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Hepatitis C is a major worldwide cause of liver morbidity and mortality. A substantial proportion of infected patients will develop chronic disease, which may progress over decades to cirrhosis. This can lead to decompensation and hepatocellular carcinoma. With the advent of the direct-acting antivirals, hepatitis C has become increasingly curable with limited adverse events and a shorter duration of therapy. This review discusses the evaluation process of the hepatitis C patient in the direct-acting antiviral era, including screening, clinical evaluation, drug-drug interactions, treatment urgency, and counseling.

**Meet the Classes of Directly Acting Antiviral Agents: Strengths and Weaknesses**  605  
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This article discusses direct-acting antiviral agents that target hepatitis C virus replication, their mechanism of action, strengths, and weaknesses. In addition, varying strategies using combinations of these agents are discussed.

**Regimens for the Hepatitis C Treatment-Naive Patient**  619  
Walid S. Ayoub and Tram T. Tran

Hepatitis C virus (HCV) infection is a leading cause of cirrhosis and hepatocellular carcinoma, globally. Most individuals infected with HCV are asymptomatic. The introduction of the newer direct-acting antiviral (DAA) therapies has led to achievement of treatment success rates of more than 90%. Sustained virologic response is the end point of therapy, and is considered a virologic cure. It is defined as undetectable HCV RNA 12 weeks after end of therapy. This article reviews current approved non-interferon-based therapy and data from clinical trials in treatment-naive patients with chronic HCV infection.

**Direct-Acting Antiviral Agents: Regimens for the Interferon Failure Patient**  629  
Tatyana Kushner and Vandana Khungar

Over the past few years, tremendous advances have been made in the treatment of hepatitis C with direct-acting antiviral agents (DAAs), allowing treatment options for patients who have failed prior treatment with interferon. In addition to interferon’s severe adverse effect profile, and the inability of many patients to tolerate it, prior interferon-containing regimens were not as effective in achieving sustained virologic response as
emerging therapies. New DAAs have demonstrated higher rates of sustained virologic response, shorter duration of treatment, and improved adverse effect profile.

**Mechanisms of Virologic Failure with Direct-Acting Antivirals in Hepatitis C and Strategies for Retreatment**

Vanessa Costilla, Neha Mathur, and Julio A. Gutierrez

The current standard of care for hepatitis C therapy is the combination of direct-acting antiviral (DAA) agents. These orally administered medications target the viral proteins and halt the hepatitis C virus lifecycle. Despite high cure rates with these novel drugs, virologic failure with DAAs are of mounting concern as real-world sustained virologic response 12 rates seem lower than expected. The mechanisms of virologic failure to DAAs are likely multifactorial, including baseline resistance variants, the efficacy of the agents used, and host factors. Salvage therapy for DAA virologic failures is an area of emerging research.

**Regimens for Cirrhotic Patients**

Paul Y. Kwo

Therapy for hepatitis C has entered the era of all-oral direct-acting antiviral agents. Sustained response rates are now greater than 90% for all genotypes, although patients with cirrhosis remain the most difficult to treat. There are limited data for patients with cirrhosis and with hepatitis C genotypes 4 and 6 with cirrhosis. Genotype 3 patients with cirrhosis need additional strategies to achieve the sustained virologic response rates seen in genotype 1 patients with cirrhosis. This article outlines the currently available therapies for patients with cirrhosis and hepatitis C across all genotypes, with suggested management strategies.

**Current Management of Hepatitis C Virus: Regimens for Peri-Liver Transplant Patients**

Varun Saxena and Norah Terrault

Chronic hepatitis C virus (HCV) infection currently remains the leading indication for liver transplant in the United States. However, recurrent HCV infection after transplant is universal in those who enter transplant with viremia resulting in reduced posttransplant graft and patient survival rates, caused in large part by progressive recurrent HCV disease. Therefore, successful treatment of HCV in the peri-transplant period, either before or after transplant, is paramount in ensuring improved posttransplant outcomes. This article reviews the experience to date treating HCV in waitlisted patients and liver transplant recipients and the unique challenges encountered when treating this population.

**Regimens for Patients Coinfected with Human Immunodeficiency Virus**

David L. Wyles

Hepatitis C virus (HCV) coinfection is prevalent in patients with human immunodeficiency virus (HIV) and has an accelerated disease course. Direct-acting antiviral (DAA) therapies that do not require interferon increase...
response rates to levels identical to those seen in HCV monoinfection. However, drug-drug interaction between antiretrovirals and HCV medication is the major consideration in deciding on the appropriate HCV therapeutic approach in patients with HIV. This article summarizes the currently available data with HCV DAAs in patients with HIV, and focuses on predicting and managing drug interaction to facilitate successful DAA-based HCV therapy in those with HIV.

Next-Generation Regimens: The Future of Hepatitis C Virus Therapy

John Vizuete, Hope Hubbard, and Eric Lawitz

The treatment of chronic hepatitis C virus (HCV) has undergone a period of rapid evolution. The era of combination direct antivirals has led to high rates of sustained viral response (SVR), limited toxicities, and more broad applicability across patient demographics. Even current therapies have their limitations, however, including genotype specificity and variable durations of treatment depending on the presence or absence of cirrhosis. Developing a fixed-duration pangenotypic regimen that can broadly treat all stages of fibrosis with equal rates of SVR in all patients, irrespective of treatment experience, is the goal of future therapies. This article reviews antivirals in development.