-acting antivirals (DAAs). With DAAs, safety and tolerability are much improved over previous treatments. In addition, nearly all persons with chronic HCV infection should be treated, because >90% of patients treated with DAA therapy in clinical trials are cured.^{10,12,13} Of course, this requires that infected patients be identified, appropriate treatment with DAAs be initiated, and treatment adherence be maintained. Regrettably, nearly 50% of people who are infected with HCV are unaware that they are infected.^{2,14,15} Yet screening is cost-effective, particularly in populations with a high prevalence of illicit injection drug use.^{16,17} However, evidence indicates that only 9% to 24% of persons diagnosed with HCV infection are treated, due to issues such as medication cost, need for an office visit for drug administration (with injectables), and patients' concern about adverse events.^{10,18-20} Treatment with DAAs has been shown to be cost-effective in the vast majority of treatment-naïve and treatment-experienced patients across all HCV genotypes.²¹⁻²⁷

In addition to the efficacy of DAAs, their safety and oral administration mean that the majority of patients with HCV infection can be successfully managed in the primary care setting, if desired, with limited referral to subspecialists.²⁸ This requires the primary care provider (PCP) to acquire the knowledge and skills for providing comprehensive care. A notable educational resource for PCPs is Project ECHO (<https://echo.unm.edu>), a learning community that links PCPs with expert specialist teams at an academic hub, who mentor and provide feedback to the PCP. Additionally, the Centers for Disease Control and Prevention has supported development of a comprehensive resource (www.hepatitisc.uw.edu). Similarly, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America maintain an online, continually updated resource for HCV management (www.hcvguidelines.org).¹³

SCREENING AND FURTHER EVALUATION

Most people with chronic HCV infection are asymptomatic or have nonspecific symptoms, such as chronic fatigue and depression. Many eventually develop chronic liver disease, which can range from mild to severe, including cirrhosis

and liver cancer. Chronic liver disease in HCV-infected people is usually insidious, progressing slowly without signs or symptoms for several decades. In fact, HCV infection is often not recognized until asymptomatic people are identified as HCV-positive when screened for blood donation or when elevated liver enzyme levels are detected during routine examination.²⁸

Screening tests

One-time HCV testing is recommended in select populations, based on demographics, possible exposures, high-risk behaviors, and medical conditions (**TABLE 1**).¹³ For persons who illicitly inject drugs and for human immunodeficiency virus (HIV)-infected men who have unprotected sex with men, annual or more frequent testing is recommended.¹³

Screening for HCV infection should begin by testing for HCV antibody, using a laboratory-based or point-of-care assay approved by the US Food and Drug Administration (**FIGURE**).²⁹ HCV can be detected 4 to 10 weeks after infection, using an enzyme immunoassay, and 2 to 3 weeks after infection using HCV ribonucleic acid (RNA) testing.³⁰⁻³² A positive test for HCV antibody indicates (1) current (active) HCV infection (acute or chronic); (2) past infection that has resolved; or (3) a false-positive result. A false-positive result is more likely in a population with low prevalence of HCV infection; one nationally representative study with an HCV infection prevalence of 1% showed a false positive rate of at least 22%.³³

Consequently, if the HCV antibody test is positive, an HCV RNA test is necessary to detect viremia and confirm active HCV infection. An HCV RNA test is also recommended in persons with a negative HCV antibody test who are either immunocompromised or who might have been exposed to HCV within the past 6 months. If HCV RNA is detected, active HCV infection is confirmed. If HCV RNA is not detected, past or resolved HCV infection or a false-positive result is demonstrated.²⁹

Further evaluation

Assessing the extent of liver damage due to chronic HCV infection is critically important in guiding the treatment plan. Liver fibrosis is most commonly described using the METAVIR score, which ranges from F0 (no fibrosis) to F4 (cirrhosis). The METAVIR score is based on standard histopathological features identified on biopsy; however, noninvasive tests can be used to approximate the METAVIR score. Liver biopsy is limited by cost, risk of complications, and sampling error, and is rarely necessary. Noninvasive methods to assess the extent of liver damage include a liver-directed physical examination, although findings are generally unremarkable. Routine blood tests—alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, bilirubin, inter-

