1000 medications and supplements are known to cause hepatotoxicity. Antibiotics remain the drugs most commonly responsible for DILI in the United States and Europe; the annual incidence of antibiotic-associated DILI is 1 in 10,000 to 100,000 individuals.

DILI may be classified by the pattern of liver injury observed. *Acute hepatocellular injury* is characterized by elevated levels of serum ALT and minimal elevations of serum ALP. *Cholestatic injury* is characterized by a disproportionately elevated level of ALP, which is synthesized and released by injured bile ducts. Liver injury that has both hepatocellular and cholestatic features is called *mixed liver injury*. DILI can also be classified into two broad categories, predictable and unpredictable, depending on the hepatotoxins involved. Predictable hepatotoxins, such as acetaminophen and carbon tetrachloride, cause dose-dependent liver injury. Acetaminophen is now the leading cause of life-threatening acute liver failure in the United States and Europe. Unpredictable hepatotoxins cause DILI in a so-called idiosyncratic fashion. Idiosyncratic reactions are difficult to predict and are not dose dependent; they occur relatively rarely in individuals with unique genetic and environmental characteristics.

Clinical and Laboratory Manifestations

DILI symptoms are similar to those associated with viral hepatitis and include malaise, anorexia, nausea and vomiting, right upper quadrant abdominal pain, jaundice, acholic stools, and dark (tea-colored) urine. Patients with cholestatic DILI may also have pruritus. Fever and rash, hallmarks of hypersensitivity, may be present with DILI caused by certain drugs such as anticonvulsants and sulfamethoxazole-trimethoprim. Cholestatic or mixed hepatitis related to amoxicillin-clavulanic acid (Augmentin) may develop shortly after the drug has been stopped, usually within 2 to 3 weeks. Nitrofurantoin (Macrobid) characteristically causes a chronic hepatitis after many weeks, months, or even years of therapy and is often associated with the presence of serum antinuclear antibodies (ANA).

Diagnosis

The diagnosis of DILI is challenging because of the lack of specific or uniform clinical features or laboratory tests in the majority of cases. A high level of suspicion for DILI is essential for diagnosis, as is the exclusion of other possible causes of liver injury. The Russel-Uclaf Causality Assessment Method (RUCAM) provides objective and consistent assessment but can be cumbersome for routine clinical use. Moreover, a recent study conducted by Grant and Rockey suggested that expert opinion outperforms RUCAM in making a diagnosis of DILI. There is definitely a need for a simple, accurate, and reproducible method for diagnosing DILI.

Hepatitis E appears to be a small but important alternative diagnosis for suspected DILI. Of 318 patients in the multicenter U.S. Drug-Induced Liver Injury Network (DILIN) with suspected drug hepatotoxicity, 9 (3%) were found to be positive for HEV IgM.

Treatment

The mainstay of management of DILI is withdrawal of the offending agent and supportive care, which is usually sufficient in cases of mild to moderate DILI. Reexposure to the implicated drug should be avoided. Specific therapies are available for some types of DILI. Timely administration of *N*-acetylcysteine (NAC) for acetaminophen overdose can be lifesaving. NAC may also improve outcomes of patients with early acute liver failure from a variety of other causes. Corticosteroids are probably ineffective for DILI from most drugs; however, a short course of steroids is sometimes used for treatment of immune-mediated DILI with the manifestations of rash, fever, and eosinophilia. Ursodeoxycholic acid is safe and may possibly hasten the resolution of jaundice and pruritus.

Complication and Prognosis

With supportive care and discontinuation of the offending drug, mild to moderate DILI usually resolves rapidly. Cholestatic liver injury may take many weeks and even months to completely resolve. Occasionally, cholestatic DILI can evolve into permanent bile duct injury with so-called vanishing bile duct syndrome. Patients who develop acute liver failure manifesting with hyperbilirubinemia, coagulopathy, and hypoalbuminemia may need liver transplantation.

CHRONIC HEPATITIS

Chronic hepatitis is defined as a sustained inflammatory process in the liver lasting longer than 6 months. On initial presentation, chronic hepatitis can be difficult to differentiate from acute hepatitis on clinical or histologic criteria alone. Except for hepatitis A, acute viral hepatitis, especially that caused by HBV or HCV, can ultimately lead to chronic hepatitis. Nonalcoholic steatohepatitis (NASH) is now the most frequent cause of chronic hepatitis in the United States and Western Europe. Several drugs can cause chronic hepatitis, the best recognized being methyldopa. In contrast to acute hepatitis, an etiologic agent is sometimes difficult to identify in cases of chronic hepatitis. The pathogenesis of these idiopathic forms may represent quiescent autoimmune disease, undetected past DILI or NASH, antibody-negative viral infection, or misdiagnosed cholestatic liver injury (e.g., primary biliary cirrhosis [PBC], primary sclerosing cholangitis [PSC]).

Chronic Viral Hepatitis

In Western countries, acute HBV infection usually occurs in adults; 5% to 10% of patients fail to clear the virus and develop chronic hepatitis. In other areas, childhood acquisition is common, and children who are infected within 2 years of birth have a much higher rate of chronic hepatitis B. HBV infection without evidence of any liver damage may persist, resulting in asymptomatic hepatitis B carriers. In Asia and Africa, many such carriers appear to have acquired the virus from infected mothers during infancy (vertical transmission).

Patients who are HBsAg and HBeAg positive and have high blood HBV DNA (>20,000 IU/mL), coupled with elevated serum aminotransferases, are in a high replicative phase (see Table 41-3). In contrast, patients in a low replicative phase are HBsAg and anti-HBe positive, have low blood HBV DNA (<20,000 IU/mL), and have near-normal or normal aminotransferase levels. Such patients can enter a high replicative phase and exhibit features of acute or chronic hepatitis B. A subgroup of patients with chronic hepatitis B who are HBeAg negative are still in a high replicative phase, as evidenced by high HBV DNA levels in blood. These patients likely have HBV with precore and/or