PRIMARY CARE REPORTS

The Practical CME Journal for Primary Care and Family Physicians

February 2017 VOL. 23, NO. 2

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STATEMENT OF FINANCIAL DISCLOSURE

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. Wise (editor) reports he is involved with sales for CNS Vital Signs. Dr. Park (author) serves on the speaker's bureau for Abbvie, Merck, Gilead, and BMS. Dr. Tobias (author) serves on the speaker's bureau for Gilead, Abbvie, and Merck. Dr. Gandhi (peer reviewer) serves on the speaker's bureau for Salix Pharmaceuticals and Allergan. Dr. Tin (author), Dr. Soe (author), Ms. Coplin (execu-tive editor), and Ms. Mark (executive editor) report no financial relationships with companies related to the field of study covered by this CME activity.

AHC Media

Hepatitis C Infection for Primary Care Providers

Hepatitis C virus (HCV) can cause both acute and chronic hepatitis. Most people are asymptomatic, but for the majority of patients who become infected with hepatitis C, it becomes a long-term, chronic infection. The best way to prevent hepatitis C is by avoiding behaviors that can spread the disease, especially injection drug use, as there is no vaccine for HCV. With the forefront of direct-acting antiviral (DAA) agents, people can now be cured from HCV infection.

Pathogenesis and Genotypes

Hepatitis C virus is a spherical, enveloped, positive-strand RNA virus that belongs to the family of flaviviruses. The natural targets of HCV are hepatocytes and, possibly, B lymphocytes. Virus replication occurs through an RNA-dependent RNA polymerase that lacks a "proofreading" function, resulting in the rapid evolution of diverse but related quasispecies within an infected person. This presents a major challenge with respect to immune-mediated control of HCV.[1,2]

In 1989, the virus was identified as the major etiological agent responsible for post-transfusion non-A and non-B hepatitis.[3-6] The natural history of HCV infection has been difficult to assess because of the commonly silent onset of the acute phase, as well as the frequent lack of symptoms during the early stages of chronic infection. Approximately 5-30% of chronically infected individuals develop cirrhosis over a 20- to 30-year period of time. Following primary HCV infection, persistent viremia and chronic hepatitis develop in the majority of cases.[7] With time, patients are at risk of developing progressive hepatic fibrosis, cirrhosis, and death from liver failure, as well as the advent of hepatocellular carcinoma (HCC).[9] In the majority of patients, acute infection progresses to chronic infection, and spontaneous clearance of viremia once chronic infection has been recognized is rare. It is estimated that cirrhosis will develop in 15-20% of those infected, which can lead to decompensation and possibly even death. Once cirrhosis is established, the risk of HCC is about 1-4% per year. HCC can occur in patients without cirrhosis, but most often the majority of patients will have at least advanced fibrosis.[1]

Six distinct but related HCV genotypes (GTs) and multiple subtypes have been identified on the basis of molecular relatedness that has geographic variation. (*See Figure 1.*) In the United States and Western Europe GTs 1a and 1b are most common, followed by GTs 2 and 3. GT 4 commonly is found in Egypt, GT 5 in South Africa, and GT 6 in Southeast Asia.[8] Knowledge of the GT is important because it has predictive value in terms of the response to antiviral therapy.[1]

EXECUTIVE SUMMARY

- Hepatitis C infection affects 170 million persons globally, and almost 500,000 persons were estimated to have died from HCV-related liver disease in 2010. An estimated 2.2 million to 3.2 million persons in the United States are chronically infected with hepatitis C virus.
- Continuous inflammatory activity in the liver may lead to hepatic fibrosis, which eventually may progress to cirrhosis, putting patients at risk for hepatic decompensation and hepatocellular carcinoma.
- The Centers for Disease Control and Prevention recommends testing patients born between 1945 and 1965, as well as those with risk factors or known exposure. Testing should be initiated with anti-HCV. For those with reactive test results, the anti-HCV test should be followed with an HCV RNA.
- Chronic hepatitis C infection is still the leading indication for liver transplantation in the Western world.
- The discovery of oral direct-acting antivirals has revolutionized treatment for chronic hepatitis C infection.

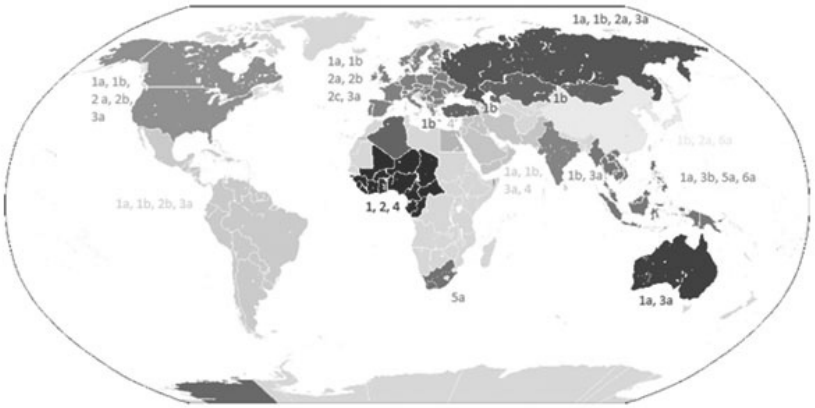
Epidemiology

Hepatitis C infection affects 170 million persons worldwide, and an estimated 2.2 million to 3.2 million persons in the United States are infected chronically with HCV.[1,10] (*See Figure 2.*) However, these numbers most likely are even higher, given that most studies of prevalence use blood donors to report the frequency of HCV and many patients are unaware they are living with HCV. In the United States, the number of new annual HCV infections has been rather stable at approximately 17,000 per year in the past decade, but the number of annual new infections in recent years is markedly lower than during the 1980s, when an estimated 230,000 persons were newly infected with HCV each year.[11]

Persons with HCV infection have all-cause mortality greater than twice that of HCV-negative persons. In the United States, the number of annual deaths related to hepatitis C recently has increased substantially, with HCV being the cause of death or contributing cause of death in approximately 15,000 people per year. (*See Table 1.*) In 2007, the number of deaths related to hepatitis C had surpassed those related to human immunodeficiency virus-1 (HIV). The number of hepatitis C related deaths is at least eight-fold greater than the number of deaths related to hepatitis B. Among the HCV-related deaths in recent years, more than 70% have involved persons 45 to 64 years of age.[12]

It is projected that 1.76 million people with chronic untreated HCV infection will progress to cirrhosis during the next 40 to 50 years. The predicted incidence peak of end-stage liver disease (ESLD) will rise in 2030, with about 38,600 cases per year. The prevalence with ESLD also is anticipated to peak in 2030, with an estimated 131,300 persons living with ESLD. Transplants are expected to peak in 2032 to 2033 at a level of 3,200 HCV-related transplants per year.[13]

