Drug-Induced Liver Disease

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KEY CONCEPTS

1. Through its normally functioning enzymes and processes the liver often causes a drug to become toxic through a process known as bioactivation.

2. Drug-induced liver disease can have many different clinical presentations: idiosyncratic reactions, allergic hepatitis, toxic hepatitis, chronic active toxic hepatitis, toxic cirrhosis, and liver vascular disorders.

3. The mechanisms of drug-induced liver disease are diverse, representing many phases of biotransformation, and are susceptible to genetic polymorphism.

4. A fulminant or severe drug-induced reaction within the liver usually involves the immune system and is marked by large-scale cell necrosis.

5. The assessment of a possible liver injury caused by drugs should include what is known in the literature, the timing involved, the clinical course, and, always, an exploration of preexisting conditions that may have encouraged the lesion’s development.

6. Liver enzyme assays in serum can help to determine if a particular type of liver damage is present.

7. Monitoring for drug-induced liver disease must be tailored to the drug and the patient’s potential risk factors.

The number of drugs associated with adverse reactions involving the liver is extensive, but in clinical practice is dominated by alcohol, antibiotics, and acetaminophen. Drug-induced liver disease is a rare but potentially fatal, often debilitating and largely unpredictable outcome of drug treatment. Its exact incidence is difficult to document but about 40,000 to 45,000 people may experience a drug-induced liver injury each year. Drug-induced liver disease accounts for as much as 20% of acute liver failure in pediatric populations and a similar percentage of adults with acute liver failure. In approximately 75% of these cases, liver transplantation is ultimately required for patient survival. Of patients who required liver transplantation according to the United Network for Organ Sharing, acetaminophen, isoniazid, antiepileptics, and antibiotics collectively account for just over 60% of cases. In a prospective analysis of 1,200 patients admitted to a hospital in South Carolina for liver dysfunction, isoniazid accounted for 21 of 132 cases with various antibiotics and sulfa drugs accounting for another 30 cases. Overall, the reported incidence of drug-induced liver disease is around 1 in 10,000 to 1 in 100,000 patients.

The liver’s function affects almost every other organ system in the body, but there are no specific diagnostic tests for drug-induced liver disease. Therefore, it is important to know the patterns of drug-related pathology in order to assess adverse reactions when they occur. The liver’s normal metabolic outcome is to decrease the reactivity of a drug or toxin, in effect deactivating it. In many of the patterns of damage that this chapter will review, the first step is a net increase in reactivity that results from the normal processes of metabolism in the liver. This now bioactivated compound if left unconjugated or otherwise unbound is free to react in uncontrolled ways within the cell.

PATTERNS OF DRUG-INDUCED LIVER DISEASE

Hepatocellular Injury

Hepatocellular injury is characterized by significant elevations in the serum aminotransferases, which usually precede elevations in total bilirubin levels and alkaline phosphatase levels. Most injuries occur within 1 year of initiating the offending agent. Hepatocellular injury can lead to fulminant hepatitis with a corresponding 20% survival rate with supportive care. For those patients who present with the combination of hepatocellular injury and jaundice, there is a 10% mortality rate. Acarbose, allopurinol, fluoxetine, and losartan are capable of causing hepatocellular injury.

Hepatocellular injuries can be further subdivided by specific histologic patterns and clinical presentations. Centrolobular necrosis, steatohepatitis (steatonecrosis), phospholipidosis, and generalized hepatocellular necrosis are each identifiable by particular biopsy results and subtle differences in clinical presentation.

Centrolobular Necrosis

Centrolobular necrosis is often a dose-related, predictable reaction; however, it also can be associated with idiosyncratic reactions. Also called direct or metabolite-related hepatotoxicity, centrolobular necrosis is usually the result of the production of a toxic metabolite (eFig. 17-1). The damage spreads outward from the middle of a lobe of the liver.

