Mechanisms of Drug-induced Liver Injury 507
Liyun Yuan and Neil Kaplowitz

Drug-induced liver injury (DILI) represents a broad spectrum of liver manifestations. However, the most common manifestation is hepatocyte death following drug intake. DILI can be predictable and dose dependent with a notable example of acetaminophen toxicity. Idiosyncratic DILI occurs in an unpredictable fashion at low frequencies, implying that environmental and genetic factors alter the susceptibility of individuals to the insult (drugs).

Drug-Induced Cholestasis 519
Kalyan Ram Bhamidimarri and Eugene Schiff

Drug-induced cholestasis manifests as an acute self-limiting injury or as a chronic perpetuating injury, resulting in duct loss and cirrhosis. The number of drugs implicated in drug-induced cholestasis grows every year as new drugs are developed and approved. Other agents such as herbals, nutritional supplements, and complementary and alternative medicines are also reported to cause cholestatic liver injury. Recent literature on molecular transporters involved in bile transport has improved our understanding of patterns of drug-induced liver injury and the mechanisms of cholestasis. This article summarizes the probable offending drugs and the diagnosis and management of drug-induced cholestasis.

Drug-Induced Steatohepatitis 533
Vaishali Patel and Arun J. Sanyal

Nonalcoholic fatty liver disease (NAFLD) is currently the most common cause of chronic liver disease in the United States. The term NALFD was first used by Ludwig in 1980 to describe the presence of hepatic steatosis and steatohepatitis in a series of patients with no identifiable cause. Since then, our insight into the pathogenesis of NAFLD has expanded significantly. We now know that NAFLD is closely related to metabolic syndrome and chronic low-grade inflammation. In the following review, the authors summarize the current evidence about drugs that lead to hepatic steatosis and steatohepatitis and pathogenic mechanisms thereof.

Histopathologic Manifestations of Drug-induced Hepatotoxicity 547
Xuchen Zhang, Jie Ouyang, and Swan N. Thung

Drug-induced hepatotoxicity is underrecognized but increasingly identified as causing acute and chronic liver disease. Several prescription drugs,
over-the-counter medications, dietary and/or supplementary agents, and herbal products are hepatotoxic. Drug-induced liver injury mimics other primary acute and chronic liver diseases and it should be considered in patients with hepatobiliary disease. Certain drugs result in specific histopathologic patterns of liver injury, which may help in sorting out the responsible drug. The diagnosis of drug-induced hepatotoxicity is challenging. It involves excluding other possible causes, careful medication history, the latent period between drug exposure and symptom onset and/or abnormal liver tests, and histopathologic findings.

Clinical Manifestations and Treatment of Drug-induced Hepatotoxicity 565
Christin M. Giordano and Xaralambos B. Zervos

With an increase of prescription medication and herbal supplement use, drug-induced liver injury (DILI) has become an increasingly important entity. Because DILI is a usually readily treatable condition, it is essential for providers to reach a diagnosis in a timely fashion. Unfortunately, varied clinical presentations, difficulties in establishing causality, and lack of a gold standard diagnostic criterion may make early diagnosis difficult. This article seeks to define commonly used terminology, describe common clinical presentations of DILI, provide an overview of current diagnostic criteria, and provide management guidelines.

Drug-induced Acute Liver Failure 575
William M. Lee

Although acute liver failure caused by drug-induced liver injury comprises a small fraction of overall drug-induced liver injury, these patients require high resource use and have relatively poor outcomes. Drug-induced liver injury caused by idiosyncrasy more often leads to death or transplantation than does acetaminophen acute liver failure, but the number of patients in each category receiving a graft is roughly the same. Efforts in the future to improve outcomes should focus on more effective treatments and better methods to identify those that might experience poor outcomes.

Acetaminophen-related Hepatotoxicity 587
Chalermrat Bunchorntavakul and K. Rajender Reddy

Acetaminophen (APAP) is the leading worldwide cause of drug overdose and acute liver failure (ALF). Single overdose ingestion and therapeutic misadventure may cause hepatotoxicity. Several factors, such as concomitant alcohol use or abuse, concurrent medications, genetic factors, and nutritional status, can influence the susceptibility and severity of APAP hepatotoxicity. Early manifestations of APAP hepatotoxicity are nonspecific, but require prompt recognition by physicians. Patients with repeated overdose tend to present late, and in such hepatotoxicity may have already evolved. N-acetylcysteine is a very effective antidote when giving within 8 hours, and is also recommended after a presentation of hepatotoxicity and ALF. The prognosis of patients with APAP-induced ALF is better than other causes of ALF. Liver transplantation should be offered to those who are unlikely to survive.
Collectively, the various classes of antibiotics are a leading cause of drug-induced liver injury (DILI). However, acute antibiotic-associated DILI can be difficult to diagnose, as the course of therapy is usually brief, and other confounding factors are often present. In addition to the broad clinicopathologic spectrum of hepatotoxicity associated with the antimicrobials, the underlying infectious disease being treated may itself be associated with hepatic dysfunction and jaundice. This review provides summarized information on several classes of antimicrobial agents, highlighting new agents causing DILI and updating information on older agents.

