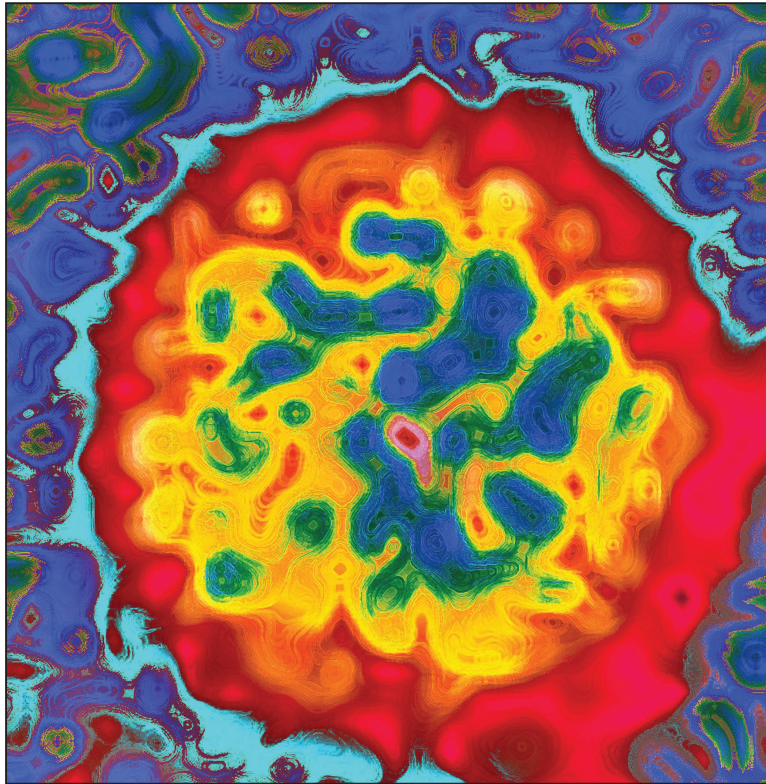


HCV Infection

Jennifer Eames, MPAS, PA-C

Cirrhosis, hepatocellular carcinoma, and liver transplantation are among the most serious potential sequelae of hepatitis C, a viral illness that affects more than 3 million US adults. Often asymptomatic until the disease converts to chronic form, HCV is diagnosed through lab studies that include an HCV antibody screen, an HCV RNA assay, and genotyping. Currently available treatments make it possible to eradicate the disease in many patients, and promising new developments are being investigated. Primary care providers play an important role in managing patients with HCV throughout testing, treatment, and follow-up.



Credit: James Cavallini/Photo Researchers, Inc

Colorized transmission electron micrograph image of the hepatitis C virus (HCV).

The hepatitis C virus (HCV) is estimated to affect 180 million people worldwide, and the CDC estimates that approximately 3.2 million persons in the United States are chronically infected with HCV.^{1,2} In recent years, reported HCV-related deaths have outnumbered those attributed to HIV infection.³ Clinicians in almost any practice area are likely to encounter patients affected by HCV.

Infection with HCV is a major risk factor for cirrhosis, a disease associated with significant morbidity and mortality; HCV-associated cirrhosis is considered the leading cause of liver transplantation.⁴

Screening for HCV is important in patients with known risk factors for the disease¹ (see Table 1^{1,2,5}). Of note, however, the CDC is in the process of expanding its recommendations to one-time screening for all Americans born between 1945 and 1965—an age-group that accounts for more than 75% of cases of HCV infection among US adults.⁶ (Clinicians interested in viewing the draft document for public comment can refer to www.regulations.gov, docket #CDC-2-12-0005.)

