Educational Objectives
- Recognize the burden of disease and the risk factors associated with hepatitis C virus (HCV) infection
- Describe the new point-of-care testing for HCV antibodies
- Discuss updates in screening mandates and linkage to care guidelines for HCV
- Analyze recently approved and emerging treatment options and understand how new agents are improving the standard of care for all HCV patients
**Epidemiology – The Silent Epidemic**

Hepatitis C is a blood-borne disease of the liver that is caused by infection with the hepatitis C virus (HCV), which can lead to serious liver problems such as cirrhosis and liver cancer. Approximately 4.1 million Americans (~1.6%) have evidence of HCV infection, with about 20,000 new infections occurring annually. Approximately 75%–85% of infected persons are chronically infected, placing them at risk for hepatocellular carcinoma (HCC), cirrhosis, and extrahepatic complications that develop over the decades following onset of infection. Data from 1999 to 2007 indicate that deaths from HCV have increased significantly, whereas those linked to hepatitis B (HBV) remained constant and HIV-associated mortality decreased.

One very important aspect to the fundamental understanding of HCV is that the vast majority of individuals who are infected are unaware of their infection status. In one study looking at more than 3 million individuals with HCV infection, only 825,000 knew they were infected. This suggests that the vast majority of uninfected patients in the United States are actually unaware that they have the virus.

**Natural History – Disease Burden Is Increasing**

Another important aspect to be realized in the epidemiology of HCV is that, although the number of patients infected with HCV peaked around the year 2000 and is now decreasing, the number of patients infected for more than 20 years is dramatically rising. These patients infected for more than 20 years are at risk for developing cirrhosis and other HCV-related complications, and it is estimated that 37% of HCV infected individuals will be cirrhotic by 2020.

HCV-associated, end-stage liver disease is the leading indication for liver transplantation in adults and a leading cause of HCC in the United States. Unfortunately, if these patients are not candidates for liver transplantation, there is a good chance they will succumb due to their liver disease. The prevalence and health outcomes of persons infected...
with HBV, HIV, or HCV are commonly compared in the United States. As shown in the figure below and previously noted, the number of deaths resulting from HIV infection is steadily decreasing while the number of deaths from HBV has essentially remained constant. However, deaths resulting from chronic HCV are dramatically increasing. HCV was the contributing or underlying cause of death for more than 15,000 individuals in 2007.5

In the United States, the prevalence of anti-HCV antibody among persons born between 1945 and 1965 is 3.25%, five times higher than among adults born in other years.14 As mentioned previously, this birth-cohort accounts for approximately 73% of HCV-associated mortality.7 The majority of these patients were likely infected during the 1970s and 1980s when new infection rates were highest.15 In addition, many of them have no idea that they are infected and are therefore not seeking treatment.

Based on these facts, the Centers for Disease Control and Prevention (CDC) have augmented previous recommendations for HCV testing. It is now recommended that persons born between 1945 and 1965 undergo one-time HCV testing without prior ascertainment of HCV risk. In addition, the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD), in collaboration with the International Antiviral Society–USA (IAS–USA), have developed evidence-based, expert-developed recommendations for HCV management, which include recommendations on HCV testing and linkage to care. This “living document” echoes the CDC’s recommendation for one-time birth cohort HCV testing. These guidelines also recommend that other persons should be screened for risk factors for HCV infection, and testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection. Furthermore, persons who inject drugs and HIV-seropositive men who have unprotected sex with men should undergo annual HCV testing. Finally, periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.16

It’s also important to recognize that the number of deaths related to HCV infection increases as the population of persons infected with HCV ages. As shown below, the burden of death from HCV is greatest in individuals between the ages of 45 to 64.5

HCV Testing and Linkage to Care
Without changes to current case identification and treatment, the cost of overall annual HCV medical spending for patients is expected to more than double from $30 billion to over $85 billion over the next 20 years.12 Furthermore, deaths from HCV are projected to increase to 35,000 a year by 2030.11
Once the need for HCV testing is established, appropriate test(s) need to be performed. Shown below is the CDC-recommended HCV testing algorithm.\textsuperscript{16}

The first test is a screening test to evaluate for the presence of anti-HCV antibodies, which indicates exposure, at some point, to HCV. The OraQuick\textsuperscript{®} HCV Rapid Antibody Test allows for point-of-care testing and provides results in 20 minutes.\textsuperscript{17} One advantage to such a test is that fewer patients may be lost to follow-up since results are available immediately allowing physicians to discuss with patients the need for further testing.