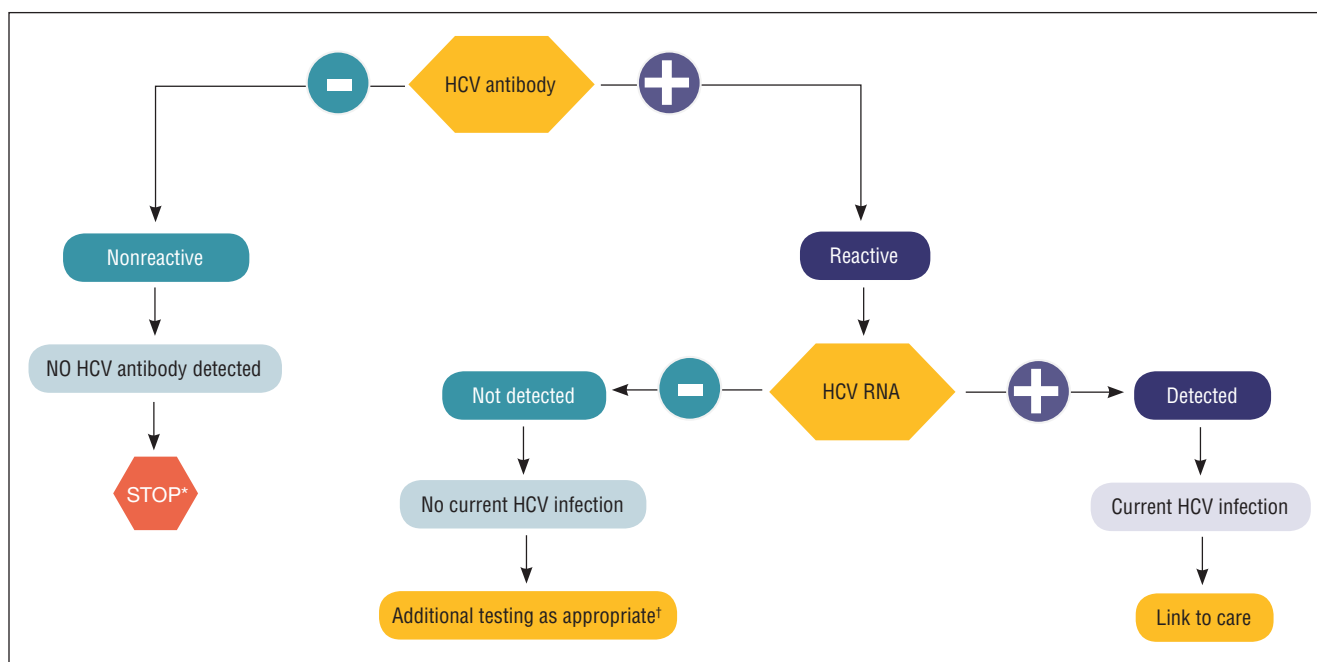
TABLE 1 People for whom one-time hepatitis C testing is recommended¹³

Birth year	Born from 1945 through 1965, regardless of country of birth, without prior ascertainment of risk
Risk behaviors	Illicit injection drug use (current or ever, including persons who injected only once) Illicit intranasal drug use
Risk exposures	Long-term hemodialysis (ever) Percutaneous or parenteral exposure in an unregulated setting Needle-stick, sharps, or mucosal exposure to HCV-infected blood (in health care, emergency medical, and public safety workers) Children born to HCV-infected women Prior recipient of transfusion or an organ transplant, including persons who: <ul style="list-style-type: none"> • were notified that they received blood from a donor who later tested positive for HCV • received a transfusion of blood or blood components or who underwent organ transplantation, before July 1992 • received clotting factor concentrate produced before 1987 Incarcerated (ever)
Other conditions and circumstances	HIV infection Sexually active, about to start pre-exposure prophylaxis for HIV Unexplained chronic liver disease and/or chronic hepatitis, including an elevated ALT level Solid-organ donor (deceased or living)

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

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FIGURE Recommended testing sequence for identifying current HCV infection²⁹



Abbreviations: HCV, hepatitis C virus; RNA, ribonucleic acid.