Patients suffering from centrolobular necrosis tend to present in one of two ways, depending on the extent of necrosis. Mild drug reactions, involving only small amounts of parenchymal liver tissue, may be detected as asymptomatic elevations in the serum aminotransferases. If the reaction is diagnosed at this stage, most of these patients will recover with minimal cirrhosis and thus minimal chronic liver impairment. More severe forms of centrolobular necrosis are accompanied by nausea, vomiting, upper abdominal pain, and jaundice. These reactions are predictable, often dose-related effects in the liver caused by specific agents. When taken in overdose,
A general diagram of biotransformation. "Hepatic blood flow, which changes proportionately with changes in cardiac output, delivers the drug to the liver. "Protein binding is most affected by nutritional status and competing drugs. "The drug is actively transported into the hepatocyte by the organic anion transport pump, a transmembrane protein. "The metabolite (drug) interacts with one of a number of enzymes, the most common being CYP2C9, 2C19, 2D6, and 3A4. This family of enzymes is regulated by the complementary DNA xenobiotic receptor. The xenobiotic receptor is in turn upregulated by other drugs, changes in cholesterol catabolism, and bile acids. The immediate result of the action of these phase I enzymes is the production of a reactive metabolite. "The unstable metabolite then reacts with glucuronidase, various transferases, or hydroxylases to form a conjugated metabolite. The efficacy of these enzymes is affected by the patient’s nutritional state and genetic polymorphism, leading to variations in individual risk for toxicity. "The conjugated metabolite is removed from the hepatocyte by the canalicular membrane export pump, one of a large family of membrane proteins (other members of this family pump conjugated metabolites back into the blood for excretion by the kidney). These proteins are subject to genetic polymorphism as well, again leading to some patients having an increased risk for toxicity. "If unable to form a conjugate, the unstable metabolite can participate in oxidative reactions that damage lipids, proteins, or even DNA. "The normal process of cellular aging, death, and reabsorption by surrounding cells. "Widespread, rapid cellular death with the creation of multiple antigens. "Activation Kupffer cells, killing cells, B-cells, and other T-cells with the associated production of inflammatory cytokines the relative numbers of which and the innate activity of each mediated by genetic polymorphism. "Drugs or active metabolites that are transported or diffuse into the mitochondria or the nucleus can damage DNA, leading to mutagenicity and ultimately hepatic cancers.
acetaminophen becomes bioactivated to a toxic intermediate known as N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is very reactive, with a high affinity for sulfhydryl groups. The protein glutathione provides a ready source of available sulfhydryl groups within the hepatocyte. When the liver’s glutathione stores are depleted and there are no longer sulfhydryl groups available to detoxify this metabolite, it begins to react directly with the hepatocyte (see eFig. 17-1). In addition, the depletion of glutathione changes the mitochondrial oxidized to reduced glutathione ratio resulting in catastrophic shifts in mitochondrial function, accelerating cell necrocytolysis. Continuing mitochondrial damage leading to fragmentation of mitochondrial DNA leads directly to necrosis. Replenishing the liver’s sulfhydryl capacity through the administration of N-acetylcysteine early after ingestion of the overdose halts this process. During the first hours after ingestion, some patients report mild symptoms of nausea and vomiting, but no elevations of the commonly measured liver enzymes are seen. Serum elevations in the liver enzymes begin 40 to 50 hours after ingestion. Circulating cell-free microRNA (liver-specific miR-122) begins to rise after only 1 hour in rat models of acetaminophen overdose. This may lead the way to earlier detection of many drug-induced liver disorders in the future.

Nonalcoholic Steatohepatitis

Nonalcoholic steatohepatitis (NASH), also known as steatohepatitis and steatonecrosis, results from the accumulation of fatty acids in the hepatocyte. In the preacute stages, this is known as nonalcoholic fatty liver disease (NAFLD). Drugs or their metabolites that cause NAFLD do so by affecting fatty-acid esterification and oxidation rates within the mitochondria of the hepatocyte (see eFig. 17-1). Hepatic vesicles become engorged with fatty acids, eventually disrupting hepatocyte homeostasis. In patients with diabetes, various dyslipidemias and even hypertension, the de novo production of free fatty acids from excess circulating carbohydrates accelerates this process of accumulation. The liver biopsy is marked by a massive infiltration by polymorphonuclear leukocytes, degeneration of the hepatocytes, and the presence of Mallory bodies.

