CME

Improving hepatitis C screening and access to treatment

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ABSTRACT

The rising prevalence of opioid use disorder and injection drug use has resulted in an increasing incidence of chronic hepatitis C virus (HCV) infection. Although older adults historically have represented the bulk of HCV infections in the United States, demographics have shifted and most new infections are presenting in younger patients. As a result, screening guidelines for HCV have evolved, moving toward a near-universal screening paradigm. Rates of screening and linkage to care remain low, attributed to the fact that underserved populations are disproportionately affected and often have limited access to specialty care. Collaborative models to treat HCV using primary care providers have been proposed to facilitate linkage to care and reduce transmission.

Keywords: hepatitis C, HCV, collaborative care, opioid use disorder, at-risk, direct-acting antivirals

Learning objectives

- Review the epidemiology of viral hepatitis C
- Review appropriate screening, laboratory testing, and follow up for hepatitis C
- Review changes to treatment criteria and medication safety profiles based on the current Infectious Disease Society of America (IDSA) and American Association for the Study of Liver Disease (AASLD) guidelines
- Recognize examples of collaborative models for hepatitis C treatment and the importance of increasing treatment access in at risk populations.

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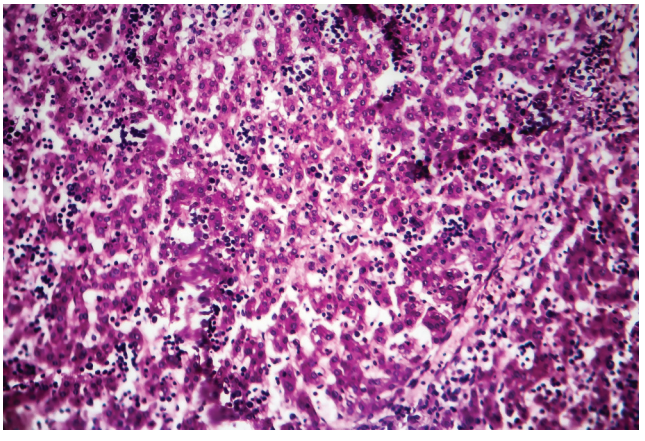

Hepatitis C virus (HCV), a leading cause of cirrhosis and hepatocellular carcinoma, chronically infects an estimated 58 million patients globally.[1] The CDC reports a continued increase in new hepatitis C cases since 2013, from 1.6 new cases per 100,000 population to 2.8 new cases per 100,000 in 2019.[2] Driving this increase is the opioid epidemic's effect on underserved populations with limited medical access, including people experiencing homelessness and those who inject drugs.[3] To meet the World Health Organization's aim to eliminate HCV globally by 2030, we must identify 90% of chronically infected patients and provide treatment access for at least 80% of them.[1] The United States is not on track to achieve this target because of inadequate screening and linkage to care. The COVID-19 pandemic has further reduced hepatitis C antibody testing volumes and prescriptions for hepatitis C treatments.[4] Because of the pandemic, 73% of health departments in the United States that offer select viral hepatitis services reduced HCV screening, and 48% reduced HCV treatment.[5]

The US Preventive Services Task Force (USPSTF) recommends screening all patients ages 18 to 79 years for HCV regardless of known risk factors.[6] HCV cure rates now exceed 95% with pan-genotypic, oral-based regimens with few adverse reactions and minimal drug-drug interactions.[7] However, at-risk populations face numerous barriers to care and treatment, including limited transportation, adherence concerns, limited geographic access to specialty

Key points

- Treatment of HCV with direct-acting antivirals is more effective and safer than previous treatments.
- Patients who are infected with HCV often have poor access to specialty healthcare.
- Multiple studies indicate that HCV can be safely treated by primary care providers in collaborative models.

care, social stigma, homelessness, active substance use, and clinicians' attitudes toward HCV treatment.[3,8,9]

With shortened durations and improved safety, pangenotypic regimens allow for a shift from the specialty setting toward a collaborative model that better uses primary care providers (PCPs) for HCV management.[7,10,11] Multiple studies support decentralized treatment of HCV and have demonstrated comparable sustained viral response rates, improved cost-effectiveness, and better patient access.[10,12-21] Decentralizing HCV management could improve our most vulnerable populations' access to hepatitis C treatment and reduce patients' addiction-related shame.[10,12,17,18,22]

