

A Brief Clinical Update on Hepatitis C—The Essentials

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ABSTRACT

Infection with the hepatitis C virus (HCV) is a common cause of cirrhosis and liver failure and the most common indication for liver transplant in the United States. Based on the prevalence of HCV infection at 1.3% of the US population, there are an estimated 74,000 people living with HCV infection in the state of Wisconsin, the majority of whom are undiagnosed. HCV infections in Wisconsin have increased, reflecting the increasing use of intravenous heroin in the state. This review discusses up-to-date guidelines for screening, diagnosis, and treatment of HCV. New direct-acting antiviral medications have revolutionized the treatment of HCV with significantly improved outcomes. High cost and limited availability of these medications present challenges in overall management of HCV.

BACKGROUND AND EPIDEMIOLOGY

Infection with the hepatitis C virus (HCV) is a common cause of cirrhosis and liver failure and the most common indication for liver transplant in the United States. HCV is a single-stranded RNA virus that is transmitted via blood. It is estimated that over 4 million people in the United States are infected with HCV.¹ Risk factors for transmission include IV drug use, sexual intercourse with someone who uses IV drugs, chronic hemodialysis, and blood transfusions prior to 1992.²

The epidemiology of HCV in Wisconsin reflects national trends. As of December, 2013, the Wisconsin Department of Health had

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received 38,354 reports of HCV infection.³ Based on the prevalence of HCV infection at 1.3% of the US population, there are an estimated 74,000 people living with HCV infection in the state of Wisconsin, the majority of whom are undiagnosed. HCV incidence has slowly increased since 2006, with an average of 2500 new cases each year.³ In 2013, Milwaukee County accounted for about 22% of all new cases, and 10% came from the Wisconsin correctional system.³ Males accounted for 57% of new cases, with increasing numbers of infections identified

in men ages 50 to 69 (Baby Boomers).^{3,4} Non-Hispanic blacks were 2 times as likely, and American Indians 3 times as likely, to be diagnosed with HCV infection as non-Hispanic whites.³ HCV incidence in people under 30 years of age has increased from 5% in 2003 to 27% in 2013 with the concomitant rise in heroin use, reflecting intravenous (IV) transmission.³

In 2012, there were 3865 hospitalizations in Wisconsin for HCV infection.³ Of these hospitalizations, almost a third also had a diagnosis of liver disease, a quarter had alcohol abuse and 10% had IV drug use. Males ages 50 to 69 were hospitalized at higher rates than females, reflecting high risk behaviors in the past. Recent statistics show similar rates of HCV infections in young people of both genders, which may lead to a more equal hospitalization rate in the future.³ Approximately 20% of all liver transplants performed in Wisconsin from 2009 to 2012 were due to chronic hepatitis C infection.³

Mortality in people with HCV infection is estimated at 3 times higher than in people without the infection.⁴ People with HCV infection die on average 22 years younger than people without the infection, and are more likely to have cirrhosis and liver and renal failure.⁵ The number of HCV-related deaths in Wisconsin more than doubled from 2000 to 2011 to almost 160.

Screening

In 2013, the United States Preventive Services Task Force (USPSTF) recommended screening for HCV infection in adults

CME

CME available. See page 270 for more information.