Alcohol is the drug that most commonly produces steatocrotic changes in the liver. When alcohol is converted into acetaldehyde, the synthesis of fatty acids is increased. The hepatocyte can become completely engorged with microvesicular fat, resulting in alcoholic fatty liver. Metabolically this type of de novo fatty acid synthesis depletes NADPH in favor of NADP⁺ and reduces the hepatocytes’ ability to respond to stress, bypassing normal apoptosis and increasing the rate of necrocytolysis. In NAFLD, the same end point is often achieved through oxidation of lipid peroxidases. If the offending agent is withdrawn before significant numbers of hepatocytes become necrotic, the process is completely reversible without long-term sequelae. If not, then ever increasing rates of necrocytolysis will induce an innate immune response and result in hepatitis.

Tetracycline produces NAFLD and NASH. The lesions are characterized by large vesicles of fat found diffused throughout the liver. The development of this reaction is related to the high concentrations achieved when tetracycline is given IV and in doses greater than 1.5 g/day. The mortality of tetracycline steatohepatitis is high (70% to 80%), and those who do survive often develop cirrhosis. Sodium valproate also can produce steatonecrosis through the process of bioactivation. Cytochrome P450 (CYP450) converts valproate to delta-4-valproic acid, a potent inducer of microvesicular fat accumulation.

Patients experiencing steatohepatitis may present with abdominal fullness or pain as their only complaint. Patients with more severe steatonecrosis will present with all the symptoms characteristic of alcoholic hepatitis such as nausea, vomiting, steatorrhea, abdominal pain, pruritus, and fatigue.

Phospholipidosis

Phospholipidosis is the accumulation of phospholipids instead of fatty acids. The phospholipids usually engorge the lysosomal bodies of the hepatocyte. Amiodarone is associated with this reaction. Patients treated with amiodarone who develop overt hepatic disease tend to have received higher doses of the drug. These patients also have higher amiodarone-to-N-desethyl-amiodarone ratios, indicating a greater accumulation of the parent compound. Amiodarone and its major metabolite N-desethyl-amiodarone remain in the liver of all patients for several months after therapy is stopped. Usually the phospholipidosis develops in patients treated for more than 1 year. The patient can present with either elevated aminotransferases or hepatomegaly; jaundice is rare.

Generalized Hepatocellular Necrosis

Generalized hepatocellular necrosis mimics the changes associated with the more common viral hepatitis. The onset of symptoms is usually delayed as much as a week or more after exposure to toxin. Bioactivation is often important for toxic hepatitis to develop. Many drugs that are associated with toxic hepatitis produce metabolites that are not inherently toxic to the liver. Instead, they bind with proteins to create haptons, which serve as neoantigens and induce the innate immune response (see eFig. 17-1).

The rate of bioactivation can vary between males and females and between individuals of the same sex. The superfamily of CYP450 enzymes metabolizes lipophilic substrates that are actively pumped into the hepatocyte by an organic anion (or cation) transporting protein. The CYP450 subgroups 2C, 2D, 3A, and 4A are regulated by the highly inducible xenobiotic receptor on complementary DNA. The receptor is found in the liver, and to a lesser extent in the cells lining the intestinal tract, and is responsible for cholesterol catabolism and bile acid homeostasis. The activity of this receptor is subject to genetic polymorphism. This results in a wide variation in the sensitivity of the population to hepatic damage.