Figure 1. HCV Genotype by Geographic Location[9]



Risk Factors and Prevention

Prevention should target those at risk of acquiring the virus and involve providing education, risk reduction counseling, HCV screening, and substance abuse treatment. The primary care physician also should offer counseling on treatment, reducing alcohol usage, and immunizing with hepatitis A, hepatitis B, pneumococcal, and influenza vaccines.[14-16] HCV-infected persons must be informed of the precautions needed to avoid exposing others to infected blood, as this is the primary mode of HCV transmission. This is particularly important for persons who use injection drugs, given that HCV transmission in this population primarily results from the sharing of needles and other infected instruments. Recently, epidemics of acute HCV due to sexual transmission in HIV-infected men who have sex with men have also been described.[14]

HCV is not spread by sneezing, hugging, holding hands, coughing, or sharing eating utensils or drinking glasses, nor is it transmitted through food or water. However, persons with HCV infection should be counseled to avoid sharing toothbrushes and dental or shaving equipment and be cautioned to cover any bleeding wound to prevent the possibility of others coming into contact with their

Figure 2. Prevalence of Hepatitis C Globally

Source: Centers for Disease Control and Prevention.

Table 1. Prevalence of Hepatitis C

Reported New Cases of HCV								
2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
694	802	849	878	781	853	1,230	1,778	2,138

Estimated Actual New Cases of HCV		
2011 (estimated)	**2012 (estimated)**	**2013 (estimated)**
16,500 (7,200-43,400)	24,700 (19,600–84,400)	29,700 (23,500–101,400)

Estimated Number of Chronic Cases in the United States	Number of Death Certificates Listing HCV as Cause			
	2010	**2011**	**2012**	**2013**
2.7–3.9 million	16,627*	17,721*	18,650*	19,368*

* Current information indicates these represent a fraction of deaths attributable in whole or in part to chronic hepatitis C
Source: https://www.cdc.gov/hepatitis/statistics/.

blood. Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of one part household bleach to nine parts water.[14]

High Prevalence Groups

Risk-based testing may not be optimal for many reasons. Several individuals with HCV infection are not aware nor report having specific risk factors for HCV infection.[17,18] In an analysis of data from a national health survey, 45% of individuals with evidence of HCV infection reported no known exposure risk.[17] In addition, even among individuals who have high risk exposure to HCV, many remain untested, as demonstrated by a study in which 72% of 1,033 injection drug users who had a reactive HCV antibody test when tested during trial enrollment were previously unaware of their diagnosis. In another study within a managed care network that included more than 550,000 adults, only 29% of those who had at least one identifiable HCV risk factor underwent testing for HCV.[19]

Surveillance data have suggested that individuals born between 1945 and 1965 in the United States reflect a disproportionate percentage of the total population of adults chronically infected with HCV. In a study of NHANES data from 2003 to 2010, persons born between 1945 and 1964 accounted for 81% of the total estimated population of chronically HCV-infected adults.[20-22] The prevalence of HCV RNA positivity among individuals in this birth cohort is estimated at 2.6%, six times higher than individuals born in other years. Hence, performing routine screening on patients born within these two decades, regardless of the presence of risk factors, will target a significant proportion of the chronically infected HCV population in the United States.[23-25] In a study involving more than 4,700 patients presenting to an emergency department in Maryland, antibody testing of excess blood samples identified 204 patients with undocumented HCV infection.[24] Of those, 26% would have been identified by risk-based testing (history of injection drug use or HIV infection), whereas an additional 49% would have been identified by screening based on birth between 1945 and 1965.

HIV-infected Individuals. Because of mutual routes of transmission, coinfection with HIV and HCV is common, and the prevalence of HCV among HIV-infected patients is greater than that in the general population. In contrast to the low potential of sexual transmission of HCV in general, increasing evidence has shown a substantial risk of sexual transmission of HCV among HIV-infected men who have sex with men. In addition, coinfection is associated with higher rates of fibrosis progression, decompensated liver disease, and liver-related morbidity and mortality compared with infection with HCV alone.

Dialysis Patients. Historically, the prevalence of HCV among patients undergoing hemodialysis has been higher than that in the general population, although the incidence is thought to be decreasing.

Incarcerated Individuals. In the United States, an estimated 16-41% of inmates have serological evidence of HCV exposure and 12-35% have chronic infection.[26,27] Thus, some

advocate routine screening for HCV in correctional facilities. Based on given information, the CDC has released recommendations for HCV testing. (*See Table 2.*)

Table 2. CDC Recommendations for HCV Testing

Recommendations for HCV Testing

- One-time HCV testing is recommended for persons born between 1945 and 1965, without prior ascertainment of risk. Testing should be initiated with anti-HCV antibody. For those with reactive test results, the anti-HCV test should be followed with an HCV RNA.
- Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.

Recommendation for HCV Testing Those with Ongoing Risk Factors

- Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure and risk of acquiring HCV.

Clinical Manifestations

The majority of persons have no symptoms or only mild symptoms, which can occur within 7-8 weeks (range 2-26 weeks) after exposure to HCV. Among those who have symptoms, the most frequent complaint is fatigue. Other less common manifestations include myalgia, arthralgia, nausea, anorexia, and weight loss. The symptoms are rarely debilitating and may be difficult to attribute to liver disease itself (i.e., depression); nevertheless, they may lead to a decrease in the quality of life, which in part may be accounted for by awareness of infection and can improve following treatment success.[1]

A number of extrahepatic diseases have been associated with chronic HCV infection. Most cases appear to be directly related to the viral infection. These include:

- hematologic diseases, such as essential mixed cryoglobulinemia and lymphoma;
- renal disease, particularly membranoproliferative glomerulonephritis;
- autoimmune disorders, such as thyroiditis and the presence of autoantibodies;
- dermatologic conditions, such as porphyria cutanea tarda and lichen planus; and
- diabetes mellitus.

Once patients develop cirrhosis, they are at risk for developing decompensation. Hepatic decompensation is characterized by the development of certain liver-related complications, including ascites, variceal bleeding, and encephalopathy. In patients with chronic HCV infection, jaundice is almost always a sign of advanced liver disease. Almost all HCV-infected patients who develop these complications have cirrhosis; however, not all patients with cirrhosis develop these complications.