PATIENT PRESENTATION/ PATIENT HISTORY

Most patients with hepatitis C present without signs or symptoms of their illness. If symptoms are present, they may include fatigue, pruritus, abdominal pain/discomfort, arthralgias, or anorexia; results on routine liver function tests may be abnormal.^{1,7-9} Liver function may appear normal in patients with HCV, although 30% of patients with a normal alanine aminotransferase (ALT) level may have significant fibrosis.¹⁰ Lichen planus is commonly associated

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with HCV infection,⁹⁻¹¹ and patients with this condition should be screened for HCV.

HCV infection most commonly presents between the fourth and sixth decades of life. Many patients have had the disease for as long as 20 years by the time they present for treatment—often after abnormal laboratory findings are discovered⁷ (but see “Can Some Patients Defer Treatment?”^{7,10,12} page 18).

Patients with *acute HCV infection* usually do not appear jaundiced or exhibit other signs of acute hepatitis. Symptomatic illness occurs in only 20% to 40% of patients with acute hepatitis C.⁷ Patients who present with acute illness (15% to 25% of patients with HCV) typically have an improved prognosis and are less likely to convert to chronicity if they survive the initial symptoms (ie, malaise, weakness, anorexia, jaundice).^{2,7} In many such patients, the body appears to mount a full immune response, and patients are often virus-free within weeks.

For 75% to 85% of patients, however, it is believed that the immune system fails to overcome the virus, and *chronic infection*, with progressive damage to the liver tissue, ensues.⁷ In chronic HCV infection, the rate of progression varies, depending on the HCV genotype, the infected host's genetic factors and lifestyle (including level of alcohol consumption), the extent of liver injury, and possible coinfection (as with HIV or hepatitis B virus [HBV]).^{1,7}

Cirrhosis and Hepatocellular Carcinoma

Complications of cirrhosis include portal hypertension, ascites, hepatic encephalopathy, esophageal varices, and hepatocellular carcinoma (HCC).¹³ In patients with HCV-related cirrhosis, HCC develops at a rate of 1% to 4% per year, with a twofold to fourfold increased risk among black patients and Asian patients, respectively, compared with whites.⁷ The risk for HCC appears to be reduced in patients who undergo treatment

TABLE 1
Persons at Risk for HCV Infection^{1,2,5}

Those who have ever injected illegal drugs, even once, even in the remote past (which patients may deny)
Patients who underwent blood transfusion or organ transplantation before July 1992
Those who received clotting factor before 1987
Patients who have undergone hemodialysis
Those exposed to blood, blood products, or body fluids of HCV-infected persons (eg, those employed in health care, emergency medicine, or public safety)
Patients infected with HIV
Sexual partners of HCV-infected persons*
Children born to HCV-infected women
Persons with body piercing or tattoos obtained in prisons, homes, and other potentially nonsterile settings
Patients with unexplained abnormal ALT levels

* Risk is low in mutually monogamous relationships.

Sources: Horan and Milbrandt. *Pediatr Health*. 2009¹; Herring. *Tachdjian's Pediatric Orthopaedics*. 2008⁹; Basu et al. *Spine (Phila Pa 1976)*. 2002¹¹; Fisher et al. *South Med J*. 2000.¹²

leading to a sustained virologic response (ie, a viral load that is no longer detectable); and the risk is increased in patients with diabetes mellitus and those with HCV genotypes 1b and 3.¹⁴⁻¹⁶

HCC is difficult to treat unless detected in its early stages. It often results in death.¹³

PHYSICAL EXAMINATION

An appropriate physical exam is critical in detecting sequelae of chronic liver disease, which may reflect complications of long-term HCV infection. The patient should be evaluated for the presence of spider angiomas, palmar erythema, scleral icterus, ascites, caput medusae, and evidence of umbilical hernias—all possible signs of advanced liver disease.^{8,9}

The initial physical exam is also an appropriate time to screen and treat patients for hypertension and diabetes, and to identify disorders that may make them poor candidates for HCV treatment. These conditions include coronary heart disease, untreated cancers or thyroid disease, kidney or autoimmune diseases, and psychiatric illness.^{1,17}