Anti-HCV antibody screening can also be performed with an indirect immunoassay with a sensitivity and specificity similar to those of FDA-approved, laboratory-based HCV antibody assays. Examples include 2 enzyme immunoassays (EIAs): 1) Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois; and 2) ORTHO\textsuperscript{®} HCV Version 3.0 ELISA, Ortho-Clinical Diagnostics, Raritan, New Jersey; and one enhanced chemiluminescence immunoassay (CIA): VITROS\textsuperscript{®} Anti-HCV assay, Ortho-Clinical Diagnostics, Raritan, New Jersey.\textsuperscript{16} The result of the anti-HCV antibody test determines next steps:

- If a patient is anti-HCV antibody negative, no additional testing would be required in most cases because there is likely no infection. Among persons with a negative anti-HCV test who are suspected of having HCV infection, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past 6 months; testing for HCV RNA can also be considered in persons who are immunocompromised.\textsuperscript{16}

- If a patient is anti-HCV antibody positive, this should not be considered a definitive diagnosis for HCV infection. A positive test result for anti-HCV indicates either current (active) HCV infection (acute or chronic), past infection that has resolved, or a false-positive test result. The positive HCV antibody test should be confirmed with an FDA-approved HCV RNA assay to confirm the presence of actively replicating virus.

- If a patient is positive for anti-HCV but negative for HCV RNA, repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of liver disease, or if there is concern regarding the handling or storage of the test specimen.\textsuperscript{16}

- If a patient is positive for anti-HCV and positive for HCV RNA, then this patient has active HCV infection and should be appropriately linked to care, beginning with an evaluation by a practitioner with expertise in assessing liver disease severity and HCV treatment options.\textsuperscript{16}
However, in most cases, it is not necessary to recommend changes in sexual practices for individuals in a long-term monogamous relationship. In young patients, particularly in individuals with multiple sexual partners, the use of barrier mechanisms should be recommended to try to prevent HCV transmission.

Persons with active HCV infection should also receive education and interventions aimed at reducing progression of liver disease. Patients should be counseled on abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be implemented. It is also recommended that patients check with healthcare providers before taking any prescription medications, over-the-counter medications, or oral supplements, as these can also potentially contribute to advanced liver damage. Additional evaluations are warranted for other conditions that may accelerate liver fibrosis, including HBV and HIV infections. Vaccination against hepatitis A (HAV) and HBV is recommended for all persons with HCV infection.

Managing Patients With HCV

As previously discussed, the first step in the management of HCV is appropriate linkage to care. This involves evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy. Treatment is recommended for patients with chronic HCV infection. The goal of treatment of HCV-infected patients is to reduce all-cause mortality and liver-related, health adverse consequences, including end-stage liver disease and HCC. This goal is realized by the achievement of virologic cure, as evidenced by a sustained viral response (SVR). SVR is defined as the continued absence of detectable HCV RNA at least 12 weeks after completion of therapy. SVR is a marker for cure of HCV infection and has been shown to be durable in large prospective studies in more than 99% of patients followed for 5 years or more. In summary, linking patients to care and treatment is a critical component of the strategy to reduce the burden of disease.

Until 2011, the standard of care for the treatment of HCV was the combination of pegylated interferon and ribavirin. This regimen involves subcutaneous self-injections of pegylated interferon and has limited efficacy and poor tolerability. Clinicians now have more sophisticated antiviral therapies to choose from that have dramatically improved the management of HCV.

Direct acting antivirals (DAAs) target the virus itself, instead of the host, and the first two agents (boceprevir and telaprevir) were approved in 2011. In 2013, two additional DAAs (ie, simeprevir, sofosbuvir) were approved and offered additional benefits. Simeprevir is an oral NS3/4A protease inhibitor for the treatment of HCV genotype 1 (in combination with peginterferon and ribavirin). Sofosbuvir is an oral nucleotide analog NS5B polymerase inhibitor for the treatment of chronic HCV. Sofosbuvir is the first direct acting antiviral agent approved for use in non-genotype 1 patients and does not require co-administration of peginterferon. The 2013 approval of sofosbuvir for genotype 1 required the co-administration with peginterferon and ribavirin.

In 2014, an additional second generation DAA was added to the HCV treatment armamentarium. Ledipasvir is an oral HCV NS5A inhibitor and is available only in combination with sofosbuvir. This combination is the first once-daily single tablet oral regimen for the treatment of chronic hepatitis C genotype 1 infection in adults.

In December 2014, another highly effective all oral treatment regimen was approved by the FDA. The 3D regimen, with or without ribavirin, contains drugs with three distinct mechanisms of action - ombitasvir (an NS5A inhibitor) + ritonavir, paritaprevir (an NS3/4A protease inhibitor) and dasabuvir (a non-nucleoside NS5B polymerase inhibitor).
Therefore, it is clear that following new screening strategies will help identify more patients with HCV. As more patients are diagnosed and cured, morbidity and mortality rates due to HCV should decrease over time.

References