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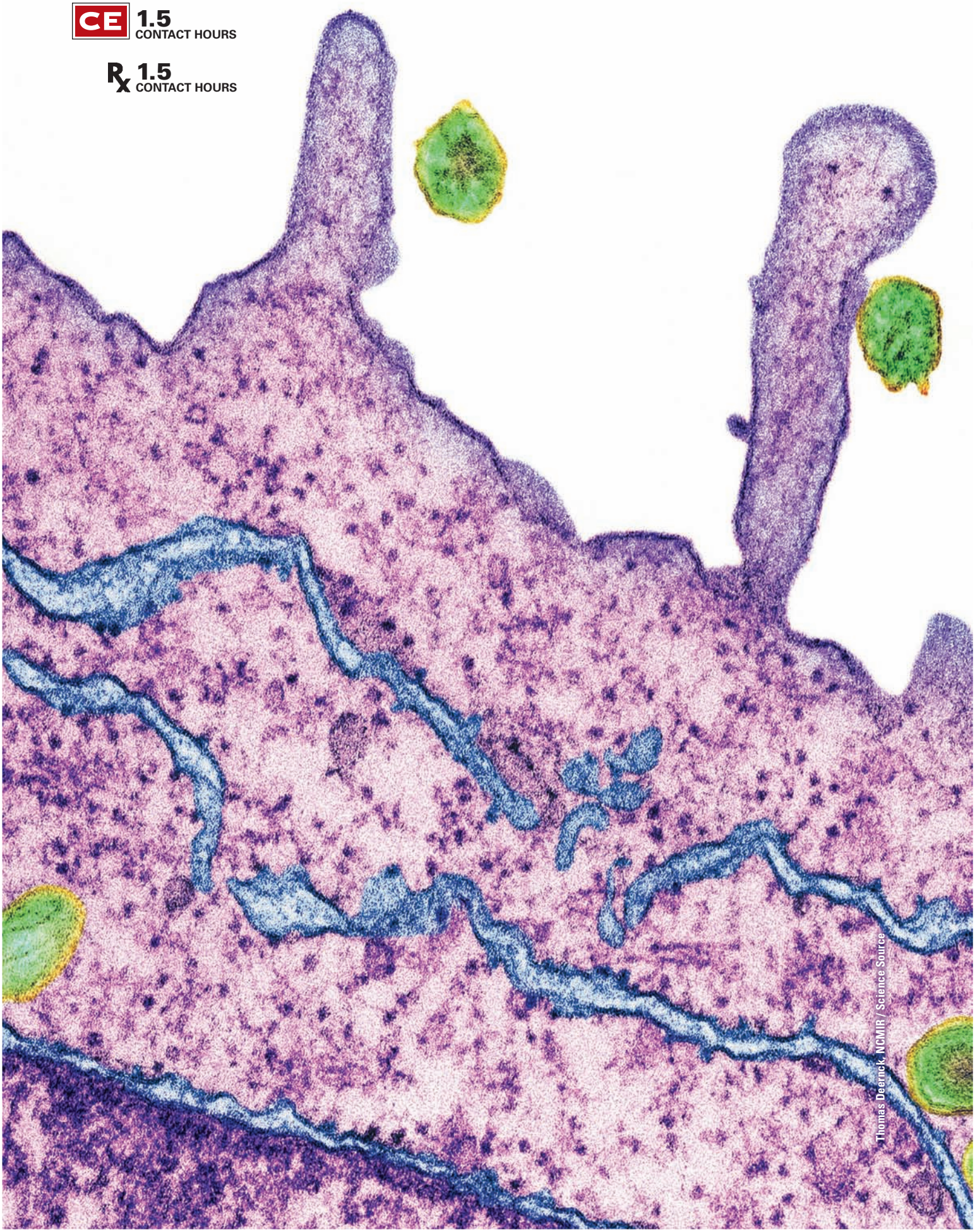

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Hepatitis C infection:
Updates on treatment guidelines

Abstract: Hepatitis C virus (HCV) is a major cause of chronic liver disease worldwide. Due to the asymptomatic nature of the infection, many acute cases of HCV infection are left undiagnosed, so screening individuals at risk is an important public health priority. New medications offer sustained virologic response rates of over 95%, fewer adverse reactions, and shorter durations of therapy. This article reviews the new treatment guidelines for the evaluation and management of patients with HCV infection.

