Chapter e56: Drug-Induced Liver Injury

William Kirchain; Rondall E. Allen

UPDATE SUMMARY

Update Summary

May 15, 2023

The following section was updated:

- Self-Assessment Questions: new correct answer choices for all questions

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Appendix 6, Drug-Induced Hematologic Disorders.

KEY CONCEPTS

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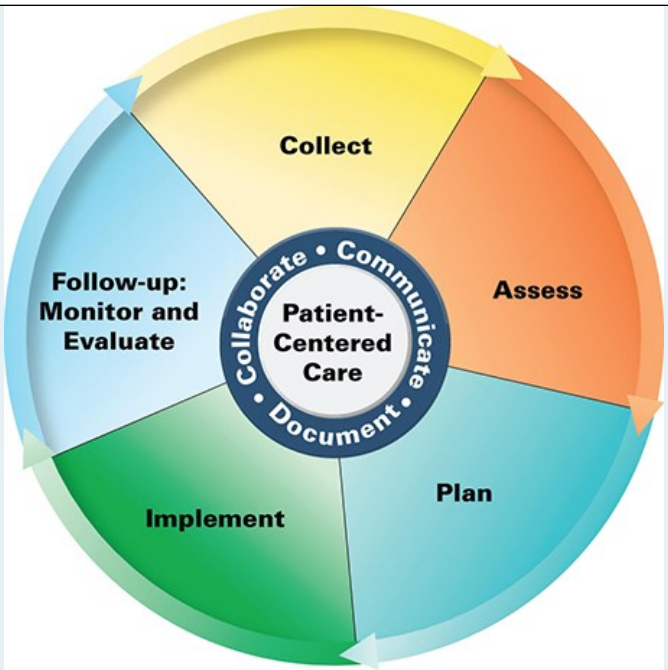
1. Through its normally functioning enzymes and processes the liver often causes a drug to become toxic through a process known as bioactivation.
2. Drug-induced liver injury (DILI) can have many different clinical presentations: idiosyncratic reactions, allergic hepatitis, toxic hepatitis, chronic active toxic hepatitis, toxic cirrhosis, and liver vascular disorders.
3. The mechanisms of DILI are diverse, representing many phases of biotransformation, and are susceptible to genetic polymorphism.
4. 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 for preexisting conditions that may have encouraged the lesion's development.
5. Liver enzyme assays in serum can help to determine if a particular type of liver damage is present.
6. Monitoring for DILI must be tailored to the drug and the patient's potential risk factors.

PATIENT CARE PROCESS

Patient Care Process for Drug-Induced Liver Injury



Collect

- Patient demographics listing, age, and pregnancy status are very important
- Patient medical history including any possible previous liver injury and illness that may indicate an alternative cause or a predisposition; and type 2 diabetes mellitus that may indicate a nonalcoholic fatty liver
- History of present illness that carefully documents each symptom with a time of onset
- Social history comprising a detailed assessment of alcohol use; intravenous drug use and other recreational substance use; along with a careful work history (see Table e56-3)
- Current medication history that prioritizes those initiated within the last 90 days and includes prescription, nonprescription, herbal, and other complementary medicines. If possible, determine exact time the medication was started prior to patient presentation
- Objective data should include
  - Liver enzyme values, Total Bilirubin, Direct and Indirect Bilirubin
  - Liver function tests, such as INR, transferrin and ammonia
  - Hepatitis A, B, C assessments
  - Objective confirmation of liver injury via biopsy, CT, MRI, or sonogram
- A literature search for reports of the patient's medications, herbs used and other substances, and liver injury
- A search of liver injury reports on LiverTox

Assess

- The pattern of liver enzyme elevation (see Table e56-4)
- The probability of each likely agent as a causative agent using RUCAM (see Table e56-2)
- The severity of the reaction

- Determine through consultation with the medical team and patient if a rechallenge with the probable causative agent is worthwhile

Plan*

- Drug therapy regimen to replace the drug or herb that must be discontinued
- Monitoring parameters to determine liver recovery, note that there will be short-term and long-term needs
- Patient education on drug or herbs to avoid in the future and any long-term issues that may need to be addressed with future drug therapy utilizing hepatically cleared agents

Implement*

- Discontinue probable drug and schedule initiation of replacement therapy
- Schedule follow-up

Follow-Up: Monitor and Evaluate

- Resolution of signs and symptoms (jaundice, abdominal distention, liver enzymes elevation)
- Recovery of stamina and strength (often takes months)
- Evaluation replacement drug regimen for safety and efficacy

****Collaborate with the patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Because it is important to compare cases of liver injury across the world and across time, we use common designations for each type of liver injury. You can see a concise and commonly accepted approach in LiverTox which is part of the NCBI Bookshelf at https://www.ncbi.nlm.nih.gov/books/NBK547852/. Look under “Phenotypes.”