Diagnosis

Two major types of tests are used to diagnose HCV: IgG assays for HCV antibodies and nucleic acid amplification testing to detect HCV RNA in blood. There are no available assays for IgM to detect early or acute infection. About 75-85% of patients who seroconvert to anti-HCV, indicative of acute infection, will progress to chronic infection and will develop detectable viremia. As a positive HCV antibody test cannot discriminate between someone who was infected previously with clearing of the infection and someone with current infection, it is pivotal that HCV RNA testing following a positive HCV antibody test be performed to assess current HCV infection. False-negative antibody test results, while uncommon, may occur early in acute infection, commonly in the initial 15 weeks after exposure and infection.[14]

A positive test result for anti-HCV indicates either active HCV infection (acute or chronic), past infection that has resolved, or a false-positive test result. Therefore, an HCV nucleic acid test to detect viremia can confirm current HCV infection and guide clinical management, including initiation of HCV treatment. HCV RNA testing also should be performed in patients with a negative anti-HCV test who are either immunocompromised (i.e., persons receiving chronic hemodialysis) or who might have been exposed to HCV within the last six months because these patients may be anti-HCV negative. An HCV RNA test also is required to detect reinfection in anti-HCV–positive persons after previous spontaneous or treatment-related viral clearance.[1]

Factors Associated with Disease Progression

Several factors appear to be essential determinants of fibrosis progression in HCV-infected patients, including baseline liver histology, age, ethnic background, gender, alcohol intake, comorbidities such as obesity or viral coinfection, and HCV-specific cellular immune response. As an example, young women and children infected with HCV tend to have slower rates of fibrosis progression. Patients with mild inflammation (portal inflammation alone or with only focal periportal extension) and no fibrosis had only a 1.2% annual risk of progressing to cirrhosis. Patients with moderate chronic hepatitis (periportal inflammation usually involving more than 30% of the limiting plate) had an increased annual risk of developing cirrhosis of 4.6%, and more than 90% developed cirrhosis within 20 years of the time of the biopsy. Nearly all patients with severe inflammation or bridging fibrosis developed cirrhosis within 10 years.[28,29]

The daily consumption of more than 50 grams of alcohol has a high probability of worsening fibrosis. Some studies have suggested that daily consumption of smaller amounts of alcohol also has a negative effect on the liver; however, these data are controversial. Excess alcohol intake also has been shown to cause steatohepatitis.[30] Persons identified

as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist.

Hepatitis B virus and HIV coinfection have been associated with poorer prognosis of HCV in cohort studies. Because of overlapping risk factors for these infections and additional benefits of their diagnosis and treatment, persons with HCV should be tested for HIV antibody and hepatitis B surface antigen (HBsAg) using standard assays for screening, and should be counseled on how to decrease their risk of acquiring these infections, including through hepatitis B virus vaccination.[14]

Patients who are obese and have components of metabolic syndrome have underlying insulin resistance and are more prone to have nonalcoholic fatty liver disease, which is a risk factor for fibrosis progression in HCV-infected persons. Therefore, HCV-infected persons who are overweight or obese (defined by a body mass index that is ≥ 25 kg/m^2 or ≥ 30 kg/m^2, respectively) should be counseled regarding strategies to reduce weight and improve insulin resistance via diet, exercise, and medical therapies. Patients with HCV infection and hyperlipidemia or cardiovascular comorbidities also may benefit from various lipid-lowering drugs. Prospective studies have illustrated the safety and efficacy of statins in patients with chronic HCV and others with compensated chronic liver disease.[31] Therefore, these agents should not be withheld in HCV-infected patients.

The Model for End-Stage Liver disease (MELD) is a scoring system for assessing the severity of chronic liver disease. It was developed initially to predict mortality within three months of surgery in patients who had undergone a transjugular intrahepatic portosystemic shunt procedure, and was subsequently found to be useful in determining prognosis and prioritizing for receipt of a liver transplant. This score is now used by the United Network for Organ Sharing and Eurotransplant for prioritizing allocation of liver transplants.[32] The score is calculated by:

MELD = 3.78 × ln [serum bilirubin (mg/dL)] + 11.2 × ln[INR] + 9.57 × ln[serum creatinine (mg/dL)] + 6.43.

Methods of Assessing Liver Fibrosis

Indirect markers of hepatic fibrosis include serologic biochemical tests that reflect alterations in hepatic function but do not directly reflect extracellular matrix metabolism. These markers include serum aminotransferase levels, platelet count, coagulation parameters, gamma-glutamyl transferase (GGT), total bilirubin, alpha-2-macroglobulin, and alpha-2-globulin (haptoglobin). They have been combined into serologic panels to predict the presence of hepatic fibrosis.

AST to platelet ratio index (APRI): The APRI is based on the AST level (AST divided by upper limit of normal) and platelet count (AST elevation/platelet) x 100. A meta-analysis of 40 studies found that for predicting significant fibrosis (F2 to F4), an APRI cutoff of 0.7 had a sensitivity of 77% and a specificity of 72 %. For predicting cirrhosis (F4), an APRI cutoff of 1.0 had a sensitivity of 76% and a specificity of 72%.[33]

FibroTest and FibroSure: FibroTest and FibroSure are identical proprietary serum tests marketed under different names in Europe and America, respectively. It involves the assessment of alpha-2-macroglobuin, alpha-2-globulin (haptoglobin), gamma globulin, apolipoprotein A1, GGT, and total bilirubin. It also takes into account the patient's age and sex. Results from the assays are combined and used to classify patients as having mild fibrosis (F0 to F1), significant fibrosis (F2 to F4), or an indeterminate stage of fibrosis. Sensitivities for significant fibrosis are approximately 60-75% and the specificity is about 80-90%, respectively.[34]

Fibroscan: Fibroscan or transient elastography measures liver stiffness and is a technique for noninvasively assessing hepatic fibrosis. Overall, for diagnosing significant fibrosis, it has an estimated sensitivity of 70% and an estimated specificity of 84%. For diagnosing cirrhosis, the sensitivity and specificity are estimated to be 87% and 91%, respectively.[35]

Treatment

Successful hepatitis C treatment is now achievable in nearly all infected patients and is reflected by a sustained virological response (SVR), defined as the continued absence of detectable HCV RNA for 12 weeks after completion of therapy.[36] An SVR is associated with a 99% chance of being HCV RNA negative during long-term follow-up, and, therefore, patients can be considered cured of the HCV infection.[37] Patients who are cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation, regression of fibrosis, and for some even resolution of cirrhosis.[38] An SVR is associated with a more than 70% reduction in the risk of HCC and a 90% reduction in the risk of liver-related mortality and liver transplantation.[39-41]

In the past, drug therapy with peg-interferon (PEG-IFN) and ribavirin (RBV) resulted in low overall cure rates and early discontinuation due to adverse reactions. The new DAAs offer not only a shorter duration of treatment with fewer adverse reactions, but greatly improved overall cure rates as high as 96%.[42] DAA therapy refers to pharmacological targets that specifically inhibit hepatitis C viral proteins. Identification of the four structural and six nonstructural proteins of HCV was possible only after the HCV RNA genome was sequenced. DAAs target the specific nonstructural components of HCV such as the NS3-4A (serine protease and cofactor), the NS5A (replication complex), and NS5B (RNA-dependent RNA polymerase). Combinations of two or more of these drugs have been shown to be highly effective in curing > 90% of patients to achieve and maintain SVR across all GTs.[43]