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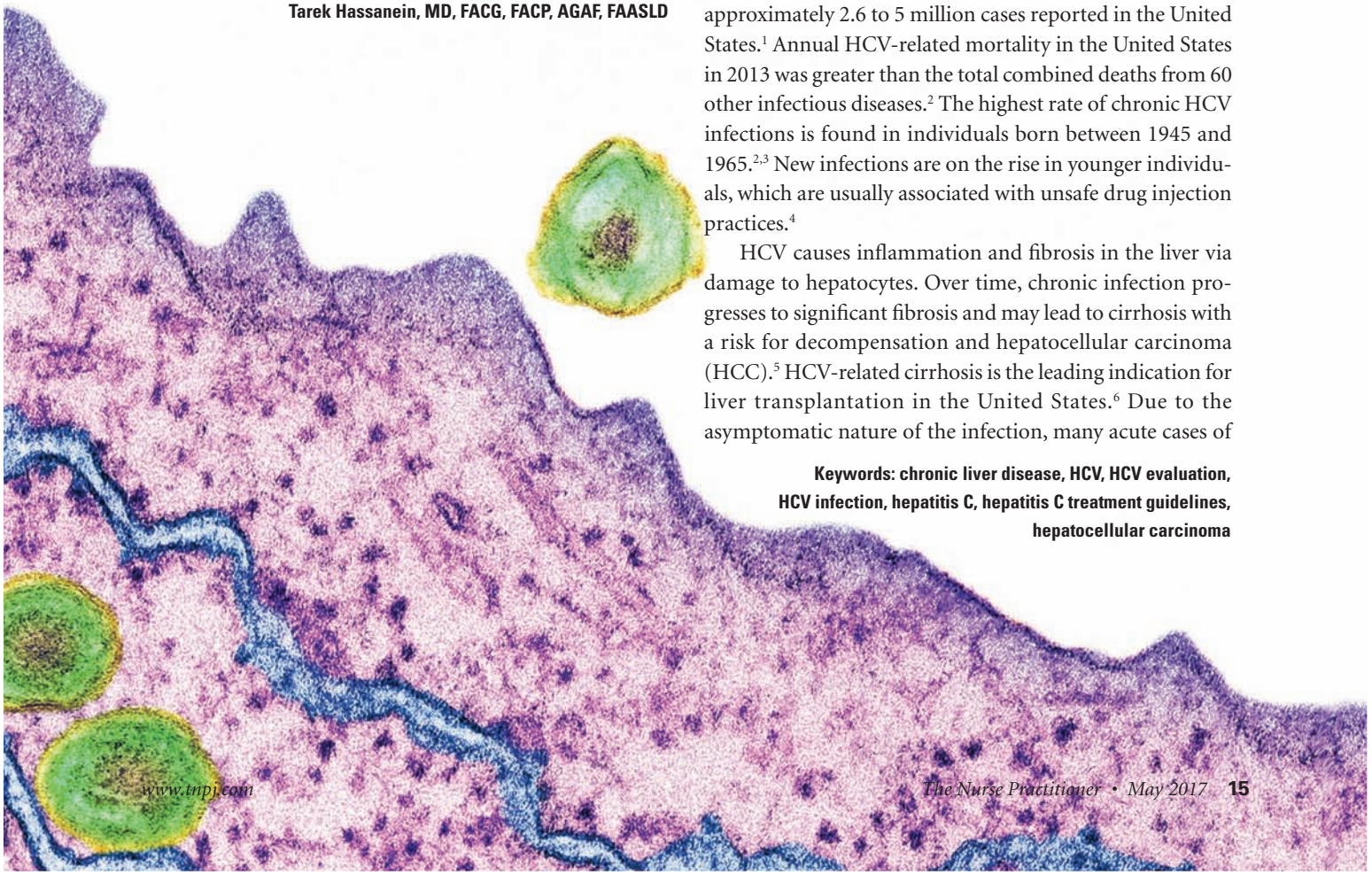


The hepatitis C virus (HCV) is a major cause of chronic liver disease worldwide. It is estimated to infect 130 to 150 million individuals globally, with approximately 2.6 to 5 million cases reported in the United States.[1] Annual HCV-related mortality in the United States in 2013 was greater than the total combined deaths from 60 other infectious diseases.[2] The highest rate of chronic HCV infections is found in individuals born between 1945 and 1965.[2,3] New infections are on the rise in younger individuals, which are usually associated with unsafe drug injection practices.[4]

HCV causes inflammation and fibrosis in the liver via damage to hepatocytes. Over time, chronic infection progresses to significant fibrosis and may lead to cirrhosis with a risk for decompensation and hepatocellular carcinoma (HCC).[5] HCV-related cirrhosis is the leading indication for liver transplantation in the United States.[6] Due to the asymptomatic nature of the infection, many acute cases of