The long-term administration of isoniazid can lead to hepatic dysfunction in 10% to 20% of those receiving the drug. Yet severe toxic hepatitis develops in only 1% or less of this population. Isoniazid simultaneously is an example of the potential predictability of drug-induced liver disease based on single nucleotide polymorphism and a lesson in the limitations of our current understanding. There are definite links to NAT2 genotype and toxicity. The risk for this reaction is also influenced heavily by the age of the patient, with older patients having a much higher risk than younger patients. In fact, age may be more important than genotype. In one prospective series focused on drug-induced liver disease, cases involving isoniazid had a median onset at 6 months of therapy with around 30% of isoniazid-induced liver disease clustered between 6 and 8 months.

Ketoconazole produces generalized hepatocellular necrosis or milder forms of hepatic dysfunction in 1% to 2% of patients treated
for fungal infections. The onset is usually early in therapy. In immuno-compromised patients in whom ketoconazole is used, special care should be taken to watch for changes in liver function.\(^3\)

### Toxic Cirrhosis

The scarring effect of hepatitis in the liver leads to the development of cirrhosis. Some drugs tend to cause such a mild case of hepatitis that it may not be detected. Mild hepatitis can be easily mistaken for a more routine generalized viral infection. If the offending drug or agent is not discontinued, this damage will continue to progress. The patient eventually presents not with hepatitis, but with cirrhosis.

Methotrexate causes periportal fibrosis in most patients who experience hepatotoxicity. The lesion results from the action of a bioactivated metabolite produced by CYP450.\(^3\) This process occurs most commonly in patients treated for psoriasis and arthritis. Periodic liver biopsies have a low yield in patients without other risk factors for liver disease, and should be reserved for select high-risk patients.\(^3\)

### Cholestatic Injury

A second pattern of hepatic damage is an injury that primarily involves the bile canalicular system and is known as cholestatic injury. Cholestatic disease is more often seen in patients over the age of 60 (compared with under age 60) and is slightly more common in males.\(^3\) In cholestatic disease, disturbance of the subcellular actin filaments around the canaliculi prevents the movement of bile through the canalicular system.\(^3\) In addition mutations in hepatic transporter genes can result in slower function prior to toxin exposure.\(^3\) The inability of the liver to remove bile causes intrahepatic accumulation of toxic bile acids and excretion products.\(^3,7\)

Drug-induced cholestasis can occur as an acute disorder (e.g., cholestasis with or without hepatitis and cholestasis with bile duct injury) or as a chronic disorder (e.g., vanishing bile duct syndrome, sclerosing cholangitis, and cholelithiasis).\(^3,8\) However, the most common form of drug-induced cholestasis is cholestasis with hepatitis. Most patients with this acute disorder present with nausea, jaundice, and pruritus.\(^7\) Elevations in serum alkaline phosphatase levels are more prominent and usually precede the elevations of other liver enzymes in serum.\(^3\) A liver biopsy is not usually required, but is sometimes pursued when other causes of cholestatic disease are suspected.\(^3\)

### Mixed Hepatocellular and Cholestatic Injury

The final pattern of hepatic damage is a combining of the previous two patterns. This presentation can be the result of three different processes. In some patients, an injury may begin as hepatocellular (or cholestatic) and simply spread so rapidly that by the time the patient presents for diagnosis and treatment, all areas of the liver are affected. In other patients, the underlying mechanism of damage is such that cells are injured regardless of their anatomical location or primary metabolic role.

### Liver Vascular Disorders

Focal lesions in hepatic venules, sinusoids, and portal veins occur with various drugs. The most commonly associated drugs are the cytotoxic agents used to treat cancer, the pyrrolizidine alkaloids, and the sex hormones. A central necrosis often follows and can result in cirrhosis. Azathioprine and herbal teas that contain comfrey (a source of pyrrolizidine alkaloids) are associated with the development of venoocclusive disease. The exact incidence is rare and may be dose related.\(^6\) Peliosis hepatitis is a rare type of hepatic vascular lesion that can be seen as both an acute and a chronic disease. The liver develops large, blood-filled lacunae (space or cavity) within the parenchyma. Rupture of the lacunae can lead to severe peritoneal hemorrhage. Peliosis hepatitis is associated with exposure of the liver to androgens, estrogens, tamoxifen, azathioprine, and danazol. Androgens with a methyl alkylation at the 17-carbon position of the testosterone structure are the most frequently reported agents that cause peliosis hepatitis, usually after at least 6 months of therapy.\(^4\)