Evaluation of the skin for “track marks,” tattoos or body pierc-

ings that may have been applied in prisons, homes, or other nonsterile settings, or nonhealing lesions that may indicate immune compromise or diabetes is important.^{5,8} Visual acuity testing and fundoscopic exams are critical to establish a baseline, because treatment with pegylated interferon has the potential to cause visual changes and retinopathy.¹⁸

Laboratory Work-up

Initial testing for HCV includes an HCV antibody test. This serum test is commonly performed as part of a hepatitis panel—testing for hepatitis A virus (HAV), HBV, and HCV. Testing for hepatitis D and E is not routinely recommended unless the patient routinely travels to the Mediterranean Basin, the Middle East, Central Asia, or West Africa (where hepatitis D is most prevalent¹⁹) or the patient is pregnant (because during the third trimester, hepatitis E infection carries a mortality rate of 20% and can be transmitted to the fetus²⁰).

If immunity to HAV and HBV are not shown on laboratory findings, it is critical to vaccinate the HCV-positive patient against these diseases. Coinfection with HAV and HCV can progress to a fulmi-

nant form of hepatitis and poor hepatic function; coinfection with HBV and HCV is associated with severe liver disease and an increased risk for HCC.^{21,22}

The patient with positive results on the HCV antibody screen should be tested next with a quantitative HCV RNA assay to confirm the presence of active infection (ie, viral load).¹ Detection of virus is considered indicative of active disease.

It is possible for a patient with positive HCV antibody test results to have no circulating virus detected on HCV RNA testing. Perhaps 15% to 25% of patients are able to clear HCV infection spontaneously within weeks to months after infection.⁷

Testing Considerations Before Treatment

Several assays are available to identify the patient's HCV genotype. It is essential to obtain this information before agents, dosing, and duration are determined, as the regimen will be tailored to the patient's HCV genotype.¹ There are six major known HCV genotypes (numbered 1 through 6) and at least 50 minor subtypes (eg, 1a, 2b, 3a).^{1,23}

Also to be considered before initiating HCV treatment is screening for *autoimmune hepati-*

tis.¹⁷ Appropriate tests include the anti-actin antibody, anti-smooth muscle antibody, antinuclear antibody, and anti-liver kidney microsomal antibody tests.^{24,25} Additionally, ceruloplasmin testing should be ordered along with the iron studies and ferritin levels obtained at the patient's first visit, to screen for *Wilson's disease*, a disorder of copper metabolism, and *hemochromatosis*, a disorder of iron metabolism.

The risks associated with HAV

Can Some Patients Defer Treatment?^{7,10,12}

Patients in the fifth decade of life with little to no fibrosis of the liver are unlikely to experience cirrhosis or death very soon (only about 10% to 15% of patients progress from HCV infection to cirrhosis within 20 years⁷); some may make an informed decision to defer currently available therapy.^{9,12} In one study of 280 treatment-naïve patients, 115 (41%) decided to forego treatment for one year, although none had contraindications to interferon-based therapy; 90% were infected with HCV genotype 1, and about 75% had had the infection for at least 16 years. Patients between ages 45 and 55 and black patients were most likely to defer treatment.¹²

About two-thirds of patients said they had made this decision because their illness was asymptomatic, and nearly as many were concerned about the adverse effects of treatment. About 10% said they were unable to afford therapy (although pharmaceutical companies often sponsor indigent care programs).¹²

At one year, nearly 90% of patients were sufficiently satisfied with their decision to continue to delay therapy. Seven percent requested a follow-up visit to discuss treatment, and about 2% had already begun treatment.¹²

Less than 5% of the patients in this study said they chose to delay treatment because they doubted the efficacy of current treatment options.¹²

or HBV coinfection have been described; patients with HCV and HAV, HBV, or HIV are at greater risk for disease progression to cirrhosis and/or HCC than are mono-infected patients.^{1,21,22,26} HIV testing is routinely recommended for patients with HCV, with repeat testing during treatment if the patient maintains any risk factors for HIV exposure. Patients with HCV who are found to be coinfecting with HIV must be treated urgently, but therapeutic components must be selected with considerable care: Serious interactions are possible among the effective agents, and antiretroviral drugs are associated with hepatotoxicity.^{1,27}