Keywords: chronic liver disease, HCV, HCV evaluation, HCV infection, hepatitis C, hepatitis C treatment guidelines, hepatocellular carcinoma

HCV infection are left undiagnosed, so screening individuals at risk is an important public health priority. In approximately 15% to 20% of acute HCV infections, the individual will mount an immune response to fight the virus and will not develop chronic infection.[5]

However, many individuals will develop chronic infection. While the disease progression is thought to be slow, some individuals have an accelerated course of the disease, in particular, those with comorbidities such as fatty liver disease, hepatitis B infection, HIV coinfections, and substance abuse issues. The disease burden of patients with end-stage liver disease is high in the United States and is expected to rise over the next few years.[7]

The National Academies of Sciences, Engineering, and Medicine recently convened a committee on a National Strategy on the Elimination of Hepatitis B and C.[8] A priority of this report addresses the feasibility of reducing the number of cases of HCV infection in the United States with the goal of eradication. Newer treatment modalities with direct-acting antivirals (DAAs) demonstrate improved efficacy and tolerability with shorter durations of therapy, resulting in a major paradigm shift for HCV infection treatment.

The hepatitis C virus

HCV is a single-stranded RNA virus belonging to the *Flaviviridae* family. The virus has numbered genotypes and lettered subtypes; in the United States, approximately 70% of cases are genotype 1 and 20% to 25% are genotypes 2 and 3.[9,10] Once the virus is established in the bloodstream, it targets hepatocytes, where it releases RNA and creates additional RNA strands through a translational process.

Risk factors for HCV infection[16,17]

- Individuals born between 1945 and 1965 (baby boomers)
- Patients with conditions associated with a high prevalence of HCV infection (patients with HIV infection; patients with hemophilia who received blood products before 1987; patients on hemodialysis; and patients with unexplained, abnormal aminotransferase levels)
- Children born to HCV-infected mothers
- Sexual partners of HCV-infected individuals
- Patients with a history of illicit I.V. or intranasal drug use (both past and present)
- Healthcare workers after a needle-stick injury or mucosal exposure to HCV-infected patients
- Recipients of transfusions or organ transplants before 1992
- Individuals who practice folk medicine (including acupuncture) and who had body piercings, tattoos, and commercial barbering services where appropriate infection control measures were not implemented
- Individuals who were ever incarcerated

HCV consists of a large polyprotein that can be broken down into smaller viral products: three structural proteins (core, E1, and E2); an ion channel (p7); and six nonstructural proteins (NS2, NS3A, NS4A, NS4B, NS5A, and NS5B).

DAAs target these proteins encoded by the viral genome, which are responsible for release of infectious particles and HCV replication. Currently, the main targets are the NS3/4A protease, NS5A, and the NS5B RNA polymerase; however, drug development is underway for additional targets.[11] With the rapid advances in treatment efficacy, tolerability, and shorter durations of therapy, it is vitally important to identify individuals with chronic hepatitis C infection in order to link them to liver disease evaluation and care.

Due to the slow, progressive, asymptomatic course of HCV infection, individuals may not be diagnosed for up to 20 to 30 years or until complications arise from advanced cirrhosis.[12] Screening individuals with identified risk factors of exposure to HCV with the anti-HCV antibody test is the optimal approach to detecting HCV infection. In the United States, I.V. drug use is the primary mode of HCV transmission.[13] The CDC and the U.S. Preventive Services Task Force recommend testing for HCV in individuals born between 1945 and 1965 regardless of risk status (see *Risk factors for HCV infection*).[14,15]

Screening for HCV may be done with any FDA-approved assays to detect the anti-HCV antibody. If the anti-HCV antibody is positive, further exploration with quantitative HCV RNA testing by polymerase chain reaction (PCR) for viral load and HCV genotype is recommended for confirmation of HCV infection.[15] If anti-HCV serology is positive but HCV RNA is negative, there are three possible explanations: the patient has completely recovered from a past HCV infection; the initial serologic test was a false positive; or the patient is acutely infected with HCV but has not yet generated significant viremia. Testing should be repeated in 3 to 6 months to distinguish acute infection from spontaneous recovery.[16]

Chronic hepatitis C infection requires evaluation of underlying liver disease as evidenced by liver fibrosis. All patients should be screened for current or past hepatitis B infection prior to initiating HCV treatment. Patients who are seronegative for hepatitis A and/or B should be immunized. If hepatitis B coinfection is detected, refer to specialty care due to the risk of hepatitis B reactivation with HCV treatment. Patients who are HIV positive need a referral for HIV care.

