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Identifying Factors and Disease Causing Drug Induced Liver Injury

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Annotation: Drug-induced hepatotoxicity or drug-induced liver injury (DILI) is an acute or chronic response to a natural or manufactured compound. DILI can be classified based on clinical presentation (hepatocellular, cholestatic, or mixed), mechanism of hepatotoxicity, or histological appearance from a liver biopsy. The true incidence is difficult to estimate, yet it has become the leading cause of acute liver failure (ALF). The two mechanisms of hepatotoxicity are intrinsic, which is dose-dependent, and idiosyncratic, which is more unpredictable.

Key words: drug-induced liver injury (DILI), antibiotic, NSAID, cardiovascular drugs, statins, amiodarone, central nervous system (CNS), valproate, phenytoin.

There are patient risk factors associated with the development of DILI, which include female sex, older age, and increased body mass index (BMI). More than 1000 medications and herbal compounds are known to cause hepatotoxicity and can be found on a searchable database maintained by the National Institute of Diabetes and Digestive, and Kidney Diseases (NIDDK) called LiverTox.

Intrinsic DILI is most commonly caused by acetaminophen, while it is less often seen in aspirin, tetracycline, and vitamin A.

Idiosyncratic DILI cases are caused by:

- Antibiotics (45.4%): amoxicillin-clavulanate (most common), sulfamethoxazole-trimethoprim, ciprofloxacin, isoniazid (INH)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Herbal and dietary supplements (HDS) (16.1%): green tea extract, anabolic steroids, multi-ingredient nutritional supplements
- Cardiovascular drugs (10%): statins, amiodarone
- Central nervous system (CNS) agents: valproate, phenytoin
- Antineoplastic drugs: tyrosine kinase inhibitors, tumor necrosis factor inhibitors, alpha inhibitors, methotrexate.

DILI can be predictable (when injury usually occurs shortly after exposure and is dose-related) or unpredictable (when injury develops after a period of latency and has no relation to dose). Predictable DILI (commonly, acetaminophen poisoning) is a common cause of acute jaundice and acute liver failure.

Hepatocellular: Hepatocellular hepatotoxicity generally manifests as malaise and right upper quadrant abdominal pain, associated with marked elevation in aminotransferase levels (alanine aminotransferase [ALT], aspartate aminotransferase [AST], or both), which may be followed by hyperbilirubinemia in severe cases. Hyperbilirubinemia in this setting is known as hepatocellular jaundice and, according to Hy's law, is associated with mortality rates as high as 50%. If hepatocellular liver injury is accompanied by jaundice, impaired hepatic synthesis, and encephalopathy, chance of spontaneous recovery is low, and liver transplantation should be considered.

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This type of injury can result from drugs such as acetaminophen and isoniazid.

Cholestatic: Cholestatic hepatotoxicity is characterized by development of pruritus and jaundice accompanied by marked elevation of serum alkaline phosphatase levels. Usually, this type of injury is less serious than severe hepatocellular syndromes, but recovery may be protracted. Substances known to lead to this type of injury include amoxicillin / clavulanate and chlorpromazine. Rarely, syndrome (progressive destruction of intrahepatic bile ducts).

Mixed: In these clinical syndromes, neither aminotransferase nor alkaline phosphatase elevations are clearly predominant. Symptoms may also be mixed. Drugs such as phenytoin can cause this type of injury.

There is no specific or diagnostic clinical presentation, laboratory test or histological pattern to aid in the diagnosis of drug-induced liver disease. Clinical features vary with the pattern and severity of injury, which vary with the particular drug and the individual patient.

- Often detected by routine drug monitoring - eg, disease-modifying antirheumatic drugs.
- Symptoms and signs are similar to other causes of liver damage. Thus, identifying drug-induced hepatitis relies on the history of exposure more than any particular finding on examination or investigation.
- Clinical evidence of sensitivity to a medication may occur on the first day of its use or not until several months later, depending on the medication.
- Usually, the onset is abrupt, with chills, fever, rash, pruritus, arthralgia, headache, abdominal pain, anorexia, nausea and vomiting.
- Later, overt evidence of liver damage, such as jaundice, dark urine and an enlarged and tender liver, may develop.
- Two general pathogenic mechanisms are recognised:

Predictable or direct: usually promptly follows an exposure to a new medication. The mechanism appears to be due to direct toxicity or a toxic metabolite - eg, paracetamol. Unpredictable or idiosyncratic: may be related to immune hypersensitivity; rash, fever and eosinophilia are typically present.

- Late-onset idiosyncratic reactions are difficult to recognise. They follow exposure by many months and usually do not display features of hypersensitivity - eg, isoniazid.

Management emphasizes drug withdrawal, which, if done early, usually results in recovery. In severe cases, consultation with a specialist is indicated, especially if patients have hepatocellular jaundice and impaired liver function, because liver transplantation may be required. Antidotes for drug-induced liver injury (DILI) are available for only a few hepatotoxins; such antidotes include *N*-acetylcysteine for acetaminophen toxicity and silymarin or penicillin for Amanita phalloides toxicity. Occasionally, corticosteroids can help in DILI with DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) or in autoimmune-like injury, as with minocycline or PD-1/PD-L1 checkpoint inhibitor toxicity.