



Infiniti Pool on the Ocean

## PIC QUESTION OF THE WEEK: 6/15/09

Q: What therapeutic category of drugs is most associated with idiosyncratic liver disease?

A: The liver plays a critical role in the metabolism and elimination of countless pharmaceuticals and other chemical compounds. Drug-induced liver injury (DILI) is relatively common and associated with significant morbidity and mortality. DILI is the leading cause of acute liver failure in the U.S. and the most common reason for FDA regulatory action involving approved medications. It is the basis for occasional removal of medications from the market (e.g. troglitazone, trovafloxacin, etc.) and, in cases of severe injury, may require organ transplantation. Nonprescription drugs, including herbal remedies and other OTC dietary supplements, are also important etiologies of DILI. The diagnosis of DILI is often difficult and delayed due to the need for exclusion of alternative causes of liver injury. It is imperative that the pharmacist understand the pathophysiologic basis of drug-induced liver disease and the laboratory values that identify liver *injury* and impaired hepatic *function*. Hepatocellular injury is reflected by increases in the transaminase enzymes AST and ALT, while cholestatic or obstructive injury is linked to elevations in alkaline phosphatase and GGT. Distinction between direct and indirect bilirubin levels can further identify the nature of hepatic injury. The references listed below provide a thorough description of the many aspects of drug-induced liver injury. The DILI *Network* (DILIN) is a cooperative effort of NIH and several major medical institutions and was established to advance our understanding of this complication of drug therapy. In 2008, the Network published data from an initial prospective study of 300 patients that identified some of the key clinical characteristics of DILI. The median time to recognition of DILI was 35 days in those with mild-moderate disease and 65 days in those with severe disease. A single prescription medication was implicated in 73% of patients and dietary supplements were responsible for 9% of the cases. Antimicrobials were identified as the most frequent single medication in 45% of patients while agents affecting the CNS were cited in 15% of patients. The mortality rate at 6 months was approximately 8%; however, slightly less than one-half of these patients died from hepatic disease. Diabetes was identified as a significant risk factor for severe injury. The most common antimicrobials included amoxicillin/clavulanate, isoniazid, nitrofurantoin, and trimethoprim-sulfamethoxazole. Initial results from this report are consistent with prior studies that identified antibiotics as the leading cause of DILI. Future publications from the DILIN will provide more insight into the early detection, diagnosis, prevention, treatment, and clinical characteristics of this significant drug-related problem.

### References:

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- Chalasani N, Fontana RJ, Bonkovsky HL, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008;135:1924-34.
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