DIAGNOSIS

HCV is a single-stranded RNA virus.[23] Progression of the disease can lead to hepatic fibrosis, cirrhosis, and hepatocellular carcinoma.[7] HCV infection is considered acute within the first 6 months of exposure, with most patients remaining asymptomatic. Symptoms lasting 2 to 26 weeks include jaundice, nausea, and right upper quadrant pain. Aminotransferase elevation is variable and is frequently greater than 10 to 20 times normal; however, hepatic failure related to acute infection is rare. After exposure to the virus, 54% to 86% of patients develop chronic hepatitis C infection measured by positive quantitative polymerase chain reaction (PCR) testing.[24] Patients with a positive screening HCV antibody test but undetectable HCV quantitative viral PCR either cleared the infection spontaneously or completed treatment with successful sustained viral response. HCV viral loads can fluctuate, and if the patient has had HCV exposure within the past 6 months, has clinical evidence of HCV, or there are concerns about the test specimen, HCV quantitative viral PCR should be repeated to ensure a second undetectable result.[25] The USPSTF now supports one-time HCV antibody screening for all patients ages 18 to 79 years.[6] Patients with high-risk activities should continue to be screened every 6 to 12 months. This includes people who inject drugs, men who have sex with men, HIV-positive patients or those on HIV preexposure prophylaxis, long-term sexual partners of those with chronic HCV infection, patients on maintenance hemodialysis, and incarcerated persons.[26] Recent advances in the screening guidelines also include screening pregnant patients at the time of each pregnancy.[27]

DIAGNOSTIC TESTING

Further diagnostics to consider for patients with detectable hepatitis C viral loads are HCV genotype, hepatitis A and B serology, HIV antibody testing, complete blood cell count, complete metabolic panel, prothrombin time, and INR (**Figure 1**).[26] Hepatic fibrosis can be assessed noninvasively with serum fibrosis panels (Fibrosure, Fibrotest) or transient elastography (FibroScan).[26] Online calculators, such as the AST to platelet ratio index (APRI) calculator and fibrosis-4 (FIB4) calculator, can be used to assess for cirrhosis quickly. Laboratory indications suggesting cirrhosis include thrombocytopenia, hypoalbuminemia, elevated prothrombin time, and elevated total bilirubin in cases of decompensation. If serum testing and ultrasound findings are inconsistent, consider elastography, MRI, or liver biopsy.

Individual progression to cirrhosis is variable, but patients with alternative causes of hepatic inflammation (such as alcohol use, nonalcoholic fatty liver disease, chronic HBV, and HIV) are at higher risk of accelerated cirrhosis.[28,29] Clinicians should refer patients with cirrhosis to a gastroenterology specialist for long-term management. Although pan-genotypic regimes remain effective in patients with compensated cirrhosis, patients require hepatoma screenings and endoscopy to evaluate for esophageal varices.[17] Following successful treatment, patients with a history of hepatitis C and cirrhosis remain at elevated risk of hepatocellular carcinoma and require continued hepatoma screening, with abdominal ultrasound and serum alpha-fetoprotein every 6 months.[30] In patients with coinciding hepatic steatosis, abdominal CT or MRI should be used because of limitations of ultrasound in patients with obesity.[30]

> Guidelines and professional societies recommend treatment for patients with ongoing substance use.

MANAGEMENT

Professional societies, including the American Association for the Study of Liver Disease (AASLD), the Infectious Disease Society of America (IDSA), the American Society of Addiction Medicine (ASAM), as well as the CDC, endorse treatment for all patients with hepatitis C viral load with more than 12 months of life expectancy, including active substance users.[7,26]

PCPs can effectively manage patients with uncomplicated hepatitis C infection in collaborative models with varying degrees of specialty support.[10,15,17,20,22,31,32] Traditionally, active substance abuse was a contraindication for HCV