The RNA polymerase NS5B does not have proofreading capability, and therefore, sequence diversity in the HCV genome exists at all times, even within individual patients. As a result, the first-generation DAAs, the NS3-4A protease inhibitors, telaprevir (TPV) and boceprevir (BOC), were ineffective as monotherapy due to naturally occurring drug resistance mutations also called

resistance associated variants (RAVs) and required coadministration with PEG-IFN and RBV. Another example, simeprevir (SMV), a once-daily NS3-4A inhibitor is not recommended for GT 1a patients who harbor the baseline Q80K resistance mutation. Sofosbuvir (SOF) circumvents this problem by targeting the catalytic site of the NS5B viral polymerase, thereby profoundly diminishing viral replication directly.[44,45] (*See Tables 3 and 4.*)

The choice between combination regimens also depends primarily on the potential for drug interactions and drug toxicity. The product prescribing information and other resources (i.e., http://www.hep-druginteractions.org) should be referenced on a regular basis to ensure safety when prescribing DAA regimens.

• Ribavirin is teratogenic, so two effective forms of contraception should be used by both men and women of child-conceiving potential during treatment and six months after treatment with RBV-containing regimens.[46] RBV also should be dosed according to weight and glomerular filtration rate (GFR). Complete blood counts (CBCs) should be followed on a routine basis due to the possibility of anemia.

• Sofosbuvir is a substrate of P-glycoprotein, so should not be used with drugs that are potent P-gp inducers, such as rifampin and St. John's wort. It also should not be used with amiodarone, as there have been reported cases of bradyarrhythmias.[47] No clinically significant viral mutations have been identified following the use of SOF. Sofosbuvir should not be used in patients with an estimated creatinine clearance < 30 mL/min.

• Dose adjustments of daclatasvir (DCV) are warranted with moderate CYP3A inducers and strong CYP3A inhibitors.

• Simeprevir (SMV), elbasvir-grazoprevir (EBR/GZR), and ombitasvir-paritaprevir-ritonavir plus dasabuvir (OBV/PTV/r/DSV) are contraindicated in patients with Child-Pugh class B or C cirrhosis. (*See Table 3.*)

The safety profiles to date of all recommended regimens are excellent.

Table 3. Child Turcotte Pugh Classification of the Severity of Cirrhosis

	Class A	Class B	Class C
Total Points	5-6	7-9	10-15
Factor	**1 Point**	**2 Point**	**3 Point**
Total bilirubin (mg/dL)	< 2	2-3	> 3
Serum albumin(g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time/INR	< 1.7	< 1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Table 4. Generic, Trade Names, Respective Manufacturer of Commercially Available Direct-acting Antivirals

Generic	Trade Name	Pharmaceutical Company	Mechanism of Action
Telaprevir (TPV)	Incivek/Incivo	Vertex Pharmaceuticals	NS3-4A protease inhibitor
Boceprevir (BOC)	Victrelis	Merck	NS3-4A protease inhibitor
Simeprevir (SMV)	Olysio/Sovriad	Janssen Pharmaceutica	NS3-4A protease inhibitor
Paritaprevir (PTV)		Abbott Laboratories	NS3-4A protease inhibitor
Grazoprevir (GZR)		Merck	NS3-4A protease inhibitor
Ledipasvir (LDV)		Gilead Sciences	NS5A inhibitor
Daclatasvir (DCV)	Daklinza	Bristol-Myers Squibb	NS5A inhibitor
Ombitasvir (OBV)		Abbvie	NS5A inhibitor
Elbasvir (EBR)		Merck	NS5A inhibitor
Velpatasvir (VEL)		Gilead Sciences	NS5A inhibitor
Sofosbuvir (SOF)	Sovaldi	Gilead Sciences	NS5B nucleos(t)ide polymerase inhibitor
Dasabuvir (DSV)	Exviera (Europe)	Abbvie	NS5B Non-nucleoside polymerase inhibitor
Ledipasvir/ sofosbuvir	Harvoni	Gilead Sciences	
Elbasvir/ grazoprevir	Zepatier	Merck	
Ombitasvir, paritaprevir, ritonavir	Technivie/ Viekirax (Europe)	Abbvie	
Ombitasvir, paritaprevir, ritonavir, dasabuvir	Viekira Pak/ Exviera (Europe)	Abbvie	
Velpatasvir/ sofosbuvir	Epclusa	Gilead Sciences	

Across numerous Phase III studies, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild, usually consisting of mild fatigue and headache. Adequate water intake commonly alleviates these

Table 5. Treatment Options for Genotype 1a and 1b Treatment-naive HCV Patients

Genotype 1a			
Cirrhosis	Compensated		SOF/VEL x 12 weeks (Class I, Level A) SOF/LDV x 12 weeks (Class I, Level A) EBR/GZR x 12 weeks (Class I, Level A) EBR/GZR + RBV x 16 weeks(NS5A polymorphism present) (Class IIa, Level B) SOF + SMV ± RBV x 24 weeks (Class IIa, Level B) OBV/PTV/r/DSV + RBV x 24 weeks (Class I, Level A) DCV + SOF ± RBV x 24 weeks (Class IIa, Level B)
	Decompensated	Anemia or RBV intolerance	SOF/VEL x 24 weeks (Class I, Level A) DCV + SOF x 24 weeks (Class II, Level C) LDV/SOF x 24 weeks (Class II, Level C)
		No anemia	SOF/VEL + RBV x 12 weeks (Class I, Level A) LDV/SOF + RBV x 12 weeks (Class I, level A) DCV + SOF + RBV x 12 weeks (Class I, level B)
No Cirrhosis	Compensated		SOF/VEL x 12 weeks (Class I, Level A) LDV/SOF x 12 weeks (Class I, Level A) OBV/PTV/r/DSV x 12 weeks (Class I, Level A) EBR/GZR x 12 weeks (Class I, Level A) DCV + SOF x 12 weeks (Class IIa, Level B) SOF + SMV ± RBV x 24 weeks (Class IIa, Level B)
	Decompensated	Anemia or RBV intolerance	SOF/VEL x 24 weeks (Class I, Level A) DCV + SOF x 24 weeks (Class II, Level C) LDV/SOF x 24 weeks (Class II, Level C)
		No anemia	SOF/VEL + RBV x 12 weeks (Class I, Level A) LDV/SOF + RBV x 12 weeks (Class I, Level A) DCV + SOF + RBV x 12 weeks (Class I, Level B)
Genotype 1b			
Cirrhosis	Compensated		SOF/VEL x 12 weeks (Class I, Level A) LDV/SOF x 12 weeks (Class I, Level A) OBV/PTV/r/DSV x 12 weeks (Class I, Level A) EBR/GZR x 12 weeks (Class I, Level A) DCV + SOF x 12 weeks (Class IIa, Level B) SOF + SMV ± RBV x 24 weeks (Class IIa, Level B)
	Decompensated	Anemia or RBV intolerance	SOF/VEL x 24 weeks (Class I, Level A) DCV + SOF x 24 weeks (Class II, Level C) LDV/SOF x 24 weeks (Class II, Level C)
		No anemia	SOF/VEL + RBV x 12 weeks (Class I, Level A) LDV/SOF + RBV x 12 weeks (Class I, Level A) DCV + SOF + RBV x 12 weeks (Class I, Level B)
No Cirrhosis			SOF/VEL x 12 weeks (Class I, Level A) LDV/SOF x 12 weeks (Class I, Level A) SOF + SMV x 12 weeks (Class I, Level A) OBV/PTV/r/DSV x 12 weeks (Class I, Level A) EBR/GZR x 12 weeks (Class I, Level A) DCV + SOF x 12 weeks (Class I, Level B)