Table 1. Risk Factors for HCV

Risk Factors Identified by the USPSTF, the AASLD/IDSA, and the CDC^{6,7,9}

Born between 1945 and 1965

Risk Factors Identified by the USPSTF and the AASLD/IDSA^{6,7}

Past or current injection drug use

Receiving a blood transfusion before 1992

Long-term hemodialysis

Being born to an HCV-infected mother

Incarceration

Intranasal drug use

Getting an unregulated tattoo

Other percutaneous exposures

Risk Factors Identified by the AASLD/IDSA Only⁷

HIV infection

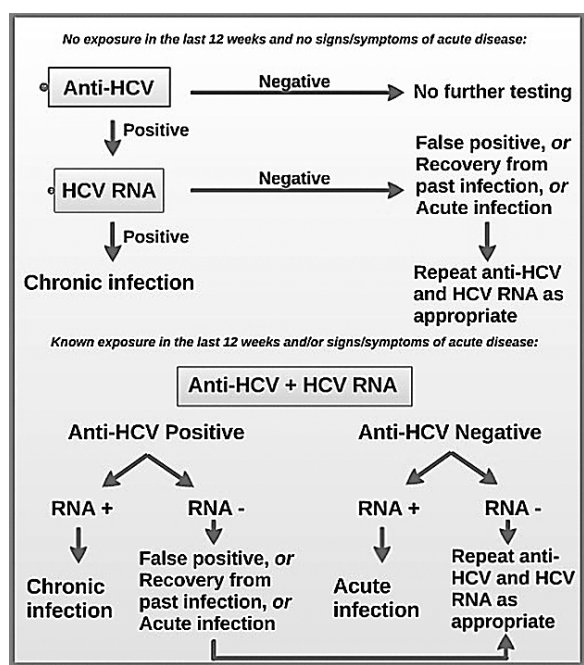
Unexplained chronic liver disease

Chronic hepatitis including elevated alanine aminotransferase levels

Solid organ donor

Abbreviations: HCV, hepatitis C virus; USPSTF, United States Preventive Services Task Force; AASLD/IDSA, The American Association for the Study of Liver Diseases/Infectious Diseases Society of America; CDC, Centers for Disease Control and Prevention.

Figure. Diagnosis of Hepatitis C



at increased risk of infection and 1-time screening in all adults born between 1945 and 1965 (Grade B recommendation).⁶ Immunoassay for HCV antibody is the preferred initial screening test for all patients, though nucleic acid amplification testing (NAT) for HCV RNA should be considered for patients with concern for exposure in the last 6 months; who are immunocompromised; or who may have been reinfected after clearing or

treating a previous infection.⁷ While no studies have attempted to link HCV screening with reduced morbidity or mortality, the USPSTF did find adequate evidence that screening tests accurately diagnose HCV infection, and that treatment with antiviral medications leads to sustained virologic response (SVR) and improved clinical outcomes.

The 2013 USPSTF review evaluated 5 studies that compared different screening strategies targeting multiple risk factors for HCV infection.⁸ No 2 studies evaluated the same strategy, but all 5 confirmed that screening strategies based on risk factors were associated with sensitivity greater than 90% and small numbers (<20) needed to screen to identify 1 case of HCV infection. Individuals with continued risks should be screened periodically, but there is not evidence to define frequency of testing. While there are no published studies evaluating the effectiveness of a birth cohort-based screening strategy, the recommendation was expanded to include persons born between 1945 and 1965, based on several factors: 76.5% of HCV prevalence occurs in this age group; previous risk-based screening was ineffective in clinical practice due to poor understanding and application of screening guidelines; and 45% to 85% of HCV-infected individuals were unaware of their infection status. These patients are more likely to be diagnosed with HCV, either because of a history of blood transfusion or presence of other, decades-old risk factors^{6,7,9} (Table 1).

The initial screening test for HCV is a serologic assay for HCV antibody (anti-HCV). A systematic review found that the sensitivity of enzyme immunoassays (EIAs) for anti-HCV ranges from 97.2% to 100% when compared to NAT, which encompasses polymerase chain reaction (PCR) as a gold standard. Data regarding the specificity of EIA are limited, but in the studies available specificity ranged from 97% to 100% when compared to PCR, even though 15% to 45% of patients who are EIA-positive are not viremic.⁸ Since the 2004 review, a rapid test for anti-HCV has become available and has received a Clinical Laboratory Improvements Amendments waiver to allow for point-of-care testing in nontraditional settings; its sensitivity and specificity are comparable to traditional anti-HCV testing.¹⁰

Diagnosis

As described above, testing for chronic HCV begins with serologic testing for anti-HCV antibody. Serologic tests are both sensitive and specific for HCV infection. If serologic testing is negative for anti-HCV, no further testing is needed. If serologic testing is positive for anti-HCV, then testing for the presence of HCV RNA is the next step in evaluation (Figure). If anti-HCV serology and HCV RNA are both positive, chronic HCV infection is confirmed. If anti-HCV serology is positive but HCV RNA is negative, there are 3 possible explanations: (1) the patient has completely recovered from a past HCV infection; (2) the initial serologic test was falsely positive; or (3) the patient is acutely