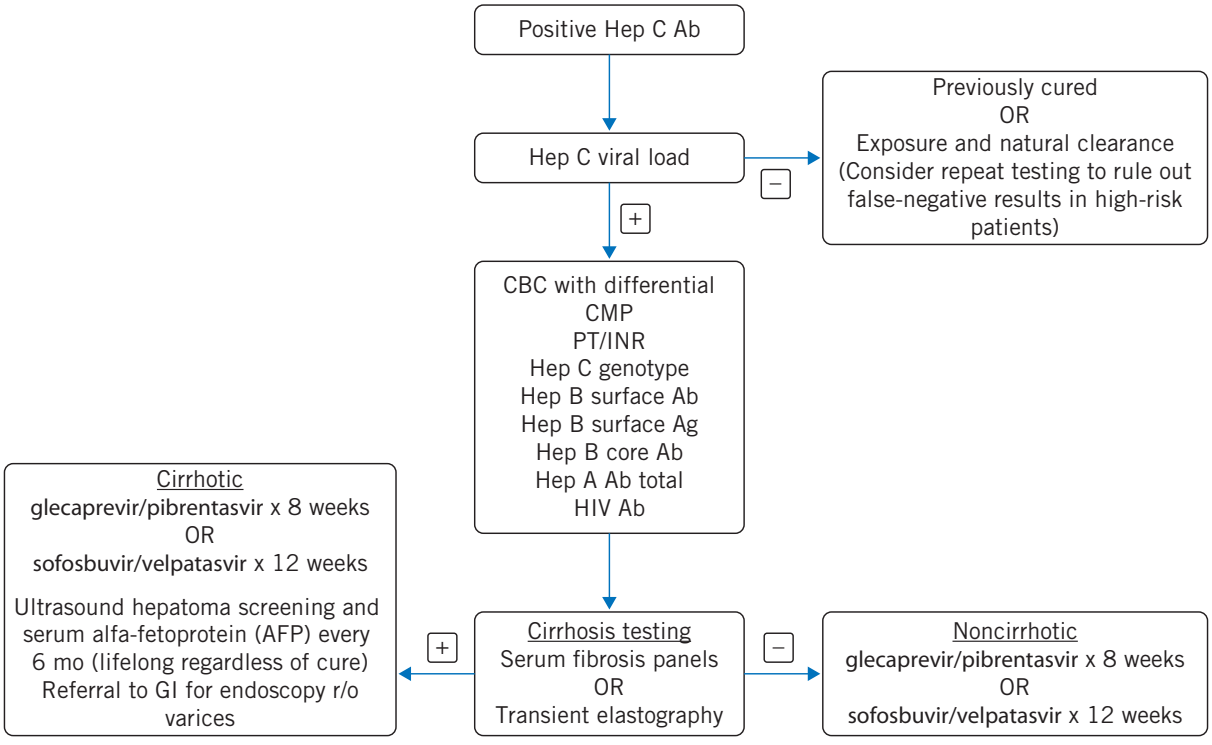

FIGURE 1. Diagnostic testing algorithm for hepatitis C

therapy. However, current guidelines and professional societies now recommend treatment even for patients with ongoing substance use. To achieve HCV elimination, engagement of this high-risk population is essential. HCV therapy may improve addiction outcomes given the symbiotic nature of addiction disorders and HCV.[33] Qualitative interviews of patients at a methadone maintenance clinic suggested that integrating HCV therapy with methadone maintenance can create psychologic and behavioral changes, reducing addiction and patients' HCV-related shame and improving their self-care.[33] Recent studies support therapy in this population with medication adherence and sustained viral response rates comparable with patients who do not have substance use.[34-36]

Reinfection of treated patients remains a concern. Still, treatment and risk reduction education results in low reinfection rates, and these concerns should not reduce consideration for treatment.[37] Only about 5% of patients become reinfected after treatment.[38] Reinfection rates of less than 2% have been demonstrated in patients who remain on medication-assisted treatment for substance use disorder.[38] Treatment of patients actively injecting substances also prevents downstream spread to other patients; a concept known as *treatment as prevention*. Before repeating treatment, obtain the patient's HCV genotype and viral load to differentiate between reinfections and late viral relapse. Because of shared risk factors, also repeat HIV Ab screening in patients with HCV reinfection.