Patients may have contracted HCV infection years prior to diagnosis and have remained asymptomatic for years, rendering them at risk for advanced liver disease upon diagnosis. Liver imaging should be performed to rule out HCC and if cirrhotic, endoscopic evaluation to evaluate portal hypertension.

Clinical evaluation

A comprehensive medical history and physical exam should focus on potential risk factors, symptoms of HCV infection impacting quality of life, complications of liver and autoimmune diseases, kidney disease, confusion, and the presence of extrahepatic manifestations of chronic hepatitis C. Screening for past and present depression, suicide risk, alcohol use/abuse, and ongoing psychiatric/substance use disorders is important. A family history of liver disease and/or liver cancer should be assessed. Abdominal findings of advanced liver disease include caput medusae (distended paraumbilical veins), ascites, and enlarged liver with splenomegaly. Other notable findings include jaundice, spider angioma, palmar erythema, Dupuytren contractures, asterixis, and hepatic encephalopathy.[17]

HCV genotyping, a quantitative HCV RNA viral load, liver function panel, comprehensive metabolic panel, thyroid function tests, complete blood cell (CBC) count, and prothrombin time with international normalized ratio are needed to establish baseline parameters and estimate the degree of liver disease. A higher baseline viral load prior to treatment does not indicate advanced or more progressive disease.[18] Additional testing by the hepatologist may be considered for patients with advanced liver disease and/or extrahepatic manifestations, including leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, and porphyria cutanea tarda through baseline serum cryoglobulins, and renal function studies. Genotype 1a patients may have NS5A resistance-associated variants (RAVs). Routine testing for RAVs is recommended in this genotype, as the presence of RAVs influences drug selection.[19]

The staging of fibrosis is important to determine the extent of fibrosis or cirrhosis. The urgency of treatment is confirmed by the staging, which predicts disease progression and clinical outcomes as well as treatment choice and duration.[18,20,21] In patients with absent or mild fibrosis, treatment initiation may be considered less urgent. Although liver biopsy has been the preferred method to assess the degree of inflammation and fibrosis, noninvasive tests such as liver elastography and direct biomarkers are becoming more widely used and accepted.[22-24]

The severity of liver cirrhosis can be classified as compensated (stage 1 with no varices present and stage 2 with varices present) and decompensated (stages 3 and 4) with signs of severe portal hypertension. Typically, cirrhotic individuals are graded by the Model for End-stage Liver Disease score or Child-Pugh score. As the score increases, so does the risk of liver failure and the development of HCC.[18]

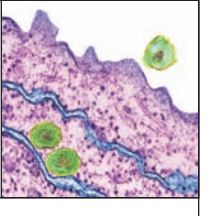
Patients with decompensated cirrhosis should be referred to a liver transplant center for management. Screening for HCC is important in patients with cirrhosis and chronic hepatitis C, both in the pretreatment phase as well as after achievement of viral eradication.[25] Although imaging modalities are not sensitive or specific as a primary diagnostic tool, they can identify masses, hepatomegaly, hepatic steatosis, splenomegaly, and complications of cirrhosis. Practice guidelines recommend imaging studies every 6 months for HCC screening in patients with cirrhosis.[18,20]

Pretreatment

Current practice guidelines strongly recommend treatment for nearly all HCV-infected patients.[18] All treatment-naive and treatment-experienced patients with compensated or decompensated liver disease due to HCV infection should be considered for therapy. The only exception to treatment is patients with limited life expectancy who cannot be remediated by treating HCV.[18,20]

A thorough assessment of the patient's mental health status and psychosocial history, the identification of behavioral risk factors for transmission and reinfection, and the exploration of past or current alcohol and/or substance abuse are important to pretreatment evaluation. The presence of chronic HCV infection often impacts a patient's quality of life. Discussions regarding values and beliefs, cultural and religious considerations, disclosure and privacy issues, and the stigma associated with HCV infection (especially when acquired from I.V. drug use) are essential.[26]

Depending on the medication regimen, pregnancy planning and contraception should be addressed in the pretreatment phase.



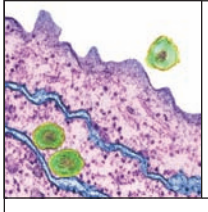
Cognitive-educational components to evaluate include health literacy, disease knowledge, modes of transmission, and attitude toward treatment. Language barriers affecting knowledge and adherence may also exist and should be addressed accordingly with trained interpreters.

Depending on the medication regimen, pregnancy planning and contraception (for both males and females) should be addressed in the pretreatment phase. This is especially relevant with regimens containing ribavirin, which is a known teratogen. Many of the newer HCV regimens have no data available on use of the drug in pregnancy or in breastfeeding; therefore, risk categories and recommendations are limited.