It is important to stratify the likelihood that a particular drug has caused this liver injury and decide what are likely candidates. The text provides the RUCAM scoring system and references some supporting literature for its use. The authors of LiverTox at https://www.ncbi.nlm.nih.gov/books/NBK547852/ have a less favorable view of RUCAM and provide several other choices for you to consider, you can score the above case and see how each approach differs. Look under “Causality.”

INTRODUCTION

The range of drugs associated with adverse reactions involving the liver is extensive, but in clinical practice is dominated by alcohol, antibiotics, antiseizure medications, and acetaminophen.[1] Complementary and herbal medicines also contribute disproportionately to this disease burden. Drug-induced liver injury (DILI) is a potentially fatal, often debilitating outcome of drug treatment. DILI is responsible for 11% to 13% of all cases of acute liver failure in the United States.[1,2]

Drug-induced liver injury accounts for as much as 20% of acute liver failure in pediatric populations and a similar percentage of adults with acute liver failure.[3] In approximately 75% of these cases, liver transplantation is ultimately required for patient survival.[4] 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.[5]

The liver's function affects every other organ system in the body; it in turn is exposed to every substance absorbed from the gut and every injected substance that enters the bloodstream.

MECHANISMS OF DRUG-INDUCED LIVER INJURY

Stimulation of Autoimmunity

Autoimmune injuries involve antibody-mediated cytotoxicity or direct cellular toxicity.[6,7] This type of injury occurs when enzyme-drug complexes migrate to the cell surface and form neoantigens. The liver plays host to all of the cells that make up the innate immune response in the body along with Kupffer cells, which act as a type of macrophage, derived from the reticuloendothelial cells. These Kupffer cells sit in anticipation along the lumen of the liver sinusoids waiting for glycoproteins, substances coated with immunoglobulins or complement factors to present themselves.[8] The reticuloendothelial cells that create the porous frame around the hepatocytes are constantly monitoring and communicating via cytokines to stimulate or regulate an immune response.[8] Neoantigens also serve as targets for cytolytic attack by killer T cells, and others.[9] Halothane, sulfamethoxazole, carbamazepine, nevirapine, fluoroquinolones, and anti-tumor necrosis factor (TNF) alpha inhibitors are associated with autoimmune injuries.[2,10] Stimulation of autoimmunity is often associated with fulminant presentations.

Dantrolene, isoniazid, phenytoin, nitrofurantoin, trazodone, and methyldopa are associated with a type of autoimmune-mediated disease in the liver called *chronic active hepatitis*.[11,12] 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 (ANA) appear in most patients. These drugs appear to form anti-organelle antibodies.[13] 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. Allergic reactions represent up to 37% of all idiosyncratic drug-induced liver injuries and are characterized by fever, rash, eosinophilia, and granulomas.[12] They are usually dose-related and have a short latency period (less than 1 month). On re-exposure to the offending agent, there is a rapid recurrence of hepatotoxicity. Minocycline, nitrofurantoin, phenytoin, amoxicillin-clavulanate, sulfamethoxazole-trimethoprim, angiotensin-converting enzyme inhibitors, and allopurinol can cause allergic reactions.[2,12,14]

3 Human leukocyte antigen (HLA) phenotypes mediate a patient's susceptibility and severity of inflammatory reactions in the liver. HLA type A*33:01 has been identified through genome-wide association studies with several drugs that have induced idiosyncratic reactions.[15] Additional HLA phenotypes exist that further increase the likelihood and severity of these reactions, which includes HLA type A*33:01; HLA type B*35:01, HLA type B*14:02, and HLA type C*08:021.[5,16] 3 HLA type B*5701 has separately been associated with reactions for flucloxacillin and abacavir.[17-20] Although not useful for management of the acutely ill patient, monocyte-derived, hepatocyte-like cell cultures can be used to confirm the culprit in an idiosyncratic reaction.[21,22] Amiodarone, isoniazid, and ketoconazole are associated with nonallergic drug-related hepatotoxicity.[14]

The nonallergic idiosyncratic reactions are devoid of the hypersensitivity features, usually have a long latency period (several months), and are not associated with rapid reinjury with rechallenge.[2] 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.