symptoms. Most adverse events occurred in treatment regimens that included RBV, which may account for anemia in up to 10%.[37]

Genotype 1

The treatment armamentarium for patients with GT 1 chronic HCV infection has changed drastically in recent years. Historically, GT 1 HCV infection has been considered the most difficult to treat compared to the other hepatitis C GTs. From 1998 to 2013, therapy evolved from IFN monotherapy, to PEG-IFN monotherapy, to PEG-IFN plus RBV, to triple therapy with PEG-IFN plus RBV plus an NS3A/4A protease inhibitor (BOC or TPV). In late 2013 and most of 2014, the standard of care for initial therapy of GT 1 consisted of PEG-IFN plus RBV plus

Table 6. Treatment Options for Genotype 2 and 3 Treatment-naive HCV Patients

Genotype 2		
Cirrhosis	Compensated	SOF/VEL x 12 weeks (Class I, Level A) DCV + SOF x 16 or 24 weeks (Class IIa, Level B)
	Decompensated	SOF/VEL + RBV x 12 weeks (Class I, Level A) DCV + SOF + RBV x 12 weeks (Class II, Level B)
No Cirrhosis		SOF/VEL x 12 weeks (Class I, Level A) DCV + SOF x 12 weeks (Class IIa, Level B)
Genotype 3		
Cirrhosis	Compensated	SOF/VEL x 12 weeks (Class I, Level A) DCV + SOF ± RBV x 24 weeks (Class IIa, Level B)
	Decompensated	SOF/VEL + RBV x 12 weeks (Class I, Level A) DCV + SOF + RBV x 12 weeks (Class II, Level B)
No Cirrhosis		DCV + SOF x 12 weeks (Class I, Level A) SOF/VEL x 12 weeks (Class I, Level A)

either SOF or SMV. Since 2015, the standard of care for GT 1 has consisted of all-oral therapy with a combination of DAAs.[37] Currently, six highly potent DAA oral combination regimens are now recommended for patients with HCV GT 1 infection with SVR 12 rates exceeding 90%. (*See Table 5.*) The regimen may differ (i.e., duration and need to add RBV) based on key patient characteristics, which include treatment history, presence of cirrhosis, subtype, and presence of certain pre-existing RAVs. Approximately 10-15% of HCV GT 1-infected patients without prior exposure to NS5A inhibitors will have detectable HCV NS5A RAVs at the population level prior to treatment. These RAVs may cause a large reduction in the activity of NS5A inhibitors (more than five-fold), which can adversely affect response to NS5A-containing regimens.[48,49] Given that the NS5A RAVs are one of the strongest pre-treatment predictors of treatment outcomes with certain regimens, testing for these RAVs prior to deciding on a therapeutic course is now recommended in select situations.[50]

For instance, when considering the use of EBR/GZR, pre-treatment NS5A resistance testing is recommended for patients with HCV GT 1a to detect the presence of virus with NS5A resistance-RAVs at the amino acid positions M28, Q30, L31, or Y93.[50,51] The presence of one or more of these high-fold change RAVs requires the addition of RBV to the regimen and extending the course of EBR/GZR to 16 weeks.[52] When considering the use of SMV plus SOF in patients with GT 1a and compensated cirrhosis, baseline NS3/4A resistance testing should be performed to determine whether the Q80K mutation is present; in this situation, SMV plus SOF should only be used in patients in whom no Q80K polymorphism is detected.[53]

For initial therapy of treatment-naive genotype 1a patients with compensated cirrhosis, three 12-week regimens with similar efficacy are recommended in the American Association for the Study of Liver Diseases (AASLD) guidelines: 1) EBR/GZR; 2) ledipasvir-sofosbuvir (LDV/SOF); and 3) sofosbuvir-velpatasvir (SOF/VEL).[37]

For retreatment of patients with GT 1a who have failed therapy previously with PEG-IFN and RBV, the same 12-week regimens are used as for initial treatment in GT 1a patients without cirrhosis. For retreatment of GT 1a patients with compensated cirrhosis, the recommended regimens are also the same as with initial treatment and compensated cirrhosis.

For initial therapy of treatment-naive GT 1b patients without cirrhosis, the same 12-week regimens are used as for GT 1a without cirrhosis, but with the following exceptions: a) baseline resistance testing is not required for GT 1b patients treated with EBR/GZR, since treatment of HCV GT 1b with EBR/GZR is not significantly impacted by baseline NS5A RAVs;[51] and b) for treatment of GT 1b, RBV is not added to the regimen OBV/PTV/r/DSV.[54]

For retreatment of patients with GT 1b who previously failed therapy with PEG-IFN and RBV, the same 12-week regimens are used as for initial treatment in GT 1b patients without cirrhosis. For retreatment of GT 1b patients with compensated cirrhosis, the recommended regimens are: 1) EBR/GZR; 2) LDV/SOF plus RBV for 12 weeks; 3) OBV/PTV/r/DSV for 12 weeks; and 4) SOF/VEL for 12 weeks.[37]

In patients with GT 1a or 1b infection who previously failed SOF plus RBV, with or without PEG-IFN, the recommended regimen is LDV/SOF plus RBV; the duration of therapy is 12 weeks without cirrhosis and 24 weeks with compensated cirrhosis.[55]