### MECHANISMS OF DRUG-INDUCED LIVER DISEASE

#### Stimulation of Autoimmunity

Autoimmune injuries involve antibody-mediated cytotoxicity or direct cellular toxicity.\(^4,44\) This type of injury occurs when enzyme–drug adducts migrate to the cell surface and form neoantigens. The liver plays host to all of the cells that make up the innate immune response system in the body along with Kupffer cells, which are a type of macrophage. These cells sit in anticipation around the hepatocytes, in the space of Disse and elsewhere waiting for antigens (or neoantigens) to present themselves. The neoantigens serve as targets for cytolytic attack by killer T-cells, and others.\(^6\) Halothane, sulfamethoxazole, carbamazepine, and nevirapine are associated with autoimmune injuries.\(^3\) Stimulation of autoimmunity is often associated with fulminant presentations.

Dantrolene, isoniazid, phenytoin, nitrofurantoin, and trazodone are associated with a type of autoimmune-mediated disease in the liver called *chronic active hepatitis*.\(^10\) Patients experience periods of symptomatic hepatitis followed by periods of convalescence, only to repeat the experience months later. It is a progressive disease with a high mortality rate and is more common in females than males. Antinuclear antibodies appear in most patients. These drugs appear to form anti-IgM antibodies.\(^23\) The exact identification of a causative agent is sometimes difficult as diagnosis requires multiple episodes occurring long after exposure to the offending drug.
**Idiosyncratic Reactions**

Idiosyncratic drug-related hepatotoxicity is rare and usually occurs in a small proportion of individuals. These adverse reactions are often categorized into allergic and nonallergic reactions. The allergic reactions are characterized by fever, rash, and eosinophilia. They are usually dose-related and have a short latency period (<1 month). Upon reexposure to the offending agent, the patient will experience rapid recurrence of hepatotoxicity. Studies show that minocycline, nitrofurantoin, and phenytoin can cause allergic reactions.2

Unlike the allergic reactions, the nonallergic idiosyncratic reactions are devoid of the hypersensitivity features and usually have a long latency period (several months). These patients often have normal liver function tests for 6 months or longer and then suddenly develop hepatotoxicity. Dependent on the medication, the incident can be independent of dose or dose related. Amiodarone, isoniazid, and ketoconazole are associated with nonallergic drug-related hepatotoxicity.2

**Disruption of Calcium Homeostasis and Cell Membrane Injury**

Drug-induced damage to the cellular proteins that are involved with calcium homeostasis can lead to an influx of intracellular calcium that causes a decline in adenosine triphosphate levels and disruption of the actin fibril assembly. The resulting impact on the cell is blebbing of the cell membrane, rupture, and cell lysis.36 Lovastatin, venlafaxine, and phalloidin, which is the active component of mushroom, impair calcium homeostasis.36–45

**Metabolic Activation of the Cytochrome P450 Enzymes**

Most hepatocellular injuries involve the production of high-energy reactive metabolites by the CYP450 system. These reactive metabolites are capable of forming covalent bonds with cellular proteins (enzymes) and nucleic acids that lead to adduct formation. In the case of acute toxicity, the enzyme–drug adduct can cause cell injury or cell lysis. Adducts that form with DNA can cause long-term consequences such as neoplasia. Acetaminophen, furosemide, and diclofenac are examples of this mechanism of liver injury.45 Individual genetic differences can play a role in the significance of this process. Patients with a single nucleotide polymorphism (SNP) that codes for slow-reacting variants of CYP450 will react differently from those with a SNP that codes for very fast-reacting variants.