Table 2. Measures of Liver Fibrosis

Measure	Commentary
Invasive	Invasive testing is the gold standard for evaluation of liver fibrosis because it distinguishes between a minimum of 3 stages of fibrosis: early/none, intermediate, and advanced/cirrhosis. ¹³ Staging historically has informed treatment decisions. However, with the advent of novel pharmacotherapies, recommendations around fibrosis evaluation and timing of treatment are in flux. ¹²
Liver biopsy	Liver biopsy distinguishes between stages of fibrosis, which may aid in treatment decisions and in determining need for ongoing screening. It also assesses severity of inflammation and/or steatosis and helps rule out other causes of liver injury. ⁷ However, it has small but real risks of pain, bleeding, and organ perforation. ¹²
Noninvasive	Noninvasive tests avoid the risks associated with liver biopsy, but have lower sensitivity and specificity and are unable to distinguish minimal disease from intermediate fibrosis. ¹³
Bedside evaluation (age, history, and physical examination)	Bedside evaluation includes assessment of disease duration, age of onset, degree of alcohol exposure, co-existing disease such as HIV, physical examination, and routine laboratory testing and imaging. Bedside evaluation accurately distinguishes minimal from advanced fibrosis but fails to identify intermediate stages. ¹³
Routine laboratory tests (AST, ALT, GGT, cholesterol, platelet count, insulin resistance)	An assortment of routine laboratory tests, and ratios between them, are used to assess liver fibrosis. All have low sensitivity, specificity, or both. ¹³
Proprietary test panels (PGA or PGAA index, Fibrotest)	Proprietary blood test panels and algorithms are not necessarily superior to routine laboratory tests. ¹³
Specialized blood or breath tests (clearance of indocyanine green, sorbitol, or galactose; C-galactose and C-aminopyrine breath tests; MEGX test; Fibrospect; European Liver Fibrosis test)	Many specialized tests have been developed to assess hepatic perfusion and metabolic capacity and the presence of extracellular matrix components that may indicate increased levels of fibrogenesis and fibrolysis; some proprietary panels combine some of these tests with more conventional approaches. These tests all lack sensitivity to detect early or intermediate fibrosis. ¹³
Conventional imaging (ultrasound, computed tomography [CT])	Conventional imaging with CT or ultrasound detect advanced disease reliably but typically miss minimal or intermediate fibrosis. ¹³
Transient elastography	Transient elastography combines ultrasound with low-frequency elastic waves to measure liver elasticity. However, because its signal only penetrates 25mm to 65mm, its use is limited in obese patients or those with ascites. False positive results have occurred in patients with acute inflammation. ^{12,13}

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; PGA, prothrombin time, gamma glutamyl transferase, apolipoprotein A1); PGAA, prothrombin, gamma glutamyl transferase, apolipoprotein A1, alpha-2 macroglobulin.

infected with HCV but has not yet generated significant viremia. In these situations, repeat HCV RNA testing in 4-6 months distinguishes acute HCV infection from recovery from old infection.¹¹ HCV RNA may be detected as little as 2 weeks following exposure,¹² so earlier repeat testing also may be reasonable.

If the patient presents with symptoms or signs concerning for acute infection, or if there is concern for recent HCV exposure, serologic testing and testing for HCV RNA should be performed simultaneously. HCV RNA may be positive as early as 2 weeks following infection, while anti-HCV does not typically appear on serologic testing until 8 to 12 weeks after infection. If there is sufficient concern for acute exposure but both serology and RNA are negative, antibody testing may be repeated in 4 to 6 months. Simultaneous anti-HCV and HCV RNA testing also is indicated in situations where serology may be falsely negative, for example in those who are immunocompromised, on hemodialysis, or have HIV.¹¹ Once the diagnosis of HCV infection has been made, HCV genotype should be determined, as this will guide treatment decisions. Baseline viral load should be documented before initiating therapy.⁷

In patients with confirmed HCV infection, the American

Association for the Study of Liver Disease/Infectious Diseases Society of America (AASLD/IDSA) recommends evaluating for liver fibrosis and cirrhosis as a way of determining appropriate treatment strategy and need for additional evaluation; eg, hepatocellular carcinoma screening, which is recommended every 6 months in patients with advanced fibrosis.⁷ Liver biopsy is the gold standard for assessing fibrosis and cirrhosis, but is associated with added medical cost and risks including perforation of other organs, bleeding, pain, and anxiety.¹¹ Many noninvasive alternatives for evaluating fibrosis are currently in use, including blood and imaging tests; and in its 2014 guidelines the AASLD/IDSA recommended liver biopsy, imaging, or noninvasive markers^{7,12, 13} (Table 2). There is no consensus that any one noninvasive alternative to biopsy is the best.