Genotypes 2 and 3

In the past, treatment of GT 2 infection achieved higher SVR rates than with GT 1 infection, even with a shorter duration of therapy and lower doses of RBV. Prior to the availability of DAAs, the standard of care for treatment-naive patients with GT 2 hepatitis C consisted of a 24-week course of PEG-IFN

plus fixed-dose RBV, with SVR rates ranging from 75-85%.[56] In 2013, the FDA approved a 12-week course with the all-oral regimen of SOF plus RBV for the treatment of GT 2 infection based on data from several studies showing SVR rates of about 95% with this regimen.[57] Several trials reported SVR rates of more than 90% with DCV plus SOF, thereby providing an RBV-free option for patients unable to tolerate RBV.[58] Recently, SVR rates greater than 99% have been observed with a 12-week course of SOF/VEL, making this the preferred regimen for the treatment of patients with GT 2 HCV.[59] (*See Table 6.*)

The recommended regimen for initial treatment of HCV GT 2 in patients without cirrhosis consists of SOF/VEL for 12 weeks with the alternative being DCV plus SOF for 12 weeks. Both of these regimens typically have SVR12 rates greater than 90%.[37]

For initial treatment of GT 2 patients with compensated cirrhosis, the recommended regimen is SOF/VEL for 12 weeks; the alternative, DCV plus SOF, should be given for 16-24 weeks.[37]

For the retreatment of GT 2 patients, with or without compensated cirrhosis, the recommended and alternative regimens are the same as for initial therapy of GT 2.[58]

For retreatment of GT 2 patients who previously failed therapy with SOF plus RBV, the recommended regimens with equal rating are: 1) DCV plus SOF (with or without RBV) for 24 weeks, or 2) SOF/VEL plus RBV for 12 weeks; the same regimens are used with or without compensated cirrhosis.[60]

Clinical trials involving patients with GT 2 or 3 infection have examined the efficacy of SOF plus weight-based RBV given for 12-16 weeks and have reported substantially lower SVR rates (30-60%) in patients with GT 3 than with GT 2 infection.[61] The relatively lower SVR rates with GT 3 were improved by using a 12-week course of SOF plus RBV plus PEG-IFN, or extending the all-oral SOF plus RBV regimen to 24 weeks.[57] The dual DAA combination of DCV plus SOF proved more efficacious than SOF plus RBV combination, but required a longer duration (16 or 24 weeks) in cirrhotic GT 3 patients; the role of RBV remained unclear when duration was extended.[62,63] Most recently, SOF/VEL has demonstrated SVR rates of approximately 95% in non-cirrhotic, treatment-naive GT 3 patients, and of about 80% or greater in those with compensated cirrhosis.[59,64]

For treatment-naive GT 3 patients without cirrhosis, two regimens are recommended with similar efficacy: 1) DCV plus SOF for 12 weeks, or 2) SOF/VEL for 12 weeks.[59,62]

For treatment-naive GT 3 patients with compensated cirrhosis, two regimens are recommended: 1) SOF/VEL for 12 weeks, or 2) DCV plus SOF, with or without RBV for 24 weeks. Baseline NS5A GT 3 resistance testing should be performed, and RBV should be added to SOF/VEL or SOF plus DCV if the Y93H mutation is detected.[59,62]

For treatment-experienced GT 3 patients without cirrhosis, two regimens are recommended with similar efficacies: 1) DCV plus SOF for 12 weeks, or 2) SOF/VEL for 12 weeks. Baseline NS5A GT 3 resistance testing should be performed, and RBV should be added to DCV plus SOF or SOF/VEL if the Y93H mutation is detected. For treatment-experienced patients with compensated cirrhosis, two regimens are recommended: 1) SOF/VEL plus RBV for 12 weeks, or 2) DCV plus SOF plus RBV for 24 weeks. The SOF/VEL plus RBV has a higher rating and is much less expensive than DCV plus SOF plus RBV.[60]

The recommended regimen for GT 3 treatment-experienced patients who have failed prior treatment with SOF consists of 1) DCV plus SOF plus RBV for 24 weeks, or 2) SOF/VEL plus RBV for 12 weeks.[60]

Genotype 4

Because of the low prevalence of GT 4 infection in the United States, relatively few patients with GT 4 have participated in clinical trials performed in the United States. In the past prior to availability of DAAs, available data suggested that treatment-naive GT 4 patients who were treated with a 48-week course of PEG-IFN plus RBV had SVR rates that ranged from 43-70%, with even lower SVR rates in GT 4 patients with cirrhosis (25-30%).[65] Available data with newer all-oral regimens in the treatment of GT 4 infection suggest SVR12 rates in treatment-naive patients are greater than 95%, similar to the excellent SVR rates seen with GT 1 infection.

For initial therapy of GT 4 patients without cirrhosis, four 12-week regimens are recommended regimens in the AASLD/Infectious Diseases Society of America (IDSA) guidance: 1) OBV/PTV/r/DSV, 2) SOF/VEL, 3) EBR/GZR,[51] or 4) LDV/SOF. Among these four regimens, the OBV/PTV/r/DSV and the SOF/VEL have the highest efficacy.[37]

For retreatment of GT 4 patients without cirrhosis who previously failed therapy with PEG-IFN and RBV, the AASLD/IDSA recommends three regimens: 1) OBV/PTV/r/DSV for 12 weeks,[66] 2) SOF/VEL for 12 weeks,[67] 3) EBR/GZR for 12 weeks (with addition of RBV and extension to 16 weeks if the patient had prior on-treatment virologic failure,[51] or 4) LDV/SOF for 12 weeks.[60] Among these four regimens, the OBV/PTV/r/DSV and the SOF/VEL have had the highest success.

The recommended regimens and ratings for the retreatment of GT 4 patients with compensated cirrhosis are the same as those for retreatment of GT 4 patients without cirrhosis, except that RBV should be added to the LDV/SOF regimen.[37]

Genotypes 5 and 6

There are relatively few studies related to the optimal treatment regimen for patients with GT 5 or 6 chronic HCV infection, particularly for DAAs with these GTs. Previous studies in treatment-naive patients with GT 5 infection that have examined the combination of IFN (either standard or PEG) with RBV for 48 weeks have reported SVR rates of approximately 60-70%.[68-70] Most studies that have looked into initial treatment of patients with GT 6 are observational and with