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.[22] The resulting impact on the cell is blebbing of the cell membrane, rupture, and cell lysis.[17] Lovastatin, venlafaxine, and phalloidin, which are the active components of mushrooms, impair calcium homeostasis.[7,23]

Cytochrome P450 Enzymes as Agents of Liver Damage

1 3 Most hepatocellular injuries involve the production of high-energy reactive metabolites by the CYP450 system. 1 These reactive metabolites can

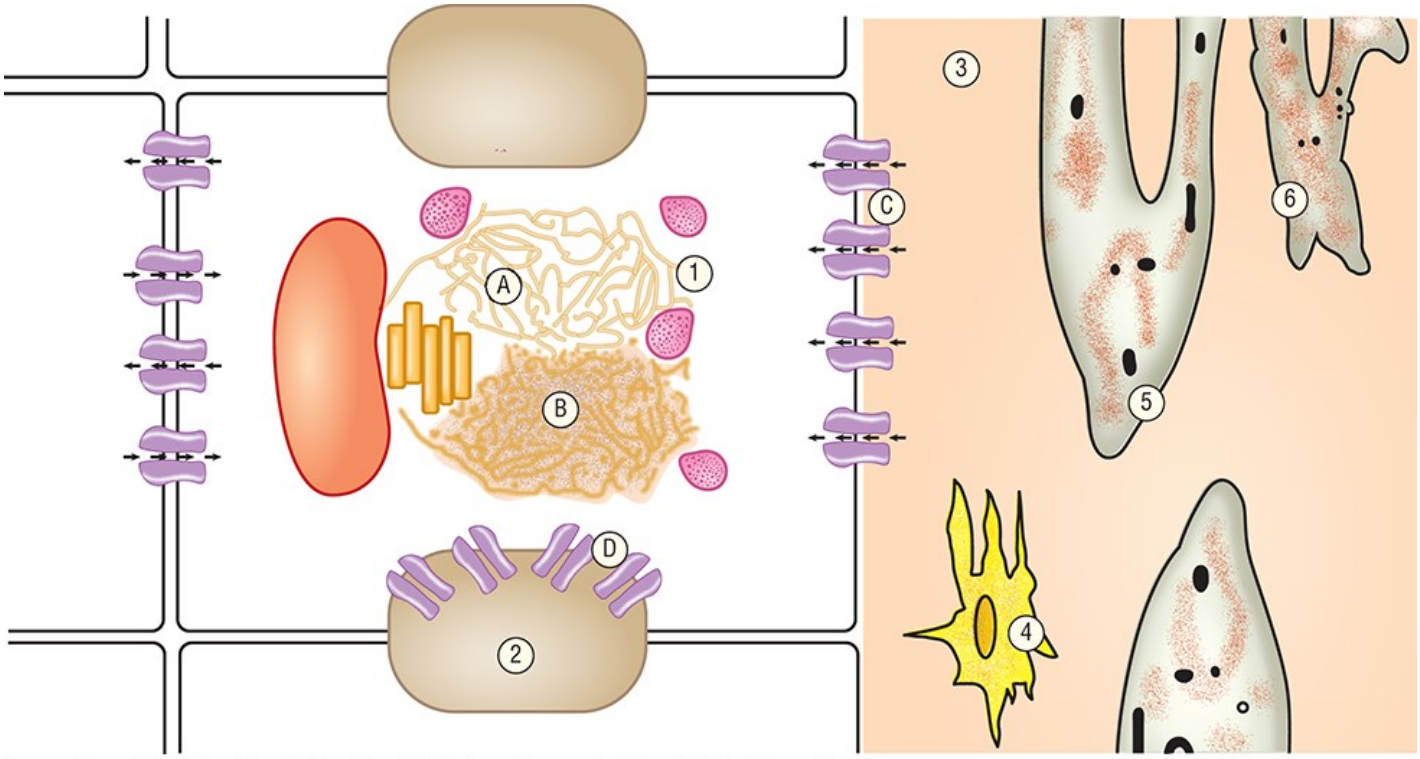
form covalent bonds with transport proteins, enzymes, and nucleic acids. In the case of acute toxicity, these enzyme-drug complexes can cause cell injury or cell lysis.[22] The complexes that form with DNA can induce neoplasia. Acetaminophen, furosemide, and diclofenac become hepatotoxin through this mechanism.[7] 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 an SNP that codes for very fast-reacting variants. These reactions will occur primarily in the smooth endoplasmic reticulum (SER) of the hepatocyte. Since the SER occupies a large portion of the cytoplasm of the hepatocyte, these reactions tend to be dispersed throughout the cell.[23]