*For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

†To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

national normalized ratio (INR), and a complete blood count (CBC), including platelet count—may be useful.¹³

It is important to note that it is common for liver enzyme levels to go up and down in HCV infection, with periodic return to a normal or near-normal level. Direct biomarker profiles, such as Hepatitis C Virus (HCV) FibroSURE and the FibroTest-ActiTest Panel, are useful noninvasive tests to assess the degree of liver fibrosis.^{34,35} Ultrasonography or computed tomography can be used to assess liver surface nodularity and spleen size, identify occult portal hypertension, and screen for hepatocellular carcinoma (HCC). Liver elastography, widely used by gastroenterologists, is useful to determine the extent of liver stiffness, as well as to distinguish patients with a high versus low likelihood of cirrhosis.³⁶ Vibration-controlled transient elastography has superior sensitivity and specificity to the AST-to-platelet ratio index (APRI) or the fibrosis-4 (FIB-4) index (**TABLE 2**).³⁷ Because no single test alone has high accuracy for staging the degree of fibrosis, the most efficient approach is to combine direct biomarkers with vibration-controlled transient elastography.¹³

Biopsy can be considered for any patient who has discordant results between the 2 modalities (direct biomarkers and vibration-controlled transient elastography) that would affect clinical decision making (eg, one shows cirrhosis, the other does not). With this approach, the need for liver biopsy is markedly reduced. Alternatively, if direct biomarkers or vibration-controlled transient elastography are not available, APRI or the FIB-4 index can prove helpful.³⁸⁻⁴⁰

CONSIDERATIONS FOR REFERRAL

Primary care providers can increasingly provide much of the management needed by patients with HCV infection. For PCPs with limited experience, it is recommended to start by managing treatment-naïve patients without cirrhosis or with well-compensated cirrhosis, but referring other patients to a liver or infectious disease specialist.

EVIDENCE-BASED TREATMENT

Goal

The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related adverse health consequences, including end-stage liver disease and hepatocellular carcinoma.^{10,13} A key objective is to achieve virologic cure—that is, sustained virologic response (SVR),¹³ defined as continued absence of detectable (≤ 25 IU/mL) HCV RNA for ≥ 12 weeks after completion of therapy (HCV antibodies remain). All patients with chronic HCV infection should be treated, except those whose life expectancy would be < 12 months despite treatment.

Benefits

Benefits of virologic cure include decreased liver inflammation (improved ALT and AST levels) and slowed progression of liver fibrosis and necrosis.⁴¹ Some patients experience resolution of cirrhosis; other manifestations of advanced liver disease, such as portal hypertension and splenomegaly, often improve.⁴¹ The risk of liver cancer may be reduced by 70% and liver-related mortality and transplantation, by 90%.⁴²⁻⁴⁴ Extrahepatic manifestations, such as cryoglobulinemic vasculitis and lymphoproliferative disorders, often improve as well.^{45,46} For these reasons, all-cause mortality is dramatically reduced.^{17,43,47,48} Last, patients typically experience considerable improvement in quality of life.^{49,50}

Prior to initiating antiviral therapy

Quantitative HCV RNA testing is recommended prior to initiation of antiviral therapy to determine the baseline viral load, because this may impact treatment duration with certain DAA regimens. Testing for HCV genotype and the absence or presence of cirrhosis helps guide selection of the most appropriate antiviral regimen. Other laboratory tests previously identified (see “Further Evaluation,” above) that have not been performed within 12 weeks prior to initiating antiviral therapy should be done.¹³ Additional pretreatment assessments include hepatitis A or B virus coinfection or past infection, as well as resistance-associated substitutions. Last, the patient’s medication regimen, including nonprescription and complementary or alternative medicines, should be evaluated for potential drug interactions because certain DAAs can interact with many commonly prescribed medications, including statins, proton-pump inhibitors, benzodiazepines, and anticonvulsants.¹³

Direct-acting antivirals available in the United States

Traditional antivirals—peginterferon alfa-2a, peginterferon alfa-2b, and ribavirin—have been used to treat HCV infection for more than a decade, but their role in 2018 is limited due to the availability of DAAs. There are 3 subtypes of DAAs:

- NS3/4A serine protease (glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir)
- Nonstructural protein 5A (NS5A) (daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir)
- Nonstructural protein 5B (NS5B) polymerase (dasabuvir, sofosbuvir).