Lifestyle changes related to the use of illicit drugs and/or alcohol abuse/dependence are best implemented in the

pretreatment phase. Optimally, patients should maintain abstinence during treatment. Counseling and referrals for substance abuse/addiction treatment are critical prior to initiating pharmacologic therapy for HCV infection and in the holistic long-term management of chronic liver disease. In some settings, individuals who inject illicit drugs are being considered for HCV treatment concurrently with substance abuse rehabilitation. This population must be educated on harm reduction techniques. Abstinence from alcohol is important to optimize DAA therapeutic response and to reduce further liver injury.[18]

Education aimed at prevention of future infection, risk factors for transmission, avoidance of blood or sperm donation, and use of barrier methods to reduce sexual transmission risk in men who have sex with men (MSM) and individuals with multiple partners is essential. When indicated, patient adherence to harm-reduction strategies for I.V. and intranasal drug use should be established. Education regarding nonregulated tattooing, avoidance of sharing personal items potentially containing blood, and not sharing toothbrushes with household members is imperative because HCV can remain viable for several weeks outside the infected host.[27]



No DAA should be given as monotherapy, so DAAs from different classes are combined to achieve reduction in HCV viral load.

A review of all medications and complementary/alternative agents the patient is taking should be addressed before beginning HCV therapy to avoid adverse reactions. Patients who plan to travel while on treatment should bring a sufficient medication supply so dosing is not interrupted. All medications should remain in their original labeled containers. Patients should also keep provider contact information with them should questions or concerns arise and if medical care is necessary during travel.

Optimal outcomes are achieved when clinician-patient communication is established in the pretreatment phase. The APRN can collaborate with the patient in planning for treatment, optimizing physical and psychological well-being, and maintaining adherence.[26] Excellent resources for patients and healthcare professionals are available through the American Liver Foundation (www.liverfoundation.org).

Antiviral therapy

Combination therapy has been the mainstay of HCV treatment since 1998.[28] In 2000, pegylated interferon and ribavirin therapy were approved, which increased success rates to 40% to 56%.[11,29] In 2011, the first DAAs (telaprevir and boceprevir) were approved for use in genotype 1 infection with pegylated interferon and ribavirin. Success rates increased to 68% to 75% while reducing the length of therapy to 24 weeks.[30,31] However, the adverse reaction profile showed poor tolerability, especially in patients with cirrhosis and are no longer given in current HCV regimens.

In 2013, a second-generation NS3/4A protease inhibitor (simeprevir) and a nucleotide analog NS5B polymerase inhibitor (sofosbuvir) were approved to be used along with pegylated interferon and ribavirin for patients with genotype 1 infection with a success rate at 89%.[32] The current interferon-free landscape has several classifications of oral, DAA medications, many now delivered in a single fixed-dose combination pill given once per day for shorter treatment durations.

The mechanism of action of these medications targets specific proteins of the viral genome to inhibit viral replication. The protease inhibitors target the NS3/4A serine protease to inhibit the cleavage of this protein-blocking HCV replication. The NS5A inhibitors target a different nonstructural protein to block replication at the stage of membranous web biogenesis.[33]

Both of these have potent antiviral activity but exhibit a low barrier to viral resistance. The NS5B inhibitors are divided into two main classes: the nucleos(t)ide inhibitors (sofosbuvir), which cause premature chain termination by binding to the active site of the NS5B RNA polymerase with a high barrier to resistance; the other being the nonnucleotide inhibitors, which bind outside the active site, causing a conformational change.[34] Some of these medications are genotype specific, and others are pangenotypic. No DAA should be given as monotherapy, so DAAs from different classes are combined to achieve rapid and durable reduction in HCV viral load. In some regimens, ribavirin may still be used to improve success rates.[18] The goal of HCV therapy is viral eradication or cure as measured by aviremia (no detectable virus) 12 weeks after the last dose of medication therapy.[18]

HCV drug regimens for treatment-naive patients without cirrhosis

Expanded treatment options with DAAs, interferon-free regimens, and emerging pangenotypic agents offer multiple drug regimens for HCV infection cures. The American Association for the Study of Liver Diseases (AASLD) has extensive evidence-based resources available for healthcare providers who care for patients with liver disease

(www.aasld.org). Specifically, for hepatitis C, AASLD in collaboration with the Infectious Diseases Society of America (IDSA) have developed clinical guidelines titled *Recommendations for Testing, Managing, and Treating Hepatitis C*, which provide comprehensive HCV guidance for providers (www.hcvguidelines.org).[18] The AASLD/IDSA website provides recommendations for patients who are initiating HCV therapy by HCV genotypes and includes treatment of patients without cirrhosis and patients with compensated cirrhosis. This information is continually updated with the best available evidence and is readily accessible on the AASLD/IDSA website.