Liver Transport Proteins and Liver Cell Communities as Agents of Liver Damage

As illustrated in Fig. e56-1, genetics and the innate roles of several proteins and cell types either accelerate or protect the liver from damage. Efflux membrane transport proteins such as organic anion transporting proteins 1B1, 1B3, and 2B1 actively pump drugs and other xenobiotics into the hepatocyte for processing and elimination from the body (Table e56-1, Fig. e56-1).[24-28] Canalicular membrane efflux transporters pump metabolites and some drugs into the bile canaliculus (Fig. e56-1). SNPs that code for various bile salt export pumps (BSEP), specifically variants of ATP-binding cassette transporters ABCB4, ABCB11, and ABCR3, are associated with rare congenital liver diseases and cholestasis during pregnancy.[29,30] These patients may have a higher risk for cholestatic liver injury. Cyclosporine A, sulindac, rifamycin, and glimepiride inhibit BSEP. Multi-drug and toxin extrusion exchanger 2 (MATE2) in the liver is important for excretion of cationic drugs such as metformin, oxaliplatin, acyclovir, and fexofenadine. There are several SNPs that are associated with modified MATE2 function.[29,30]

Figure e56-1

Regions and structures of importance for drug-induced liver injury. 1. cytoplasm; 2. biliary canaliculus; 3. liver sinusoids; 4. hepatic stellate cells; 5. sinusoidal endothelial cells; 6. Kupffer cells; A. smooth endoplasmic reticulum; B. rough endoplasmic reticulum; C. uptake transport membrane proteins; D. efflux transport membrane proteins.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

TABLE e56-1

Important Transport Protein Families

Sinusoidal Membrane Uptake Transporters (remove drugs from blood)	
Organic Anion Transporting Polypeptides	1B1, 1B3, and 2B1 are the most important uptake proteins for drugs. Subjects with SNP (174Ala) showed lower transport efficiency for 1B1, resulting in less efficient uptake
Organic Cation Transporting Polypeptides	OCTP-1 is the hepatic form. Genetic SNP appears to be rare or rarely effect OCTP-1
Canalicular Membrane Efflux Transporters (pump metabolites into the bile)	
ATP-Binding Cassette; Transporter B1	Facilitates the biliary elimination of amphiphilic drugs
ATP-Binding Cassette; Transporter C2	Facilitates the biliary elimination of glutathione, glucuronide, and sulfate conjugates. SNP (C-24T) is associated with a risk of diclofenac hepatoxicity
ATP-Binding Cassette; Transporter G2	Facilitates the biliary elimination of methotrexate, pitavastatin, rosuvastatin, and most fluoroquinolones
Bile Salt Export Pumps	Facilitates the biliary elimination of bile acids along with pravastatin and vinblastine. Multiple SNPs exist; some result in rare congenital liver diseases. Cyclosporine A, sulindac, rifamycin, and glimepiride inhibit BSEP
Multi-Drug and Toxin Extrusion Exchanger 2	Facilitates the biliary elimination of metformin, cimetidine, oxaliplatin, acyclovir, and fexofenadine along with other cationic drugs. Multiple types and distributions of SNP have been identified, which modify transport rates
Sinusoidal/Basolateral Membrane Excretory Transporters (pump metabolites back out to the blood or into other hepatocytes)	
ATP-Binding Cassette; Transporter C3	Facilitates the excretion of glucuronide conjugates
ATP-Binding Cassette; Transporter C4	Facilitates the excretion of adefovir, ganciclovir, methotrexate, 6-mercaptopurin, and steroids
ATP-Binding Cassette; Transporter C**s**	Upregulated in response to cirrhosis
Organic Solute Transporter Alpha/Beta	Facilitates the excretion of estrone; related compounds and bile acids

Data from References 27,28.