Initial DAA therapy in treatment-naïve people with HCV

The selection of initial antiviral therapy in a patient with treatment-naïve chronic HCV must be individualized based on genotype, the presence or absence of compensated cir-

TABLE 2 Calculated measures of liver fibrosis³⁷

Test	Calculation	Interpretation
APRI	$[(AST/AST\ ULN)/platelets^a] \times 100$	>0.7 ($\geq F2^c$): significant fibrosis likely >2 (F4 ^c): probable cirrhosis
FIB-4	$(Age^b)(AST)/(Platelets^a)(\sqrt{ALT})$	<1.45 (<F2 ^c): excludes fibrosis >3.25: cirrhosis highly likely

Abbreviations: $\sqrt{}$, square root; ALT, alanine aminotransferase [U/L]; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase [U/L]; AST ULN, aspartate aminotransferase upper limit of normal; FIB-4, fibrosis-4 index.

^a $\times 10^9/L$.

^bIn years.

^cThe METAVIR fibrosis score.

rhosis, comorbidities, and concomitant medications. Certain treatment recommendations require testing for the presence or absence of NS5A resistance-associated substitutions, but there are fixed-dosage regimens available that are pan-genotypic and do not require baseline resistance testing for non-cirrhotic treatment-naïve patients. Recommended regimens for initial therapy in treatment-naïve patients with the most common genotypes of HCV infection are listed in **TABLE 3**.^{13,51} These DAA regimens are appropriate for most patients within the group based on efficacy, tolerability and toxicity profiles, and treatment duration—the latter of which may depend on patient characteristics such as race, HIV status, and viral load. Some of these regimens may not be appropriate in children, HIV/HCV coinfection, decompensated cirrhosis, Child-Turcotte-Pugh prognosis class B or C, HCV infection post-organ transplantation, and severe renal impairment, as well as post-kidney transplantation.

Monitoring for treatment response and safety is important, much of which can be done by telephone, texting, or e-mail.¹³ However, quantitative HCV RNA testing is recommended after 4 weeks of therapy to assess initial response. An undetectable HCV RNA level is observed by Week 4 in most patients who do not have cirrhosis, but may take longer in those with cirrhosis. Repeat viral load testing ≥ 12 weeks after treatment completion is essential to assess cure. Virologic relapse after 12 weeks is rare. Last, working with a specialty pharmacy that offers hepatitis services is recommended to facilitate prior authorization and medication delivery, as well as to assist with patient education, drug selection based on insurance requirements, and avoidance of drug interactions.

Counseling people with active HCV infection

A key component of treatment is preventing further liver damage. Therefore, patients with current HCV infection should be educated about interventions to reduce the progression of liver disease and to prevent HCV transmission.^{13,28} Education about preventing HCV transmission is especially important for per-

sons who illicitly inject drugs, are HIV-infected, or have multiple sex partners or a sexually transmitted infection.

Patients should be advised to abstain from alcohol, because daily consumption of >50 g of alcohol has a high likelihood of accelerating fibrosis; this equates to approximately 4.5 oz of 40% hard liquor or 3.5 servings of 12 oz of beer or 5 oz of wine.^{7,13,28} Other conditions that accelerate liver fibrosis, such as overweight or obesity, hyperlipidemia, and cardiovascular comorbidities, should be managed. Hepatotoxic drugs (such as acetaminophen, >2 g/d; amoxicillin-clavulanate; and isoniazid) and nephrotoxic drugs (such as acyclovir, nonsteroidal anti-inflammatory drugs, and rifampin) should be avoided.²⁸

Several vaccinations are particularly important for persons with HCV infection, including against hepatitis A and hepatitis B. In patients with HCV infection and cirrhosis, vaccination against pneumococcal infection is important.^{13,28}