Clinical Course

The time course of acute HCV infection has been difficult to clearly define, as most individuals have mild, nonspecific symptoms at the onset of infection, and therefore do not seek care, going undiagnosed.¹⁴

In a prospective cohort of 632 individuals identified through clinical referral, prison surveillance, or community

outreach with documented HCV seroconversion or those with acute, symptomatic HCV infection, about half of participants reported symptoms consistent with acute infection.¹⁵ The most commonly reported symptoms are self-limited flu-like symptoms, but a few individuals develop the typical symptoms of hepatitis, including jaundice, abdominal pain, anorexia, and dark urine. Fifteen percent to 25% of acutely infected individuals spontaneously clear the viremia, while 75% to 85% of individuals develop chronic HCV infection, defined as the presence of HCV RNA in the blood for at least 6 months. While greater than 80% of clearance of HCV occurs within the first year after infection, spontaneous clearance of HCV after acute infection can vary considerably; in 1 prospective study of 179 IV drug users, clearance varied from 94 to 620 days after initial viremia.¹⁶ Re-infection after clearance of acute HCV has been documented in HIV-positive patients.

For the vast majority of patients, the clinical course of chronic HCV infection remains benign. The majority are asymptomatic. The most common symptoms include mild arthralgias and myalgias. Mild, fluctuating elevations of liver enzymes occur during the course of the illness. HCV infection commonly has been associated with several hematologic, rheumatologic, dermatologic, renal, and endocrine disorders in several small, observational studies. However, the prevalence of many of these disorders is confounded by the presence of other risk factors. A case control study of 34,204 hospitalized veterans with HCV infection showed an increase in the prevalence of porphyria cutanea tarda, lichen planus, vitiligo, cryoglobulinemia, membranoproliferative glomerulonephritis, and non-Hodgkin's lymphoma.¹⁶ While this study did show an association of HCV infection with diabetes, the association was not statistically significant after controlling for age. However, a later meta-analysis of 34 retrospective and prospective case control studies showed an increased risk of diabetes (OR 1.8, CI 1.20-2.40) in patients with HCV infection.¹⁷ The prevalence of mixed cryoglobulinemia is extremely variable in several series, with rates as low as 1.9% and as high as 51% in individuals with HCV infection; conversely, the prevalence of patients with essential cryoglobulinemia with either anti-HCV antibodies or HCV RNA in serum or precipitate is widely variable, but greater than 80% in some series.¹⁶⁻¹⁹ Only about one-quarter of individuals develop clinical manifestations of cryoglobulinemia syndrome, which include glomerulonephritis, peripheral neuropathy, purpura, and arthritis.

In chronic HCV infection, 10% to 20% of individuals develop cirrhosis, typically over 20 to 30 years. However, the course of progression is highly variable and nonlinear, depending on several demographic factors. Younger age, female sex, and white race are associated with lower risk of progression to advanced liver disease.¹⁴ Of patients with who develop cirrhosis from HCV, 1% to 4% will develop hepatocellular carcinoma (HCC) each year, and 20% per year will further progress to decompensated cirrhosis. Once signs of decompensation develop, the 5-year mortality rate approaches 50%.¹⁴ Chronic HCV infection is the most common reason for liver transplant in the United States.

Razavi et al developed a model to project the progression of disease and the future cost burden of HCV.²⁰ The peak prevalence of chronic HCV occurred in 1994 and is now declining. Due to the lag time of the development of cirrhosis, the peak prevalence of compensated cirrhosis will occur in 2015, with the peak in decompensated cirrhosis in 2019, the peak in HCC in 2018, and peak in liver-related deaths in 2020.