Nonsteroidal Anti-Inflammatory Drug–Induced Hepatotoxicity

Nonsteroidal anti-inflammatory drugs are among the most prescribed medications worldwide. After antibiotics and anticonvulsants they are considered the most common medications associated with drug-induced liver injury mainly through an idiosyncratic form of hepatotoxicity. In rare cases severe hepatotoxicity has been described with significant morbidity and mortality. Genetic risk factors have been reported with diclofenac and lumiracoxib. Postmarketing surveillance and monitoring is crucial to identify severe cases of hepatotoxicity.

Antiretroviral and Anti–Hepatitis C Virus Direct-Acting Antiviral-Related Hepatotoxicity

Antiretroviral-related hepatotoxicity occurs commonly in patients with human immunodeficiency virus (HIV). Liver injury ranges from unconjugated hyperbilirubinemia and nodular regenerative hyperplasia to lactic acidosis and toxic hepatitis. Effective antiretroviral therapy has changed coinfected patients’ primary morbidities and mortality to chronic liver disease rather than complications from HIV. Treatment for hepatitis C virus (HCV) is strongly encouraged early in all coinfected patients. However, drug–drug interactions must be considered to ensure safe and tolerable use alone or in combination with antiretroviral therapies. The first-generation and newer HCV direct-acting antivirals are promising in coinfected patients, with minimal side effects and hepatotoxicity.

Chemotherapy-Induced Hepatotoxicity

Most hepatotoxicity secondary to chemotherapy is idiosyncratic and, therefore, neither dose dependent nor predictable. Some chemotherapy is cleared by the liver and requires dose adjustment in the face of significant liver dysfunction. In addition, preexisting abnormal liver function has been shown to increase the risk of hepatotoxicity. In addition to typical hepatocellular injury, other presentations, including cholestasis and hepatic sinusoidal obstruction syndrome, also commonly occur. The outcomes can range from asymptomatic liver function test abnormalities,
which resolve spontaneously, to cirrhosis, which occurs despite discontinuation of the chemotherapeutic agent.

**Drug-Induced Liver Injury from Antiepileptic Drugs**

Jennifer S. Au and Paul J. Pockros

Drug-induced liver injury is a potential complication of innumerable medications. Most cases do not occur in a predictable, dose-dependent manner, leading to delayed recognition of a drug’s hepatotoxic potential until after its release into the market. The estimated occurrence is 1 in 10,000 to 100,000 patients. However, the rates are likely higher because many cases go unrecognized owing to lack of reporting or missed diagnosis. This article reviews the most commonly associated antiepileptic drugs.

**Lipid-Lowering Agents and Hepatotoxicity**

Michael Demyen, Kawtar Alkhalloufi, and Nikolaos T. Pyrsopoulos

Lipid-lowering therapy is increasingly being used in patients for a variety of diseases, the most important being secondary prevention of cardiovascular disease. Many lipid-lowering drugs carry side effects that include elevations in hepatic function tests and liver toxicity. In many cases, these drugs are not prescribed or they are underprescribed because of fears of injury to the liver. This article attempts to review key trials with respect to the hepatotoxicity of these drugs. Recommendations are also provided with respect to the selection of low-risk patients and strategies to lower the risk of hepatotoxicity when prescribing these medications.

**Liver Injury Induced by Herbal Complementary and Alternative Medicine**

Victor J. Navarro and Leonard B. Seeff

Herbal and dietary supplement use is common. Most marketed products consist of complex mixtures. Although they are perceived as safe, instances of hepatotoxicity attributable to these products underscore their potential for injury, but the exact component that is responsible for injury is difficult to discern. The lenient regulatory environment in the United States, which opens the possibility of adulteration and contamination, adds to the challenge of disease attribution. Although many different herbal and dietary supplements have been reported to cause liver injury, in the United States, products used for bodybuilding and weight loss are the most commonly implicated.

**Hepatotoxicity and Drug Interactions in Liver Transplant Candidates and Recipients**

Neehar D. Parikh and Josh Levitsky

In this article the medications that have been shown to increase rates of drug-induced liver injury in patients with cirrhosis and the important drug-drug interactions in recipients of liver transplantation are reviewed. In general, the risk of drug-induced liver injury in patients with cirrhosis does not seem to be higher when compared with the noncirrhotic population. There are, however, 2 classes of agents that have been implicated—medications used to treat tuberculosis and medications used to treat...
human immunodeficiency virus infection. However, with careful monitoring, even significant interactions can be effectively managed.

How to Avoid Being Surprised by Hepatotoxicity at the Final Stages of Drug Development and Approval 749

Arie Regev

Drugs that caused severe drug-induced liver injury (DILI) in humans have typically not shown clear hepatotoxic signals in preclinical assessment. However, clinical trial databases may show evidence of a drug’s potential for severe DILI if clinical and laboratory data are evaluated for evidence of milder liver injury. The most specific indicator during a clinical trial for a drug’s potential to cause severe DILI is occurrence of cases of drug induced hepatocellular injury accompanied by altered liver function (eg, elevated direct bilirubin). Meticulous causality assessment of hepatic cases and strict adherence to hepatic discontinuation rules are critical components of this approach.