Before HCV treatment begins, it is essential to obtain baseline values: liver function testing (aspartate aminotransferase, ALT, alkaline phosphatase, bilirubin), coagulation testing (prothrombin time and partial thromboplastin time), and thyroid testing (thyroid-stimulating hormone, triiodothyronine, thyroxine),¹ as changes may occur as a result of

anti-HCV therapy. It is also important to establish a baseline complete blood count (CBC) and electrolyte levels in order to identify, and later monitor, the presence of anemia, thrombocytopenia, and renal or other abnormalities.

Finally, it is important to screen the patient early for HCC by testing for serum alpha-fetoprotein (AFP, ie, tumor marker).²⁸ Serum AFP must then be monitored at six-month intervals (with a recommended threshold of 400 ng/mL, but even readings as modest as 6 to 20 ng/mL) for elevations that may indicate HCC.^{29,30}

Liver Studies

In addition to the recommended AFP monitoring, the patient should undergo an imaging study of the liver twice yearly. Ultrasound is the most cost-effective screening tool for most patients (with high specificity but varying sensitivity); when combined with a serum AFP reading of 10 ng/mL or greater, ultrasound has a sensitivity of 100% for detection of HCC.²⁹ However, if lesions are found, or if a patient has known cirrhosis, CT or MRI is more accu-

rate in detecting small lesions of the liver (specificity, 100%).²⁹

Liver biopsy is recommended for certain patients to stage liver fibrosis; biopsy may not be necessary, for example, in patients with genotypes 2 and 3, as 80% of these patients react to standard therapy with sustained virologic response.¹ Detection of advanced fibrosis or cirrhosis increases the urgency for treatment to avert associated complications.³¹

Thanks to radiologic guidance, the risk for liver biopsy-related complications has been reduced; less than 1% of patients, according to 2008 study results, required hospitalization because of post-procedural pain or bleeding³²; these are risks for which patients should be prepared,¹ in addition to possible perforation of the bowel or lung, bile leak, or hematoma formation.³³ Less than 10% of patients require analgesia two hours after the procedure,³⁴ although prophylactic analgesia (as with sublingual tramadol and oral lorazepam) has been found helpful in reducing pain and anxiety.³⁵

TREATMENT/MANAGEMENT

According to information from the CDC and practice guidelines from the American Association for the Study of Liver Diseases (AASLD),^{1,2} early diagnosis of HCV and treatment with currently available interventions can lead to cures in 75% of cases; otherwise, serious, life-threatening complications can be expected. In patients treated for HCV infection, *cure* (or *sustained virologic response*) is defined by an undetectable viral load, 24 weeks after completion of therapy.¹ Patients with these test results are no longer able to transmit the virus to others.

For the past decade, pegylated interferon (or *peginterferon*) combined with ribavirin has been considered the standard of care for HCV; treatment response rates, depending on race and genotype, can range from 35% to 80%.^{36,37} Two forms of peginterferon, alfa-2a and alfa-2b, are FDA approved for treatment of chronic hepatitis

►PRIMARY POINT

Patients coinfecting with HCV and HIV must be treated urgently, but therapeutic agents must be selected with great care to avoid interactions and hepatotoxicity.

