core promoter mutation. Patients infected with HBV in high replicative phase are at high risk for cirrhosis and hepatocellular carcinoma. Such patients and those who have already progressed to early cirrhosis are the primary candidates for antiviral therapy.

Currently, seven drugs are approved for the treatment of adults with chronic hepatitis B in the United States, including interferon-α and its pegylated form and five nucleos(t)ide analogues (lamivudine, telbivudine, adefovir dipivoxil, tenofovir disoproxil, and entecavir). The primary aim of therapy is to eliminate or permanently suppress HBV and thus reduce the activity of hepatitis and slow or limit the progression of liver disease. It is important to start therapy with a nucleos(t)ide analogue that has a high genetic barrier to resistance, such as entecavir or tenofovir, as first-line therapy. Long-term follow-up studies have shown interferon-based therapy increases HBsAg seroclearance over time. HBsAg seroclearance is less common in patients who are treated with nucleos(t)ide analogues rather than interferon-based therapy.

In patients with HBV and HDV coinfection, the fate of HDV is determined by the host response to HBV, which in more than 95% of adults results in viral clearance. By contrast, HDV superinfection of an individual with chronic hepatitis B usually results in chronic HDV infection. Treatment with nucleos(t)ide analogues is not effective in reducing HDV replication. The accepted practice for treatment of chronic HDV infection is weekly pegylated interferon for at least 48 weeks. In patients with a high concentration of HBV DNA, the addition of a potent nucleos(t)ide analogue to inhibit HBV replication is logical, but long-term effectiveness has yet to be defined.

Chronic hepatitis C develops in up to 75% of individuals who are acutely exposed to HCV. Approximately 1.6% of the United States population (4.1 million people) are positive for antibodies to HCV (anti-HCV), and 3.2 million of them have chronic infection. Up to 20% of HCV cases progress to cirrhosis, usually within 20 years after infection. HCV has six major genotypes, of which genotype 1 is the most common in the United States, followed by genotypes 2 and 3. The genotype determines the treatment regimen and duration of therapy. The goal of antiviral therapy is to achieve an sustained virologic response (SVR), defined as undetectable HCV RNA levels (aviremia) 6 months after treatment discontinuation. As many as 80% of patients with genotype 2 or 3 disease achieve SVR after receiving dual therapy consisting of weekly pegylated interferon-α and daily ribavirin for 24 weeks. In contrast, only about 50% of patients with genotype 1 disease can achieve SVR after receiving the dual therapy for 48 weeks. With the addition of direct-acting antivirals (DAA), especially the first generation NS3/4 protease inhibitors boceprevir and telaprevir (both approved in May 2011), to pegylated interferon and ribavirin, up to 70% of patients with genotype 1 hepatitis C can achieve SVR in 24 weeks. However, the addition of a first-generation DAA to interferon- and ribavirin-based treatment for hepatitis C results in increased potential for side effects, drug-drug interactions, and a high pill burden. With the addition of the once daily, second generation protease inhibitor simeprevir (approved in November 2013) and the NS5B polymerase inhibitor sofosbuvir (approved in December 2013) to pegylated interferon and ribavirin, up to 90% of patients with genotype 1 hepatitis C can achieve SVR in as little as 12 weeks. For the first time, patients with genotype 2 and 3 hepatitis C can be treated with an interferon-free regimen consisting of sofosbuvir and ribavirin. Several new DAAs with novel mechanisms of action—such as NS5B polymerase inhibitors, NS5A inhibitors, and new NS3/4 protease inhibitors—are either under review for approval or under development.

Among organ transplant recipients, the consumption of game meat, pork products, or mussels may result in HEV infection, which is most commonly asymptomatic without jaundice. About 60% of such infections become chronic, and up to 10% of patients progress to cirrhosis. Treatment includes careful reduction in immunosuppression, which results in viral clearance in 30% of patients on ribavirin monotherapy.

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) has several clinical forms that share typical histologic findings including significant hepatic inflammation with a preponderance of plasma cells and fibrosis. Type 1, or classic, AIH is characterized by the presence of hypergammaglobulinemia as well as ANA or anti–smooth muscle antibodies (ASMA). Type 2 AIH is characterized by the presence of anti–liver/kidney microsomal antibodies (anti-LKM1) and the absence of ANA and ASMA. The type 1 variant can affect people of any age or gender, whereas the less common type 2 variant primarily affects girls and young women. A third type of AIH with antibodies to soluble liver antigen or liver-pancreas antigen (anti-SLA/LP) is no longer considered a unique entity because these antibodies may be found in type 1 and 2 variants as well. There are also uncommon overlap variants of AIH that have features of both AIH and other liver diseases such as PBC or PSC.

There are no pathognomonic features of AIH, and the diagnosis is made by a combination of factors. A simplified diagnostic algorithm that includes the presence of autoantibodies, hypergammaglobulinemia, typical liver histology, and absence of viral hepatitis has proved useful in identifying patients with AIH. Extrahepatic manifestations such as amenorrhea, rashes, acne, vasculitis, thyroiditis, and Sjögren's syndrome are common. Evidence of hepatic failure and the presence of chronic disease on liver biopsy are often discernable at the time of diagnosis. Indications for treatment include abnormal liver function tests and significant hepatic inflammation on biopsy.

Corticosteroids are the mainstay of treatment, typically in combination with azathioprine as a steroid-sparing agent. This regimen is efficacious in most patients (>80%) and in many instances prolongs survival.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) has a spectrum of presentations from simple steatosis, which usually does not progress to advanced liver disease, to NASH, which may exhibit or lead to cirrhosis. It is the most common cause of abnormal liver function tests among adults in the United States and western Europe. NAFLD is commonly seen in people with central obesity, hypertension, diabetes, and hyperlipidemia, although it can be observed in persons with normal weight as well. Insulin resistance plays a central role in the pathophysiology of NAFLD. Estimates indicate that about 30 million Americans have NAFLD; of these, 8.6 million have NASH and almost 20% have signs of