Table 7. Treatment Options for Treatment-naive HCV Genotype 4, 5, and 6 Patients

Genotype 4			
Cirrhosis	Compensated		SOF/VEL x 12 weeks (Class I, Level A) OBV/PTV/r/DSV + RBV x 12 weeks (Class I, Level A) LDV/SOF x 12 weeks (Class IIa, Level B) EBR/GZR x 12 weeks (Class IIa, Level B)
	Decompensated	Anemia or RBV intolerance	SOF/VEL x 24 weeks (Class I, Level A) DCV + SOF x 24 weeks (Class II, Level C) LDV/SOF x 24 weeks (Class II, Level C)
		No anemia	SOF/VEL + RBV x 12 weeks (Class I, Level A) LDV/SOF + RBV x 12 weeks (Class I, level A) DCV + SOF + RBV x 12 weeks (Class I, level B) SOF + RBV up to 48 weeks
No Cirrhosis			SOF/VEL x 12 weeks (Class I, Level A) OBV/PTV/r/DSV + RBV x 12 weeks (Class I, Level A) LDV/SOF x 12 weeks(Class IIa, Level B) EBR/GZR x 12 weeks (Class IIa, Level B) OBV/PTV/r/DSV + RBV x 12 weeks (FDA)
Genotype 5			
Cirrhosis	Compensated		SOF/VEL x 12 weeks(Class I Level A) LDV/SOF x 12 weeks(Class IIa Level B)
	Decompensated		SOF/VEL+ RBV x 12 weeks (FDA)
No Cirrhosis			SOF/VEL x 12 weeks (Class I, Level A) LDV/SOF x 12 weeks (Class IIa, Level B)
Genotype 6			
Cirrhosis	Compensated		SOF/VEL x 12 weeks(Class I Level A) LDV/SOF x 12 weeks (Class IIa Level B)
	Decompensated		SOF/VEL x RBV x 12 weeks (FDA)
No Cirrhosis			SOF/VEL x 12 weeks (Class I, Level A) LDV/SOF x 12 weeks (Class IIa, Level B)

small sample sizes, reporting SVR rates of 70-80% with PEG-IFN plus RBV when given for 48 weeks (and only slightly lower when given for 24 weeks). Limited data with a 12-week course of either SOF/VEL or LDV/SOF suggest high SVR rates for initial therapy of GT 5 or 6.[71,72]

Experience with treatment of GT 5 or 6 in the United States is limited. Recommendations for initial treatment or retreatment are based on in vitro data and limited experience in clinical trials.

The recommended regimen for initial treatment or retreatment of patients with GT 5 or 6 is a 12-week course of 1) SOF/VEL or 2) LDV/SOF; these recommendations are the same for patients without cirrhosis and with compensated cirrhosis.[37] (*See Table 7.*)

Treatment Considerations in Specific Populations

Patients with Cirrhosis. Treatment of HCV in patients with compensated cirrhosis (Child-Turcotte-Pugh class A) is a high priority because of the risk of developing severe liver-related complications. For patients with hepatitis C-related cirrhosis, treatment of hepatitis C is associated with significant reversal in hepatic fibrosis and decreased risk of developing HCC, especially when the patient achieves an SVR with therapy.[38] For patients with HCV and compensated cirrhosis, the regimen choice and duration is essentially the same as the approach in patients without cirrhosis; however, in certain circumstances for patients with cirrhosis, the regimen duration may need to be extended and the addition of RBV may be indicated. With the use of new therapies, patients with hepatitis C and cirrhosis can have similar SVR 12 rates as those without cirrhosis, especially with adjustments in therapy duration when indicated.[73] Treatment regimen recommendations are included in Tables 5-7.

Options are limited for patients with decompensated cirrhosis, and antiviral treatment should be undertaken only by an expert in the management of such patients, preferably at a transplant center. Patients with decompensated cirrhosis or a MELD score > 10 should be evaluated for liver transplantation prior to initiation of HCV therapy. Patients with decompensated cirrhosis who are undergoing HCV antiviral therapy should have frequent clinical and laboratory

monitoring.

HIV-HCV Coinfection: In patients with chronic hepatitis C, coinfection with HIV can accelerate the progression of hepatic fibrosis. Hence, treatment of HCV should be a high priority in coinfected patients. Treatment with PEG-IFN and RBV resulted in lower SVR rates among coinfected compared with monoinfected patients,[74,75] but studies of DAAs (either in IFN-based or IFN-free combinations) have demonstrated similar SVR rates among both groups.[76-79] Regardless, drug-drug interactions between antiretroviral agents and HCV antiviral agents may be significant. Antiretroviral therapy may slow liver disease progression in HIV/HCV coinfected patients and, therefore, should be considered for all coinfected patients regardless of CD4 cell count. For coinfected patients whose CD4 cell counts are < 200 cells/mm^3, it may be advisable to wait for further immune reconstitution prior to initiating HCV therapy, particularly since most HCV treatment trials have excluded such patients.[80,81]

Patients with Renal Impairment: Renal function, including an estimation of CrCl or GFR, must be assessed before initiating any hepatitis C treatment. Based on the estimated CrCl or GFR value, patients with renal impairment are classified as having mild (50-80 mL/min), moderate (30-50 mL/min), or severe (< 30 mL/min) disease.

Based on the available limited data, the AASLD/IDSA hepatitis C guidance provides genotype-specific recommendations for the treatment of patients with severe renal disease, including those with ESRD.

• *Patients with Mild Renal Impairment (CrCl 50-80 mL/min):* No dosage adjustment needed when using any of the recommended agents or regimens to treat HCV.

• *Patients with Moderate Renal Impairment (CrCl 30-50 mL/min):* No dosage adjustment needed when using standard dosing of any of the following medications or regimens:
a) DCV; b) LDV/SOF; c) OBV/PTV/r; d) OBV/PTV/r/DSV; e) SMV; f) SOF; or g) PEG-IFN alfa-2a. The dose of PEG-IFN alfa-2b should be reduced by 25% (1.125 mcg/kg once weekly) and the RBV dosing should be reduced to a schedule of 200 mg alternating with 400 mg every other day.

• *Patients with Severe Renal Impairment (CrCl < 30 mL/min) or ESRD:* The following regimens are recommended, based on GT, when the urgency to treat is high, the patient does not have cirrhosis, and renal transplantation is not an immediate option.

• *Genotype 1a:* The recommended regimen is standard dose OMB/PTV/r/DSV combination with reduced-dose RBV (200 mg three times weekly to 200 mg once daily).

• *Genotype 1b:* The recommended regimen is standard dose OBV/PTV/r/DSV, but note that limited data exist with this regimen in patients with renal failure.

• *Genotype 2:* The recommended regimen is PEG-IFN plus dose-adjusted RBV.

• *Genotype 3:* The recommended regimen is PEG-IFN plus dose-adjusted RBV.

• *Genotype 4:* The recommended regimen is standard dose OBV/PTV/r, but note that limited data exist with this regimen in patients with renal failure.

• *Genotype 5 or 6:* The recommended regimen is PEG-IFN plus dose-adjusted RBV.