**Stimulation of Apoptosis**

Apoptosis represents a distinct pattern of cell lysis that is characterized by cell shrinkage and fragmentation of nuclear chromatin. Apoptotic pathways are triggered by interactions between death ligands (tumor necrosis factor and Fas ligand) and death receptors (tumor necrosis factor receptor 1 and Fas). These interactions activate caspases, which cleave cellular proteins and eventually lead to cell death.46

**Mitochondrial Injury**

Drugs that impair mitochondrial structure, function, or DNA synthesis can disrupt β-oxidation of lipids and oxidative energy production within the hepatocyte.46 In acute disease, prolonged interruption of β-oxidation leads to microvesicular steatosis, whereas, in chronic disease, macrovesicular disease is present. Severe damage to the mitochondria eventually leads to hepatic failure and death. Aspirin, valproic acid, and tetracycline cause mitochondrial injury by inhibiting β-oxidation and amiodarone via disruption of oxidative phosphorylation.36 Inborn errors in mitochondrial metabolism can predispose a patient to these types of disruptions in function.

**Liver Neoplastic Disease**

A large body of the current literature on adverse reactions and the liver addresses the development of neoplasms following drug therapy. Both carcinoma- and sarcoma-like lesions have been identified. Fortunately, hepatic tumors associated with drug therapy are usually benign and remit when drug therapy is discontinued. Except in rare instances, these lesions are associated with long-term exposure to the offending agent.47 Androgens, estrogens, and other hormonal-related agents are the most frequently associated causes of neoplastic disease. The model for drug-induced hepatic cancer is polyvinyl chloride exposure. Used in the production of many types of plastic products, polyvinyl chloride induces angiosarcoma in exposed workers after as few as 3 years of exposure.48

**ASSESSMENT OF DRUG-INDUCED LIVER DISEASE**

The best and most important technique for assessing and monitoring drug-induced liver disease is the patient’s history. Questions addressing the patient’s drug use along with a thorough review of systems are essential (eFig. 17-2). Drugs for recreational purposes must not be overlooked. Cocaine has been directly linked to liver disease.53 Ecstasy, the street name of methylenedioxymethylamphetamine, has induced deadly fulminant hepatitis.54 The more pervasive impact of street drugs on the incidence of hepatic disease is the concomitant injection or ingestion of adulterants. Many of these adulterants are either directly toxic or serve to enhance the toxicity of the drug (eTable 17-1).

It is also important to determine nondrug hepatic disease risk from occupational or environmental exposure. Arsenic, for example, is known to induce both acute and chronic hepatic reactions.44 Even if exposure to an environmental toxin does not produce a hepatic reaction, it may predispose a patient to a hepatic reaction when a drug is added.49–52 tab 1 not cited eTable 17-2 lists some of the more common hepatic toxics found in occupational or environmental exposures that can add to the risk for developing a hepatic lesion.55 Immune-mediated chronic liver diseases can often be tracked to geographic clusters that correspond to known toxic waste sites around the world.55

A person’s use of alternative medicines must be solicited. In the prospective series of cases noted earlier, from an area of the country where traditional medicine usage is commonplace, herbal remedies and other traditional medicines accounted for 14 of 132 cases of drug-induced liver disease.56 Comfrey tea is a common cause of hepatocellular damage. With the Chinese remedy jinbujuan, or the more elegantly presented chaparral capsules containing greese wood leaves, the end of therapy with these types of agents is occasionally severe disability or death from fulminant hepatic failure.56 Pennyroyal oil, margosa oil, and clove oil cause a dose-related hepatotoxicity.56

The nutritional status of a patient can be as important to the development of a drug-induced liver disease as the hepatotoxin itself.49–52 Patients who are malnourished because of illness or long-term alcohol abuse make up the most troublesome group.57 Low serum levels of vitamins E and C along with lutein and the α- and β-carotenes are associated with asymptomatic elevations in transaminases. Conversely, high serum iron, transferrin, and selenium levels are also associated with asymptomatic elevations of transaminases.58

All potential drug reactions should be judged as to the timing of the reaction versus drug administration, pharmacokinetic...
eFIGURE 17-2  An approach to determining a drug monitoring plan for patients prescribed potentially hepatotoxic drugs.