Roles for the APRN in the assessment and management of patients with HCV infection continue to develop across multiple settings, encompassing pretreatment evaluation and patient education, monitoring during treatment, and follow-up for long-term liver health after sustained virologic response (SVR) is achieved. APRNs are positioned to play a pivotal role in chronic hepatitis C in the new era of DAAs where successful outcomes for viral eradication are likely and treatment is well tolerated. APRNs involved in the care of these patients must be knowledgeable about specific drug regimens for tailored treatment as well as optimization of liver health following SVR.

DAAs target HCV through inhibition of viral replication. The combinations of two or three oral DAAs from different classes target viral enzymes and proteins across the virus lifecycle, improving efficacy with high barriers to resistance.

DAAs have favorable safety profiles and low occurrence of adverse reactions (unlike prior regimens). Treatment duration for treatment-naive patients is 8 to 12 weeks, and patients with advanced liver disease may require a 24-week duration of therapy. Options will vary depending on genotype, cirrhosis status, and previous treatment experience. Five options for genotype 1a treatment-naive patients without cirrhosis are currently FDA approved.

Elbasvir and grazoprevir. This fixed-dose combination contains elbasvir, an HCV NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor. It is given as a once-daily combination pill for 12 weeks. Lab testing for the presence of NS5A RAVs is indicated prior to prescribing. Baseline NS5A RAVs are a strong predictor of treatment outcomes, and if therefore detected, an addition of weight-based ribavirin and extension to 16 weeks of therapy is an alternative approach. SVR rates are over 95%.[35]

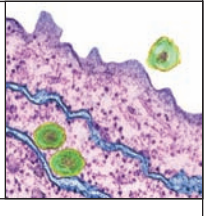
Ledipasvir and sofosbuvir. Ledipasvir is a potent inhibitor of HCV NS5A, a viral phosphoprotein that plays an important role in viral replication. Sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase, the key enzyme mediating HCV RNA replication. The ledipasvir and sofosbuvir combination is given as a fixed-dose daily pill for 12 weeks. SVR rates range from 93% to 99% across studies with highest cure rates in patients without cirrhosis.[36]

In June 2016, a combination of sofosbuvir (NS5B inhibitor) and velpatasvir (NS5A inhibitor) was approved in a fixed-dose combination as a pangenotypic (G1-G6) regimen. This is given in a 12-week regimen with SVR rates of 98%.[18]

Ombitasvir, paritaprevir, and ritonavir with dasabuvir. With this regimen, ombitasvir, paritaprevir, and ritonavir are combined as a fixed-dose tablet, and dasabuvir is a separate tablet. Ombitasvir is an NS5A inhibitor with potent pangenotypic antiviral activity, paritaprevir is an inhibitor of the NS3/4A serine protease, and ritonavir is a potent inhibitor of CYP3A4 enzymes that is used as a pharmacologic booster for paritaprevir. Dasabuvir is a nonnucleoside NS5B polymerase inhibitor. This combination is given with weight-based ribavirin for 12 weeks. Ribavirin may potentially reduce viral breakthrough and improve SVR rates in genotype 1a patients. The weight-based dosages of ribavirin are given twice daily, and the SVR rates range from 97% to 99%.[37]

Sofosbuvir and simeprevir. Sofosbuvir, a nucleotide analog inhibitor of HCV NS5B polymerase, and simeprevir, second-generation NS3/4A HCV protease inhibitor, are given together for 12 weeks; however, the two drugs are not FDA approved as a regimen. SVR rates equal or exceed 92%; however, it may be lower in cirrhotics.[38,39]

APRN roles in the assessment and management of patients with HCV infection continue to develop across multiple settings.



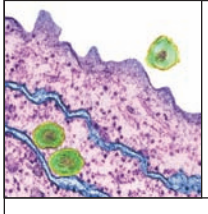
Sofosbuvir and daclatasvir. Sofosbuvir with daclatasvir daily for 12 weeks is another treatment option. The exact mechanism by which daclatasvir inhibits the NS5A replication complex is unclear, but it is believed that it inhibits viral RNA replication and virion assembly. SVR rates are reported at more than 95% across populations in clinical trials.

