

# HOSPITAL PHYSICIAN®

## GASTROENTEROLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Gastroenterology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in gastroenterology. Each quarterly manual reviews a topic essential to the current practice of gastroenterology.

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## Drug-Induced Liver Disease

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Cover Illustration by Christine Armstrong

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# Drug-Induced Liver Disease

James H. Lewis, MD, FACP, FACG

## INTRODUCTION

Several hundred medicinal agents, chemicals, and herbal therapies can potentially cause hepatic injury.<sup>1</sup> Regarded as “a penalty for progress” by Hans Popper 40 years ago,<sup>2</sup> drug-induced liver disease (DILD) appears to be increasing in incidence, reflecting a growing number of new agents introduced into clinical use in the past several years as well as increased recognition of hepatotoxicity among older agents.

## INCIDENCE

The frequency of DILD is 4% to 10% of all adverse drug reactions.<sup>3,4</sup> A significantly higher percentage of acute hepatitis cases are the result of drug-induced liver injury, and drugs are responsible for more than 50% of all cases of fulminant hepatic failure in the United States.<sup>5,6</sup> Most of these cases are due to acetaminophen, but numerous other agents are also responsible, most notably isoniazid (INH) and other antituberculosis drugs. DILD is responsible for 15% of all liver transplants performed in the United States; again, acetaminophen represents about half of these cases.<sup>7</sup> It should not be surprising, therefore, that DILD is the most common reason that drugs are abandoned during clinical development phases or have restrictions placed on their use following marketing and is a leading reason for their removal from the marketplace.<sup>8</sup>

In reports by Pillans<sup>4</sup> and by Jmelnitzky et al,<sup>9</sup> approximately 60% of cases of DILD involved female patients, consistent with the general notion that with a few exceptions (eg, amoxicillin-clavulanate<sup>10,11</sup>), women are more susceptible to DILD. **Table 1** lists patient-related factors that may enhance susceptibility to DILD.

## AGENTS CAUSING DILD

Most medicinal agents that cause liver injury do so rarely, on an idiosyncratic basis. Only a few compounds are intrinsically hepatotoxic when taken in sufficient dosage; the prime example is acetaminophen. Agents causing unpredictable idiosyncratic injury can be divided into those associated with immunoallergic manifesta-

tions (eg, fever, rash, eosinophilia) and those not associated with such features (**Table 2**). The latter group are thought to act through reactive metabolites formed in the course of their use.<sup>1,15,16</sup> Drugs acting through hypersensitivity mechanisms represented approximately 30% of cases reported by Jmelnitzky et al.<sup>9</sup>

## MORPHOLOGIC PATTERNS OF INJURY

DILD can take the form of any known hepatic disorders associated with other etiologies.<sup>1,15</sup> The pathology can be broadly divided into acute hepatocellular or cholestatic injury and chronic liver disease, which can include chronic cholestasis mimicking primary biliary cirrhosis (PBC), chronic active hepatitis simulating autoimmune hepatitis, steatohepatitis, vascular diseases, and neoplastic lesions of the liver<sup>10,11,16–19</sup> (**Table 3**). In the series by Jmelnitzky et al,<sup>9</sup> approximately 90% of patients with drug-induced hepatotoxicity presented with acute forms of liver disease and the remainder presented with chronic liver disease. Among patients presenting with acute DILD, acute hepatocellular injury (including instances of acute liver failure) was seen in 41%, acute cholestatic hepatitis in 24%, bland cholestasis in 15.5%, and indeterminate acute injury in 10%.<sup>9</sup> In their series, the average time for liver-associated enzymes (LAEs) to normalize after the drug was discontinued varied according to the type of acute injury but was considerably longer with cholestatic injury—4 weeks for acute hepatocellular injury, 12 weeks for bland cholestasis, and 16 weeks for cholestatic hepatitis. A similar time to recovery was noted by Galan et al.<sup>20</sup> For drugs causing acute injury with complete recovery biochemically and clinically, it is expected that histologic recovery will also be complete. There are no unequivocal examples of acute hepatotoxins leading to subclinical injury after the agent has been withdrawn and enzymes have normalized.<sup>21</sup>

Integral to the ability to recognize DILD is an understanding of the biochemical correlates of injury. In general, hepatocellular, cholestatic, and mixed patterns of injury may be recognized, all of which can be subdivided into acute and chronic injury patterns. **Table 4** lists many of the disorders that are in the differential diagnosis of acute DILD, with associated laboratory findings.