Notes: \(^a\)Serious reactions would include those that occur rarely but have a very high morbidity or mortality rate. Common reactions would be reported in 1% or more patients taking the drug. \(^b\)Concomitant therapy with another hepatotoxic drug will elevate the potential risk of a reaction and should lead to more frequent monitoring.

c considerations, the information in the literature records about previous reactions, the inclusion of alternative nondrug causes, and close clinical observation when the drug in question is stopped. It is also important to keep in mind that most elevations in liver enzymes will not be associated with a drug. In a study of all patients admitted to a hospital in the United Kingdom with elevated liver aminotransferases, only 9% of cases involved a drug other than alcohol as the possible cause.\(^2\) In all cases, titers of serum antibodies to hepatitis A, B, and C should be drawn. Even in cases in which the drug is absolutely targeted as the cause, viral hepatitis may be a complication.\(^49–52\)

eTABLE 17-1  An Approach to Evaluating a Suspected Hepatotoxic Reaction

<table>
<thead>
<tr>
<th>Points</th>
<th>-3</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
<th>+3</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the temporal relationship? (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From the start of therapy</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>From the end of therapy</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Is there evidence of the concurrent use of a hepatotoxin?</td>
<td>Yes</td>
<td>Maybe</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Is there an alternate cause, such as, viral hepatitis?</td>
<td>Yes</td>
<td>Most likely—Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Are there extrahepatic signs or symptoms?</td>
<td>No</td>
<td>No</td>
<td>Yes (+1 for each)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dermatologic: rash, palmar erythema, cutaneous vasculitis</td>
<td>—</td>
<td>—</td>
<td>No</td>
<td>Yes (+1 for each)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dermatologic: spider nevi, white nails (aka Terry’s nails)</td>
<td>—</td>
<td>—</td>
<td>No</td>
<td>Yes (+1 for each)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hematologic: coagulation disorders</td>
<td>—</td>
<td>—</td>
<td>No</td>
<td>Yes (+1 for each)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Endocrine disorders: insulin resistance, thyroid dysfunction</td>
<td>—</td>
<td>—</td>
<td>No</td>
<td>Yes (+1 for each)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Endocrine disorders: adrenal insufficiency, hypogonadism</td>
<td>—</td>
<td>—</td>
<td>No</td>
<td>Yes (+1 for each)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Skeletal muscular: arthralgias, arthritis</td>
<td>—</td>
<td>—</td>
<td>No</td>
<td>Yes (+1 for each)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Neurological: encephalopathy</td>
<td>—</td>
<td>—</td>
<td>No</td>
<td>Yes (+1 for each)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Portopulmonary hypertension</td>
<td>—</td>
<td>—</td>
<td>No</td>
<td>Yes (+1 for each)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Does the literature support a connection with this drug?</td>
<td>Listed in the product labeling</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
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<tr>
<td>Published reports in the literature</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No information available, reaction is undocumented</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Results from a rechallenge with the drug</td>
<td>Negative</td>
<td>—</td>
<td>Inconclusive</td>
<td>—</td>
<td>—</td>
<td>Positive</td>
</tr>
</tbody>
</table>

??, Uncertain.

A total score <7 makes it unlikely that this is a hepatotoxic reaction. As the score approaches 14; the possibility that this is a hepatotoxic reaction increases toward certainty.