Genotype 1b treatment options are the same as genotype 1a with the exception that ribavirin is not indicated with ombitasvir, paritaprevir, and ritonavir with dasabuvir in genotype 1b as it is in genotype 1a. In genotype 1a and 1b viral subtypes, ledipasvir and sofosbuvir can be considered for patients for 8 weeks (instead of 12 weeks) in

treatment-naive genotype 1 patients without cirrhosis who have pretreatment HCV RNA viral loads of less than 6 million international units (IU)/mL.[40] Not all real-world studies support the 8-week regimen, and the guidelines state that this should be done at the discretion of the practitioner. SVR rates in genotype 1b with all regimen options are over 95%.[18]

Two options are FDA approved for genotype 2 treatment-naive patients without cirrhosis. Option one is daily fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks. SVR rates are 99% with this regimen.[41] Option two is daily daclatasvir with sofosbuvir for 12 weeks; while not approved by the FDA for this, genotype studies have shown effectiveness.[42,43] Daclatasvir dosing may need to be adjusted when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors.[18]

Genotype 3 infection has been the most challenging to achieve high SVR rates; however, a new regimen recently received FDA approval for use in this genotype. Daily fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks is recommended. Another option for genotype 3 is sofosbuvir and daclatasvir for 12 weeks. SVR rates are 97% to 98% with these regimens.[44,45]



Common adverse reactions of direct-acting antivirals include fatigue, headache, nausea, muscle/joint pain, and mild flulike symptoms.

Four treatment options are available for genotype 4 patients. The most commonly prescribed option is a fixed-dose combination of ombitasvir, paritaprevir, and ritonavir with the addition of weight-based ribavirin for 12 weeks. This regimen has shown a 100% SVR rate in clinical trials with limited postapproval studies.[46] Elbasvir and grazoprevir or ledipasvir and sofosbuvir or velpatasvir and sofosbuvir for 12 weeks can also be used in this genotype with SVR rates above 97%.[18]

While genotype 5 and 6 are less common, two options are approved for use. Ledipasvir and sofosbuvir or velpatasvir and sofosbuvir for 12 weeks is recommended with SVR rates of 95% to 100%.[47]

For those patients with cirrhosis and/or those who have been previously unsuccessfully treated for HCV, refer to the AASLD/IDSA guidelines for additional recommendations based on genotype. All of these approved DAA agents carry a class-wide FDA warning for individuals coinfected with hepatitis B (HBV) and HCV due to the risk of HBV reactivation during or after HCV treatment (www.fda.gov).

Monitoring during treatment

All patients receiving treatment for HCV infection should be assessed for therapeutic response; this is typically done at week 4 and at the end of therapy by HCV-PCR RNA viral load testing. In most cases, aviremia occurs by week 4, although detectable virus does not typically alter the course of a treatment regimen. It is important to know that despite high cure rates with DAAs (over 95% in most cases), some treatment-emergent resistance is being seen as more patients are being treated.[18]

Many commonly used drugs interact with DAAs and can lead to toxicity or decreased effectiveness of the DAAs or concomitant drugs. An HCV drug interaction checker is recommended for all prescribing clinicians prior to beginning treatment (www.hep-druginteractions.org).[48]

The most commonly reported adverse reactions of DAAs include fatigue, headache, nausea, muscle/joint pain, and mild flulike symptoms. Potential skin reactions include rashes and photosensitivity (sunscreen should be used). Sleep disturbances/insomnia are also reported. Anemia can occur in ribavirin-containing regimens and may require ribavirin dose adjustment. An increase in serum bilirubin and elevation of liver enzymes may also occur during treatment. Monitoring of the CBC and comprehensive metabolic panel should be done at baseline and during treatment as indicated to assess for safety and tolerability.[18]

Serial visits during treatment with necessary lab testing and monitoring for adverse reactions is important throughout treatment. Evaluation of patient adherence, which is essential to viral eradication, is also done at each visit. Individualized treatment is best achieved through ongoing communication between the APRN and the patient's hepatologist, primary care provider, and other clinicians involved in the patient's care during HCV treatment.

New technology-enabled approaches that incorporate tools and resources are also available to help providers manage patients in between office visits. Care management pathways for HCV-related liver disease have been developed that provide personalized treatment, communication between patients and providers, and strategies to improve adherence and lifestyle choices as well as address comorbid substance abuse and mental health issues. Pretreatment, through treatment, and posttreatment support are essential to ensure the benefits of viral eradication, help patients maintain liver health, and continue surveillance for liver disease complications.[49]

Posttreatment considerations

An end-of-treatment (EOT) response, defined as aviremia, is tested by serum quantitative HCV-PCR RNA viral load

testing. EOT viral load is checked at completion of the HCV medication course. Viral load is repeated at 12 weeks following EOT, at which time patients who remain aviremic are considered to have an SVR. SVR is considered a durable virologic cure with chance of relapse at less than 1% in individuals who achieve SVR. Relapse is defined as any viremia that occurs after an EOT response.[50]