TABLE 2
HCV Genotypes and Associated Treatment Options^{1,39-45}

Genotype	Treatment regimen/options	Treatment duration	Comments
1	Peginterferon alfa-2a (SQ 180 µg/wk) AND ribavirin, weight-based (po 800 to 1400 mg/d) Recommended addition: EITHER boceprevir (po 800 mg, every 7 to 9 h with food) OR telaprevir (po 750 mg every 7 to 9 h with food*)	48 wk 12 wk, starting at week 5 12 wk	Found in 70% to 75% of US cases Not to be used as monotherapy or with another protease inhibitor
2 and 3	Peginterferon alfa-2a AND ribavirin (po 800 mg/d)	24 wk	80% of patients achieve SVR
4	Peginterferon alfa-2b (SQ 1.5 µg/kg/wk) AND ribavirin (po 800 to 1400 mg/d)	36 to 48 wk, depending on SVR at weeks 4, 12	Most common in Middle East
5	Peginterferon/ribavirin	Limited research	Most common in South Africa
6	Peginterferon/ribavirin	48 wk	Most common in southeast Asia

* Foods containing fat are recommended.

Abbreviations: HCV, hepatitis C virus; SQ, subcutaneous; SVR, sustained virologic response.

Sources: Ghany et al. *Hepatology*. 2009¹; Kamal et al. *Hepatology*. 2007³⁹; Hofmann et al. *Dtsch Arztebl Int*. 2012⁴⁰; Kwo et al. *Lancet*. 2010⁴¹; Klibanov et al. *Pharmacotherapy*. 2012⁴²; Cunningham and Foster. *Therap Adv Gastroenterol*. 2012⁴³; Jacobson et al. *N Engl J Med*. 2011⁴⁴; Zeuzem et al. *N Engl J Med*. 2011.⁴⁵

C; both forms are administered subcutaneously in combination with oral ribavirin.^{1,38}

The choice between peginterferon alfa-2a and alfa-2b and the recommended duration of treatment are dependent on the patient's HCV genotype (see Table 2^{1,39-45}) and prior exposure to treatment. These complex regimens are best managed by specialists in gastroenterology, hepatology, or infectious disease—clinicians who are familiar with the agents' associated adverse effects, the elements of attentive monitoring, and protocols for dosing adjustments.⁴⁶

► PRIMARY POINT

Adding boceprevir or telaprevir to standard therapy can dramatically increase rates of sustained virologic response in patients with HCV genotype 1 infection.

As noted in the AASLD guidelines,¹ alcohol consumption constitutes a risk for worsening fibrosis and possibly for HCC. Additionally, drinking in excess may facilitate replication of HCV

RNA, interfering with therapy. Thus, patients should be urged to discontinue alcohol use during treatment for HCV—or at least restrict it to an occasional drink.

New Agents to Improve Cure Rates

HCV genotype 1 accounts for 70% to 75% of cases in the US, but with current standard treatment, a sustained virologic response is achieved in only 45% to 50% of these patients³⁷ (including 30% of black patients and 50% of whites).^{1,36,38} However, adding one of two new protease inhibitors to the current peginterferon/ribavirin regimen has the potential to increase sustained virologic response rates to as high as 90% to 95% in early virologic responders with genotype 1 infection, both treatment-naïve and previously treated; and in some patients, to shorten treatment to 24 weeks.^{41,42,44,45} Both boceprevir and telaprevir were approved by

the FDA in May 2011.

Both agents are given for 12 weeks during standard peginterferon/ribavirin therapy. Depending on the patient's viral response, the overall regimen may be shortened or extended. Neither telaprevir nor boceprevir is administered as monotherapy,^{47,48} nor are they ever administered together. As with any protease inhibitor, resuming treatment after the agent has been stopped incurs a risk for drug resistance.⁴⁰

Both new agents are taken every 7 to 9 hours, with a meal or snack.^{47,48} The telaprevir dose should be taken with non-low-fat food.⁴⁷

Drug interactions are common. Patients also being treated for HIV and those being treated for HCV genotype 1 infection with either of the two new protease inhibitors must very carefully communicate any prescription drug changes to their treating provider. Substances of greatest concern act via the cytochrome P450 3A (CYP3A) pathway. Examples include ritonavir, St. John's wort, statins, and daily-

dosed sildenafil (as used to treat patients with pulmonary hypertension).