Patients with hepatitis C infection who require renal transplantation should be evaluated for hepatitis C treatment; the treatment of hepatitis C prior to renal transplantation is strongly preferred over treatment of hepatitis C post renal transplantation. Several trials are underway for the treatment of HCV in patients with severe renal disease.[82-84]

Monitoring During Interferon-free Regimens

For patients receiving hepatitis C therapy, the AASLD/IDSA recommends obtaining a quantitative HCV RNA level at baseline, at four weeks after starting therapy, and at 12 weeks after completing therapy;[37] additionally, healthcare providers may consider obtaining HCV RNA levels at the end of treatment and 24 weeks after completing therapy. The European Association for the Study of the Liver Clinical Practice Guidelines recommend obtaining a week 2 HCV RNA level as an early evaluation of adherence.[85]

Clinical assessment during treatment with an IFN-free regimen focuses on adherence to the regimen and emergence of adverse effects. In contrast with the AASLD/IDSA strategy, some experts do not routinely recheck the HCV RNA after a detectable level at week 4 in patients believed to have reliable adherence, since the vast majority of these patients achieve SVR. However, if adherence is a concern, it is recommended to recheck the HCV RNA in two weeks, and if there is a greater than 10-fold increase, then obtain expert consultation and consider stopping therapy.

An undetectable HCV RNA level 12 weeks after initiation of treatment generally translates into a long-term cure of HCV infection.[36] Some experts will check an HCV viral load at 24 weeks or even at one year after the completion of treatment to confirm that the patient has achieved an SVR.

For patients receiving hepatitis C therapy, the AASLD/IDSA guidance recommends obtaining the following safety laboratory studies four weeks after starting therapy:

• CBC,

• serum creatinine level (and calculated GFR), and

• hepatic function panel: albumin, total bilirubin, direct bilirubin, ALT, AST, and alkaline phosphatase.

Patients who do not achieve an SVR 12 should continue to have regular follow-up and periodic reassessment for treatment, especially when additional new DAA medications become available.

Asymptomatic Increases in ALT Levels Less than 10-Fold: Patients with an increase in ALT levels that is less than 10 times the upper limit of normal, but without symptoms suggestive of acute hepatitis (weakness, nausea, vomiting, or jaundice), should have close surveillance and repeat ALT levels checked

at treatment weeks 6 and 8. If the ALT levels remain persistently elevated, discontinuation of therapy should be considered.

Symptomatic Increase in ALT Levels of Less than 10-Fold: If a patient has any increase in ALT levels less than 10 times the upper limit of normal, that is accompanied either by symptoms suggestive of acute hepatitis or increases in other hepatic function panel labs, HCV therapy should be discontinued promptly and the patient should undergo close monitoring for liver toxicity.

A 10-fold or Greater Increase in ALT Levels: Patients who have a 10-fold or greater increase in ALT levels, regardless of the presence of clinical symptoms, should have HCV therapy discontinued promptly and undergo close monitoring for liver toxicity.

For individuals with advanced fibrosis despite achieving SVR, liver cancer screening dictates evaluation every six months. Once complications of cirrhosis have occurred, liver transplantation is the only effective therapy.

Conclusion

Hepatitis C is highly prevalent in the Western World and is the leading etiology of liver transplantation in the United States. Patients affected can progress to having hepatic fibrosis, liver cirrhosis, and then HCC. There have been six identified genotypes that vary geographically. Initial diagnostic tests include an HCV antibody and, if reactive, then will include RNA quantitative testing as well as genotyping. HCV FibroSure and/or Fibroscan are commonly used to assess the degree of fibrosis. Historically, hepatitis C has been known as a tough-to-treat entity, given the lack of SVR with the previous drugs and the number of adverse reactions to those drugs, including RBV and IFN therapy. Just recently within the past couple of years, with the advent of direct acting antiviral agents, treatment success rates exceed 90%. Treatment options then are based on the genotype, degree of fibrosis, treatment-naive vs. treatment experienced, and comorbid conditions. Given the high efficacy of DAAs, screening efforts should be continued in high-risk cohorts to halt the progression of hepatitis C and to prevent further morbidity and mortality.

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CME Questions

1. What is the most common genotype of hepatitis C in the United States?
   a. Genotype 1
   b. Genotype 2
   c. Genotype 3
   d. Genotype 4
   e. Genotype 6
2. One-time hepatitis C screening is recommended in which population?
   a. All persons with HIV infection
   b. Persons born from 1945 through 1965
   c. Patients who have ever received long-term hemodialysis treatment
   d. All of the above
   e. None of the above
3. In the process of initiating hepatitis C treatment, which of the following tests is *not* recommended?
   a. Serum alcohol level
   b. Serum ammonia level
   c. FibroSure or FibroTest
   d. Hepatitis B serology
   e. Hepatitis C genotype and RNA level

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4. Which of the following medications is considered to be teratogenic?
   a. Harvoni
   b. Ribavirin
   c. Sofosbuvir
   d. Viekira Pak
   e. Velpastavir
5. Which of the following hepatitis C Genotype patients currently have the lowest SVR rates when treated with oral antiviral therapy?
   a. Genotype 1a
   b. Genotype 1b
   c. Genotype 2
   d. Genotype 3
   e. Genotype 6
6. A 58-year-old former intravenous drug user was found to have elevated liver enzymes. Further testing revealed he was positive for hepatitis C, Genotype 1a. A liver biopsy showed bridging fibrosis and nodular formation. Endoscopy showed two columns of small esophageal varices. Which of the following regimens should *not* be offered to the patient?
   a. Ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak)
   b. Velpatasvir/sofosbuvir ± RBV
   c. Ledipasvir/sofosbuvir ± RBV
   d. Daclatasvir + sofosbuvir
7. A 50-year-old woman with Genotype 1a hepatitis C compensated cirrhosis is currently on Harvoni (ledipasvir/sofosbuvir). She is at week 3 of the total 12 weeks duration treatment plan. What testing interval of SVR do you recommend?
   a. HCV RNA at week 12 only
   b. HCV RNA at week 4, week 8, and week 12, and no further testing needed
   c. HCV RNA at week 4 and week 12 and no further testing needed
   d. HCV RNA at week 4, week 12, week 24, and 1 year
   e. HCV RNA at 1 year only
8. Based on the current AASLD guideline, which of the following is a treatment option for a hepatitis C Genotype 3 patient without cirrhosis?
   a. Sofosbuvir + simeprevir
   b. Ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak)
   c. Daclatasvir + sofosbuvir
   d. Elbasvir/grazoprevir
   e. Sofosbuvir/ledipasvir

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PRIMARY CARE REPORTS™ (ISSN 1040-2497) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326. Telephone: (800) 688-2421 or (404) 262-7436.

Executive Editor: Leslie Coplin
Senior Accreditations Officer: Lee Landenberger

GST Registration No.: R128870672

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Primary Care Reports,***
P.O. Box 550669, Atlanta, GA 30355.

Back issues: $26. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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