Several factors can impact the trajectory of HCV liver disease. Alcohol use of greater than 50 grams per day and metabolic syndrome have been associated with acceleration of fibrosis, and even HCC.^{21,22} Treatment of chronic HCV infection with pegylated interferon with ribavirin that achieves SVR has been shown to reduce (1) progression to fibrosis and cirrhosis, (2) incidence of HCC, (3) liver-related complications (ascites, encephalopathy, gastrointestinal bleeding), (4) liver-related deaths, and (5) all-cause mortality.²³ Long-term outcomes with new direct-acting antivirals for hepatitis C are not yet known. However, in a meta-analysis of 49 studies including 8534 individuals, the 5-year re-infection after SVR was 0.9% in "low risk" patients, and as high as 21.8% for HIV/HCV co-infected patients.²⁴

In chronic HCV infection, HCC occurs almost exclusively in patients with cirrhosis. Screening for HCC in the setting of chronic HCV infection should therefore be limited to individuals with advanced fibrosis, as described above.

Prevention of Progression and Transmission of HCV Infection

Abstinence from alcohol is recommended, despite the lack of consistent evidence that smaller doses of alcohol contribute to progression of liver disease. In addition, brief intervention for at-risk alcohol use, and treatment and referral for alcohol use disorder is effective in reducing alcohol use in HCV-infected individuals. Due to similar risk factors and worse prognosis, all HCV-infected patients should be evaluated for HIV and HBV infections. Hepatitis A and B vaccine series should be completed for susceptible patients. IV drug users should be counseled on safe practices, including needle exchange. HCV is not transmitted through casual household contact. Sexual transmission of HCV is rare, but may be much higher amongst heterosexuals with increasing numbers of partners and men who have sex with men, particularly when partners are HIV co-infected.

Pharmacotherapy of Active HCV Infection

From the early to mid-1990s treatment for hepatitis C focused

on the use of standard interferon.²⁵ Early treatment regimens resulted in sustained virologic response (SVR) ranging from 6% with 6-month treatment to 12% with a 12-month treatment course. The addition of ribavirin to standard interferon in the mid-1990s improved SVR to 34% with 6-month therapy and 42% with 12-month therapy. The introduction of pegylated interferon (peginterferon) mono-therapy in early 2000 improved SVR to 39% with 12 months of treatment, and to up 55% when co-administered with ribavirin. Until recently, peginterferon and ribavirin have been the mainstays of treatment with activity against all hepatitis C genotypes.²⁶

Two protease inhibitors, boceprevir and telaprevir, were the first generation of direct-acting antiviral (DAA) agents introduced in early 2011 as additions to traditional peginterferon and ribavirin regimens.²⁶ These agents improved SVR rates up to 75% in some subgroups of patients. But regimens containing interferon and ribavirin remained complex with the need for injections, long durations of treatment and significant side effects. Rapid development of new DAA agents since the fall of 2013 has brought improvement in SVR, shorter treatment duration, and shift from need for interferons and ribavirin, thus reducing adverse events and simplifying medication administration (Table 3).

The second-generation DAA agents have unique pharmacological and pharmacokinetic profiles. Table 4 describes the mechanism of action, basic dosing recommendations, metabolic pathways, drug interactions, and side effects.

While treatment is recommended for all patients with chronic hepatitis C infection, those with advanced fibrosis, compensated fibrosis, liver transplants, and extrahepatic disease are recommended for immediate treatment.⁷ Before starting treatment for hepatitis C, drug interactions should be evaluated because patients with hepatitis C tend to be older and may have comorbid conditions, including HIV and history of organ transplant.³¹ In patients being treated for HIV or using immunosuppressive agents, significant drug interactions are possible with some DAA agents. A website developed by the University of Liverpool (www.hep-druginteractions.org) may be useful in exploring potential drug-drug interactions.

Baseline laboratory tests including complete blood cell count (CBC), international normalized ratio (INR), hepatic function panel, thyrotropin (TSH) (if interferon is part of regimen), and glomerular filtration rate (GFR) should be obtained as well as hepatitis C genotype and subtype and quantitative viral load. Monitoring of CBC, creatinine, GFR and hepatic panel should be repeated 1 month after beginning treatment.

Table 3. Introduction of Second Generation Direct-Acting Antivirals for Treatment of Hepatitis C and Sustained Virologic Response (SVR) Outcomes

FDA Approval	Regimen	SVR %
November 2013 ^{26,27}	simeprevir (Olysio)+ribavirin +/-peginterferon	59-100
December 2013 ^{26,28}	sofosbuvir (Solvadi)+ribavirin+/-peginterferon)	59-93
October 2014 ^{26,29}	ledipasvir/sofosbuvir (Harvoni)	94-99
November 2014 ²⁶	sofosbuvir+simeprevir	92
December 2014 ³⁰	ombitasvir/paritaprevir/ritonavir+dasabuvir (Viekira Pak)	91-100

Abbreviations: SVR, sustained virologic response; FDA, Food and Drug Administration.