FOLLOW-UP

Patients who do not achieve SVR retain the possibility of continued liver injury and the potential to transmit HCV. Such patients should be monitored for progressive liver disease and considered for retreatment when alternative treatments are available.¹³

All patients who achieve SVR should clearly understand that they are not immune to HCV and can become reinfected. Specific liver follow-up for patients who achieve SVR is based on the degree of underlying liver fibrosis.¹³ Patients with F0-F2 fibrosis do not need further liver monitoring or follow-up, as achievement of SVR halts progression of HCV-related liver disease. Patients with advanced fibrosis (F3 or F4) may experience improvement in fibrosis, but they are considered to be at persistent risk of developing HCC.⁵² Accordingly, these patients should have surveillance for HCC with hepatic ultrasonography every 6 months. Patients with confirmed cirrhosis (F4) require a baseline upper endoscopy to screen for varices. Last, patients at ongoing risk of HCV infec-

TABLE 3 Recommended antiviral therapy for treatment-naïve people¹³

Group	Fixed-dosage combination direct-acting antiviral regimens	
	8 weeks	12 weeks
Genotype 1a without cirrhosis	Glecaprevir 300 mg/pibrentasvir 120 mg ^a Ledipasvir 90 mg/sofosbuvir 400 mg ^b	Elbasvir 50 mg/grazoprevir 100 mg ^c Ledipasvir 90 mg/sofosbuvir 400 mg Sofosbuvir 400 mg/velpatasvir 100 mg
Genotype 1a with compensated cirrhosis		Elbasvir 50 mg/grazoprevir 100 mg ^c Glecaprevir 300 mg/pibrentasvir 120 mg ^a Ledipasvir 90 mg/sofosbuvir 400 mg Sofosbuvir 400 mg/velpatasvir 100 mg
Genotype 1b without cirrhosis	Glecaprevir 300 mg/pibrentasvir 120 mg ^a Ledipasvir 90 mg/sofosbuvir 400 mg ^b	Elbasvir 50 mg/grazoprevir 100 mg Ledipasvir 90 mg/sofosbuvir 400 mg Sofosbuvir 400 mg/velpatasvir 100 mg
Genotype 1b with compensated cirrhosis		Elbasvir 50 mg/grazoprevir 100 mg Glecaprevir 300 mg/pibrentasvir 120 mg ^a Ledipasvir 90 mg/sofosbuvir 400 mg Sofosbuvir 400 mg/velpatasvir 100 mg
Genotype 3 without cirrhosis	Glecaprevir 300 mg/pibrentasvir 120 mg ^a	Sofosbuvir 400 mg/velpatasvir 100 mg
Genotype 3 with compensated cirrhosis		Glecaprevir 300 mg/pibrentasvir 120 mg ^a Sofosbuvir 400 mg/velpatasvir 100 mg ^d

(Regularly updated treatment recommendations may be found at <https://www.hcvguidelines.org>.)

^aThis is a 3-tablet coformulation. Please refer to prescribing information.

^bNon-black, HIV-uninfected, HCV RNA <6 million IU/mL.

^cWithout baseline NS5A resistance-associated substitution (RAS) testing for elbasvir (Includes genotype 1a RASs at amino acid positions 28, 30, 31, or 93, known to confer antiviral resistance).

^dRAS testing for the Y93H resistant variant is recommended for cirrhotic patients. If present, ribavirin should be included in the regimen or sofosbuvir/velpatasvir/voxilaprevir should be considered.

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tion should have periodic reassessment for HCV reinfection with HCV RNA testing (not testing for HCV antibody, which will likely remain positive), and counseling on prevention of reinfection. Additionally, any flare in liver enzymes should prompt evaluation for reinfection.

SUMMARY

Chronic HCV infection is a common, yet often asymptomatic, infection that can be successfully managed in the primary care setting. To achieve this, screening—particularly of high-risk groups—is an essential first step in a comprehensive management plan that is linked to individualized antiviral therapy with DAAs, based on genotype, stage of disease, comorbidity, and other patient variables. ●

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