There are over 180 million people with chronic hepatitis C (HCV) infection worldwide with between 2.7 and 3.9 million people in the United States alone. HCV most significantly affects Asia and Africa, with rates up to 15% in countries such as Egypt and up to 30% in certain regions such as Punjab, Pakistan. HCV places a significant burden on the public health infrastructure, as it remains the leading cause of chronic liver disease, accounting for 50% to 75% of primary liver cancers and being responsible for 30% of all liver transplantations. It was estimated to have cost the United States $5.5 billion in 1997, comparable to the national cost of asthma of $5.8 billion in 1994. This number is only expected to grow as the current HCV population ages, increasing overall rates of end-stage liver disease and of primary liver cancer.

The evolution of directly acting antivirals has ushered in a new era for chronic HCV. The main mechanism of action of most DAAs is the inhibition of an enzyme (protease or polymerase), although others inhibit the assembly of the replication complex (NS5A inhibitors). Such all-oral therapy regimens are very well tolerated and achieve high response rates even without the backbone of pegylated interferon. NS3/4A is a serine protease essential for viral replication. Inhibitors of NS3/4A have a high potency but a low barrier to resistance and are not effective against all HCV genotypes. NS5A is a zinc-binding phosphoprotein that plays an important but currently unclear role in HCV replication. NS5B is an HCV RNA-dependent RNA polymerase, which plays a crucial role in HCV replication. Nucleotide inhibitors have been found to be pan-genotypic and possess high potency and a high barrier to resistance, as the active site of NS5B is highly conserved across all HCV genotypes. Nonnucleoside inhibitors allosterically target the NS5B region and inhibit the initiation stage of RNA synthesis. This class of inhibitors displays a low barrier to resistance, mild potency, and limited effectiveness across all HCV genotypes.

Ongoing drug development strategy has involved targeting several replication steps of the virus, and the drugs that act at various steps of the viral replication have been...
additive or even synergistic in their antiviral effects and have led to high SVR rates with much better tolerability than interferon-based regimens. Currently, as it stands, the role of ribavirin appears unclear in the therapeutic landscape of chronic HCV.

This issue of *Gastroenterology Clinics of North America* has a diverse range of topics and a highly recognized international author representation. Thus, it provides a global perspective on HCV infection. There are challenges unique to the various regions of the world and among these include the heterogeneity in host and viral factors, and, most importantly, the difficulty with access to expensive therapy. The issue has diverse topics of epidemiology, natural history, pathogenesis, and treatment options for the various populations, including those with the various genotypes, advanced liver disease, and other special populations, including children. I hope you find this issue useful in your understanding of the current status of HCV and also in your day-to-day practice.

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