Package inserts accompanying all agents used should be reviewed for monitoring parameters and associated recommendations.

Monitoring for Treatment Effectiveness and Complications

Patients are closely monitored for treatment effectiveness by repeated measurements of HCV RNA (ie, weeks 4, 12, 24, then at four- to 12-week intervals; at end of treatment; and 24 weeks after treatment ends). A viral load not detectable at week 4 indicates a good chance for a cure.¹ If at week 12 the viral load remains detectable, the patient with HCV genotype 1 is unlikely to respond to triple therapy; similarly, dual therapy is not likely to produce a cure in patients with HCV genotype 2 or 3. Without a 2-log drop in viral load by week 12, the patient has only an 8% chance of achieving a sustained virologic response.⁴⁹⁻⁵¹ In these cases, treatment should be discontinued or modified.⁵¹

Regular visits and frequent blood testing make it possible to avoid potential disease- and treatment-related complications. At a minimum, it is recommended that a CBC, serum creatinine, and ALT level be measured at weeks 2, 4, 8, 12, 16, 20, and 24 of therapy.¹ If significant abnormalities are detected (eg, anemia, thrombocytopenia, neutropenia), the clinician may decide to monitor the patient more closely. Measures of liver and kidney function, electrolytes, and coagulation times are part of the recommended monitoring parameters at regular intervals. In addition, interferon therapy is associated with thyroid dysfunction, so relevant monitoring is advised every 12 weeks.¹

Anemia, neutropenia, thrombocytopenia, and other hematologic complications are known adverse effects of HCV therapy—particularly in cirrhotic patients.^{1,52} Ribavirin use (especially aggres-

TABLE 3
Management of HCV Treatment–Associated Complications^{1,41,43,45,55-57}

In addition to anemia and other hematologic complications, patients being treated for HCV may experience any or all of the following:

Complication/adverse effect	Management options	Comments
Flu-like symptoms: fatigue, myalgia, headache, arthralgia, fever, chills, nausea	Patient-administered acetaminophen before injections; hydration, rest	Symptoms typically worst during initial weeks of therapy
Injection-site reactions	Cool/ice packs, acetaminophen*; weekly rotation of injection sites	
Psychiatric disorders (eg, depression, suicidal ideation)	Dosing adjustments; use of SSRIs; referral	Use of standard peginterferon/ribavirin therapy is contraindicated in patients with a history of psychiatric illnesses
Rashes	Steroid preparations, OTC moisturizers, avoidance of sun/heat	Most common in patients taking protease inhibitors
Alopecia	Condition should improve once therapy is completed	Severe symptoms are rare
Anorectal discomfort	OTC remedies until treatment ends	Associated with telaprevir use
Dysgeusia (taste changes)	Optimal oral hygiene, use of sugarless gum or hard candies	Occurs in about one-fourth of patients taking boceprevir

* Acetaminophen dosing should be reduced in patients with advanced cirrhosis or liver decompensation.

Abbreviations: HCV, hepatitis C virus; OTC, over-the-counter.

Sources: Ghany et al. *Hepatology*. 2009¹; Kwo et al. *Lancet*. 2010⁴¹; Cunningham and Foster. *Therap Adv Gastroenterol*. 2012⁴³; Zeuzem et al. *N Engl J Med*. 2011⁴⁵; Fried. *Hepatology*. 2002⁵⁵; Dollarhide et al. *J Clin Gastroenterol*. 2007⁵⁶; Tavakoli-Tabasi and Bagree. *J Clin Gastroenterol*. 2012.⁵⁷

sive use, as for patients with recurrent infection or post-liver transplantation⁵³) is associated with hemolytic anemia,⁵⁴ as is protease inhibitor use.^{41,45} In cases of profound anemia, dosing reduction or treatment discontinuation may be necessary. Severe cases of hemolysis may require transfusion, but treatment with epoietin alfa has been found helpful in some patients.^{52,53} Conventional iron

► PRIMARY POINT

Treatment with epoietin alfa may be helpful for patients who experience severe hemolysis or low neutrophil counts as a result of treatment for HCV.

supplementation is not an effective treatment for hemolytic anemia resulting from ribavirin use.