For regimens with peginterferon, TSH should be obtained every 12 weeks. Quantitative viral load testing also is recommended to monitor response during treatment.

Pharmacologic recommendations for therapy are based on hepatitis C genotype (and subtype), whether this is initial treatment or retreatment, and degree of fibrosis.⁷ For patients undergoing initial treatment, the presence or absence of cirrhosis influences therapy, and in those patients who have experienced treatment failure, the type of treatment previously received and the presence or absence of cirrhosis also influences recommendations. Because of the frequent changes in treatment recommendations, the most up-to-date information should be obtained from the website: <http://www.hcvguidelines.org>.

The newer DAA medications and combinations form the cornerstone of initial treatment of all 6 hepatitis C genotypes.⁷ For example, for treatment-naïve patients with genotype 1b, the 3 combinations of DAA agents approved in 2014 are recommended as initial therapy. While other genotypes are treated with different drug combinations, all regimens include newer DAA medications.

Insurance coverage for medications has garnered significant attention due to the cost of the newest treatment options, which typically exceed \$100,000 per course of therapy. Prior authorization criteria of several Dane County insurance providers typically include presence of advanced fibrosis or cirrhosis, HCC, or failure of pegylated interferon with ribavirin. The prescription needs to be written by physicians in the following specialties: gastrointestinal (GI), hepatology, infectious disease, or transplant medicine. Patients are excluded if they have advance renal disease. The restriction of use of the most effective regimens for HCV to specialty practitioners as well as the enormous cost may limit the ability to address the current HCV disease burden. Prediction models show that a combination of increased diagnosis, increased treatment, and high efficacy therapies offer the largest reduction in HCV-related morbidity and mortality.³² Comanagement of patients between specialty and primary care providers offers one promising solu-

Table 4. Direct Acting Antivirals Pharmacologic Profiles

Direct-Acting Antiviral Side Effects	Class	Administration	Elimination	Drug Interactions	
simeprevir ²⁶	NS3A/4 protease inhibitor	Take with food; 150 mg once daily	Highly protein bound; metabolism CYP450 3A	Many drug interactions possible —eg, CYP3A4 inducers and inhibitors	Rash, pruritis, photo sensitivity, transient increase in bilirubin
sofosbuvir ²⁶	NS5B polymerase inhibitor	Take without regard to food; 400 mg once daily	Prodrug—requires metabolism to active form. Renal elimination (80%)	Inducers of P-glycoprotein may decrease concentration	Mild to moderate fatigue, headache, insomnia, diarrhea, and anemia
ledipasvir ³¹	NS5A inhibitor	Take without regard to food; 90 mg once daily	Highly protein bound; excreted via feces	No significant CYP450 activity; inducers of P-glycoprotein may reduce concentration; increases in stomach pH may decrease solubility and concentration of ledipasvir.	Since studied in combination with sofosbuvir, similar profile
ombitasvir ^{33,34} paritaprevir/ ritonavir and dasabuvir	NS5A inhibitor NS3/4A protease inhibitor No antiviral properties-booster nonnucleoside and NS5B polymerase inhibitor	Take with food; (ombitasvir 25 mg plus paritaprevir 150 mg plus ritonavir 100 mg combination tablet) 1 tablet daily along with dasabuvir 250 mg tablet twice daily	All agents highly protein bound; ombitasvir is hydrolyzed, other 3 agents metabolized by CYP450; ritonavir is highly potent CYP450 inhibitor.	Combination may have inhibitory effect on metabolism of drugs like pravastatin, rosuvastatin ARBs, and calcium channel blockers; CYP3A inducers may decrease concentration; CYP2C8 inhibitors may increase dasabuvir concentration.	Overall well-tolerated when not used with ribavirin; paritaprevir associated with transient bilirubin elevation.

tion to manage the upcoming surge of HCV-infected patients who will be identified by broader screening and would benefit from medical therapy.

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