TREATMENT OVERVIEW

HCV consists of 10 mature viral proteins, including nonstructural proteins NS5A and NS5B. These proteins are the targets of the direct-acting antiviral medications for the treatment of uncomplicated HCV such as sofosbuvir (NS5B polymerase inhibitor), velpatasvir (NS5A inhibitor), and glecaprevir (NS3/4A protease inhibitor).[23] In treatment-naive patients without cirrhosis, daily sofosbuvir/velpatasvir for 12 weeks or daily glecaprevir/pibrentasvir for 8 weeks are safe and effective.[26] These medications are pan-genotypic, safer than previous treatments using interferon and ribavirin, and have cure rates over 95%.[7,10,17,32] Adverse reactions, which resolve following treatment completion, are mild and include headache and fatigue as the most common.[7,17] Less common adverse reactions include nausea, anemia, insomnia, diarrhea, and rash.[39,40] Because of the potential of reactivating previous hepatitis B infection, patients with positive hepatitis B core antibodies should have liver function test monitoring or be referred to a specialist based on the nature of specialty collaboration.[7] Patients who are not immune would benefit from hepatitis A and B vaccination.[7] Direct-acting antiviral medications are not recommended during pregnancy.[7] Patients whose uncomplicated HCV fails to respond to treatment should be referred to a specialist for alternative therapies such as sofosbuvir/velpatasvir/voxilaprevir or combination regimes containing ribavirin.[41]

When prescribing medications, consider medication interactions and use specialty pharmacies and online interaction checkers such as www.hepdruginteractions.org/checker to minimize drug-drug interactions.[7,38] As the pH in the stomach increases, absorption of sofosbuvir decreases; thus, appropriate dosing intervals for antacid medications are required. Patients using sofosbuvir-containing regimes should avoid proton pump inhibitors or take them 12 hours apart from HCV medication.[7,38] Patients should not take P-glycoprotein inducers such as rifampicin and carbamazepine with sofosbuvir/velpatasvir or glecaprevir/pibrentasvir.[7,38] Note that concomitant use of amiodarone and sofosbuvir-containing regimes is contraindicated because it can result in potentially life-threatening bradycardia.[7,38] Women should avoid using oral contraceptives containing estrogen in combination with protease inhibitors such as glecaprevir because of the risk of liver enzyme elevation.[7,38] However, those taking estrogen-containing contraceptives can safely use sofosbuvir/velpatasvir.[7,38] Patients should avoid taking HIV protease inhibitors with glecaprevir/pibrentasvir because of a potential increase in ALT levels.[39,40] Because of these and other possible medication interactions, patients with HIV may benefit from specialty care for HCV treatment.[7]

> Telehealth may improve patient access to specialty care, but does not improve the limited number of specialists.

PRIMARY CARE TREATMENT

A meta-analysis published in 2019 that reviewed primary care and community-centered hepatitis C treatment indicated that these models could improve uptake and completion of treatment while maintaining comparable cure rates.[10] The ASCEND trial published in 2017 found therapy by PCPs in urban federally qualified health centers to be safe and effective.[42] By integrating hepatitis C treatment in sexual health clinics in Baltimore, Md., the clinics were able to improve HCV treatment access in underserved populations.[31] The San Francisco Health Network implemented a successful primary care treatment model using specialty e-referrals for HCV treatment guidance, increasing treatment access for patients in marginalized populations.[20]

A cost analysis published in 2020 indicated that the use of PCPs improved treatment uptake and reduced cost compared with hospital-based treatments, supporting outpatient treatment modalities.[12] A collaborative model, Project ECHO, using specialty clinicians who advised PCPs through telehealth, was cost-effective and improved patient access.[13] Telehealth may improve patient access to specialty care, but alone does not improve the limited number of specialists, long specialty wait times, and patient discomfort with new clinicians.[13,43]

The availability of simplified treatment algorithms, the safety profile of direct-acting antiviral medications, and the potential for improved patient access all support the increased use of collaborative models to deliver hepatitis C treatment.[12] These community-based approaches have multiple benefits, including reduced stigmatization of marginalized communities and increased trust in local healthcare systems.[31,33,34]

CONCLUSION

Hepatitis C is an infectious disease affecting primarily vulnerable and at-risk populations who have multiple barriers to treatment.[10,17] Treatment has improved in efficacy, safety, and ease of prescribing.[10,26] Reducing obstacles to treating high-risk populations is essential to achieve viral eradication.[10,17] Current evidence supports the ability of PCPs to treat uncomplicated hepatitis C infection safely and effectively.[10,17,42] Use of AASLD/IDSA guidance and drug interaction tools can help clinicians navigate treating patients with uncomplicated HCV. Online continuing education also is available to improve clinician comfort with HCV management.[44] PCPs can lead the way toward eradicating this debilitating disease. **JAAPA**

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