For patients with low absolute neutrophil counts, treatment dosing reduction was once standard management.^{45,52} More recently, the use of epoietin alfa or

a granulocyte colony-stimulating factor (eg, filgrastim) has been found helpful in raising neutrophil counts.⁵²

Intervention for thrombocytopenia is not typically undertaken unless the total platelet count indicates a risk for spontaneous bleeding. In some patients, a new oral thrombopoietin mimetic called *eltrombopag* may reduce the need for dose reduction or early termination of therapy.⁵²

Ribavirin is a major teratogen. This agent is listed in pregnancy category X, and its label carries a black box warning advising patients to avoid pregnancy while undergoing therapy and for six months following therapy. It has such a high potential for teratogenicity that male patients are even advised not to impregnate their female partners while on therapy or six months following therapy.⁵⁴ Preg-

nant women should never handle ribavirin. It is important to educate medical professionals and office staff about this risk.

For management of other adverse reactions to one or more components of HCV treatment, see Table 3.^{1,41,43,45,55-57}

PATIENT EDUCATION/ FOLLOW-UP DISCUSSION

Patient education is critical to successful treatment for HCV. Patients should be encouraged to avoid viral transmission to sexual partners by using condoms. They should also be advised to avoid sharing razors or toothbrushes with others in the home.¹ Any patient with known HCV, HIV, or HBV should avoid undergoing body piercing or tattooing in any nonprofessional, nonsterile setting, where transmission may occur.⁵ Even successfully treated patients retain an HCV antibody and will test positive for HCV, making them ineligible to donate blood.

Six months after treatment, a viral load is drawn. If no active virus is found, patients will not need monitoring or follow-up labs unless they have known cirrhosis. Fibrosis is reversible in some patients following HCV treatment. However, if active disease is found at the six-month posttreatment follow-up visit, then the treatment was not effective, and the patient is considered a *responder-relapser*. Many such patients then consider enrolling in a drug trial or awaiting the potential approval of new treatments.

Herbal therapies, such as milk thistle and licorice root, have been widely tried by patients with HCV infection. The literature is mixed regarding the effectiveness of these substances or their potential for reducing liver function testing abnormalities. To date, no herbal compound has been proven to eradicate the virus. Most hepatologists encourage patients who take interferon, ribavirin, and/or protease inhibitors to avoid herbal or OTC substances with any potential for drug interactions or other complications.

ON THE HORIZON

Promising developments suggest a brightening future for patients with HCV infection. Researchers throughout the world are currently investigating new combinations of agents, effective against a wider range of genotypes and subtypes, that can control HCV infection without the emergence of drug-resistant strains. The near future may see more protease inhibitors added to current regimens and other direct-acting antivirals possibly replacing old treatment components. As is true of HIV, a vaccine for HCV will be difficult to develop; but in the meantime, new drug combinations will be created with a goal of sustained virologic response rates nearing 100% and ever-shorter treatment regimens.^{37,58}

CONCLUSION

Since signs or symptoms are often not seen in patients infected

with hepatitis C, it is important for primary care providers to question patients regarding known risk factors. At-risk patients should be screened using antibody testing, followed by confirmation of any positive results by HCV RNA testing. The patient's HCV genotype must be identified next, as it plays a key role in the therapeutic decisions to be made.

Because HCV therapy is complex, it is best managed by specialists who are experienced in all the aspects of each patient's regimen and who remain abreast of new therapeutic developments. Nevertheless, primary care providers can serve their patients well by acting as knowledgeable, supportive members of the health care team, accompanying their patients through the challenges of treatment and follow-up. **CR**

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