Individualized annual monitoring may be performed thereafter at the clinician's discretion, especially in patients at risk for reinfection (I.V. drug users, MSM, prison populations). Following SVR, antibodies to the HCV typically remain detectable indefinitely. Patients must be aware that the presence of antibodies, in the absence of viremia, does not indicate active HCV infection and that they will likely remain antibody positive for life. Accordingly, antibodies do not confer immunity to reinfection. Retesting for HCV in treated patients should always be done by viral load testing, not by HCV antibody testing.[18]

The APRN must be well informed regarding the potential sequelae of HCV infection. Posttreatment visit scheduling is indicated for resolution of any treatment-related adverse reactions. Although it is well established that eradication of HCV reduces risk of progression of liver disease, other factors confer risk for advancing fibrosis and cirrhosis and hepatic decompensation.

HCC is a well-known risk in patients with advanced fibrosis/cirrhosis, and regular screening with imaging for HCC should be done every 6 months. Established guidelines should be followed in monitoring of all patients with chronic liver disease, especially those with more advanced fibrosis including cirrhosis. Clinical guidelines recommend interval assessment of fibrosis via noninvasive methods. It is essential to educate patients on an ongoing basis regarding risk factors for reinfection and fibrosis progression.[18,50]

Special considerations

Many patients have comorbid conditions or special considerations that should be assessed when making treatment decisions, such as kidney impairment or end-stage kidney disease, fatty liver disease/steatosis, coinfection with HBV or HIV, and post solid organ transplant patients. Another factor to consider is the use of concurrent medications that may be affected by or impact the efficacy of the HCV regimen. The AASLD/IDSA guidelines address many of these concerns.

Ongoing developments

Work continues toward absolute cure and optimal health outcomes in the battle against chronic HCV of all genotypes. The intent is to close the gaps in treatment responses for hard-to-treat resistant strains, for patients decompensated due to cirrhosis or with previous treatment failures, and for patients with limited kidney function.[51] Shorter course treatment durations with second- and third-generation DAAs and new drug combinations with reduced pill burden are under investigation for achieving viral eradication.

The anticipated new combination of DAAs using sofosbuvir (NS5B inhibitor) and velpatasvir (NS5A inhibitor) was FDA approved June 2016. The ASTRAL Phase 3 Program conducted a 5-armed study assessing the effectiveness of sofosbuvir and velpatasvir, a second-generation NS5A inhibitor, using a 12-week regimen in HCV genotypes 1-6. Patients included were treatment naive, treatment experienced, noncirrhotic, cirrhotic, and those coinfected with HIV. The study reported SVR rates regardless of genotype (pangenotypic), prior treatment, and coinfection equal or superior to prior approved medication regimens.[52]

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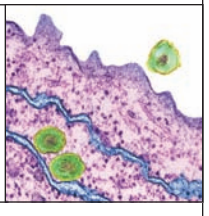

The integrated data revealed that the most resistant genotype 3 had the lowest efficacy to treatment at 12 weeks (95%) across ASTRAL-1, -2, and -3. RAVs are the result of viral replication errors that impact amino-acid chains in the virus. These "wild" variants affect DAA efficacy, specifically when these errors occur at susceptible positions in HCV genotypes 1a and 3.[18] Retreatment using sofosbuvir and velpatasvir in addition to ribavirin for 24 weeks for treatment failures in the 12-week regimen resulted in high SVR rates 12 weeks posttreatment and was well tolerated.[53]

The Surveyor studies are ongoing to evaluate safety and efficacy for a pangenotypic regimen using ABT-493 300 mg, a next-generation protease inhibitor and ABT-530 120 mg, an NS5A inhibitor. This once-daily combination given for 8 or 12 weeks is well tolerated with promising response rates in naive and treatment-experienced patients.[54]

Implications for APRNs

This is an exciting time in the era of hepatitis C treatment, with many more individuals reaching cure with newer DAA regimens. Recent registry data report the durability of SVR for the DAA regimens at 99.7% over a 3-year period.[55] It is well known that reaching SVR impacts overall morbidity and mortality for individuals with chronic hepatitis C.

Therefore, it is critical that patients are appropriately screened and linked into appropriate care. The APRN is vital to the identification, education, evaluation, treatment, and management of patients with chronic hepatitis C. It is only through a whole team approach that the goal of viral eradication, a halt in new cases of viral transmission, and an impact in improvement of liver disease outcomes will be reached. NP

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