\(^a\)Drug, herbal remedy or other occupational exposure known to be potentially hepatotoxic.
Often there is no good clinical test available to determine the exact type of hepatic lesion, short of liver biopsy. There are specific patterns of enzyme elevation that have been identified and can be helpful (eTable 17-3). The specificity of any serum enzyme depends on the distribution of that enzyme in the body. Alkaline phosphatase is found in the bile duct epithelium, bone, and intestinal and kidney cells. 5′-Nucleotidase is more specific for hepatic disease than alkaline phosphatase, because most of the body’s store of 5′-nucleotidase is in the liver. Glutamate dehydrogenase is a good indicator of centrolobular necrosis because it is found primarily in centrolobular mitochondria. Most hepatic cells have extremely high concentrations of transaminases. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are commonly measured in serum. Because of their high concentrations and easy liberation from the hepatocyte cytoplasm, AST and ALT are sensitive indicators of necrotic lesions within the liver. After an acute hepatic lesion is established, it may take weeks for these concentrations to return to normal.

Serum bilirubin concentration is a sensitive indicator of most hepatic lesions and has significant prognostic value. High peak bilirubin concentrations are associated with poor survival. Other important findings that indicate poor survival are a peak prothrombin time greater than 40 seconds, elevated serum creatinine, and low arterial pH. The presence of encephalopathy or prolonged jaundice are not good signs for the survival of the patient and are strong indicators for transplantation.

Bilirubin concentrations and serum enzyme elevations give a static picture of the liver’s condition and are not good indicators of hepatic function. Clinically available tests to predict hepatic function include measurement of serum proteins (albumin or transferrin). As a hepatic function decreases, serum protein concentrations in the body decrease at a rate determined by each protein’s own elimination rate. Overhydration and starvation can also decrease serum protein concentrations. Changes in the prothrombin time often occur earlier than the changes in albumin or transferrin. The response of the prothrombin time to the administration of 10 mg of parenteral vitamin K is often used to differentiate between hepatic and extrahepatic disease.

**eTABLE 17-3 Relative Patterns of Hepatic Enzyme Elevation versus Type of Hepatic Lesion**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Abbreviations</th>
<th>Necrotic</th>
<th>Cholestatic</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase</td>
<td>AlikPhos, AP</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>5′-Nucleotidase</td>
<td>5-NC, SNC</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>γ-Glutamyltransferase</td>
<td>GGT, GGTP</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Aspartate amino transferase</td>
<td>AST, SGOT</td>
<td>↑↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Alaine amino transferase</td>
<td>ALT, SGPT</td>
<td>↑↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>LDH</td>
<td>↑↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

↑, <100% of normal; ↑↑, >100% of normal; ↑↑↑, >200% of normal.

**Measurement of Liver Function**

A good compound for a liver function test would theoretically be (a) nontoxic and lacking any pharmacologic effect; (b) either rapidly and completely absorbed orally or easily administered via a peripheral vein; (c) eliminated only by the liver; and (d) easily measured (drug and its metabolite) in blood, saliva, or urine.

A liver biopsy has been performed, the injury should be classified by the histologic findings. In cases in which there is no biopsy, the pattern of serum liver enzyme elevation can estimate the type of injury. Hepatocellular injuries are marked by elevations in transaminase that are at least two times normal. If the alkaline phosphatase is also elevated, a hepatocellular lesion is still suspected when the elevation of ALT is notably higher than the elevation of alkaline phosphatase. If the magnitude of elevation is nearly equal between ALT and alkaline phosphatase, the lesion is likely cholestatic.

A liver injury is acute if it lasts less than 3 months; it is considered chronic after 3 months of consistent symptoms or enzyme elevation. A liver injury is severe if the patient has marked jaundice, the prothrombin time does not improve by more than 50% after the administration of vitamin K, or if encephalopathy is detectable. If an acute liver injury progresses from normal to severe in a matter of a few days or weeks, it is considered fulminant.

**ABBREVIATIONS**

ALT alanine aminotransferase
AST aspartate aminotransferase
CYP450 cytochrome P450 liver enzyme system
NAFLD nonalcoholic fatty liver disease
NAPQI N-acetyl-p-benzoquinone imine
NASH nonalcoholic steatohepatitis
NAT2 N-acetyltransferase 2 genotype
SNP single nucleotide polymorphism

**REFERENCES**

Organ-Specific Function Tests and Drug-Induced Diseases

SECTION


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