Hepatic stellate cells (HSC) reside within the space of Disse (Fig. e56-1).[29] They are important for the storage and processing of lipids and vitamin A through the production of cytoglobin.[31] When activated by cytokines from the sinusoidal endothelial and Kupffer cells, the HSC transform into damage repair cells.[32] However, when there is extensive damage, HSC will significantly reduce the amount of cytoglobin they produce. This loss of cytoglobin is associated with an acceleration of fibrosis and neoplastic responses to the damage.[31] HSC show some degree of genetic diversity along with the effects of

aging particularly in pursuing their repair roles.[31-33,35,36]

The Kupffer cells are liver-centric specialized monocytes. [1] They phagocytize foreign materials in the blood from the central vein and mediate inflammatory reactions. Large-scale activation of the Kupffer cells is the first step toward hepatitis.[29,30,33,34]

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 receptor. These interactions activate caspases, which cleave cellular proteins and eventually lead to cell death.[37]

Mitochondrial Injury

Drugs that impair mitochondrial structure, function, or DNA synthesis can disrupt β-oxidation of lipids and oxidative energy production within the hepatocyte.[21,38] In acute disease, prolonged interruption of β-oxidation leads to microvesicular steatosis, whereas in chronic disease, macrovesicular disease is present.[37] 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.[21]

Liver Neoplastic Disease

Carcinoma- and sarcoma-like lesions have developed following drug therapy. Fortunately, hepatic tumors associated with drug therapy are usually benign, remitting when drug therapy is discontinued. Usually, these lesions are associated with long-term exposure to the offending agent.[39,40] 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 in as few as 3 years of a high-quality exposure.[4,39,41]

ASSESSMENT: THE PATTERN OF LIVER ENZYME CHANGES

[2] [5] [5] [5] Drug-induced liver injury is categorized in two ways. The most common way to categorize DILI is by the pattern of liver enzyme changes. Through this approach two questions can be answered: (1) Is this liver injury? and (2) What type of liver injury is likely emerging? In severe cases a liver biopsy is used to categorize DILI by the pattern of histological changes. For the majority of DILI cases, the first indicator of injury is the elevation of the enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (Alk Phos) and total bilirubin. Additional liver enzymes and other laboratory findings that will be useful include 5′-nucleotidase (5-NT), γ-glutamyltransferase (GGTP), lactic dehydrogenase (LDH), and antismooth muscle antibodies (ASMA). Liver kidney microsomal auto-antibodies (LKM-1) are indicative of autoimmune hepatitis. Micro-RNA (mRNA) values are elevated in steatosis and ballooning inflammation. These laboratory findings break out into three primary categories of DILI: (1) hepatocellular damage, (2) cholestatic damage, and (3) mixed hepatocellular cholestatic damage.

Hepatocellular Injury

[2] [5] Hepatocellular injury is characterized by significant elevations in the serum aminotransferases, which usually precede elevations in total bilirubin levels in serum and alkaline phosphatase levels.[42] Hy's law defines hepatocellular injury as an increase in ALT that is at least three times above the upper limit of normal (UNL) with concurrent rise in TBL to a point at least 2 UNL without a significant rise in the Alk Phos (Table e56-2).[43,44] The US Food and Drug Administration (FDA) along with the Council for International Medical Sciences recommend evaluating the ratio of the ALT to the Alk Phos as well. Hepatocellular injury then becomes defined as ALT > 3 UNL plus TBL > 2 UNL plus R = (Measured ALT/Upper Normal Limit of ALT) ÷ (Measured Alk Phos/Upper Normal Limit of Alk Phos), where R > 5.[2,43,44]

TABLE e56-2

Roussel Uclaf Causality Assessment Method (RUCAM)

Criteria	Result	Score	Result	Score

Timing (days) from…				
…start of therapy	5-90	+2	<5 or >90	+1
… or cessation of therapy (except slowly metabolized drugs)			≥30	+1
Result of unintentional rechallenge of drug/herb alone	Alk Phos > 2XN	+3	Alk Phos ≤ Normal	−2
Result of unintentional rechallenge drugs/herbs given	Alk Phos > 2XN	+1	Alk Phos ≤ Normal	0
Previous reports of this drug and this reaction in…	Product labeling	+2	Published literature	+1
Concurrent hepatoxic drug/herb?	No	0		
If yes, Is hepatoxic drug/herb timing…	Consistent	−2	Inconsistent	0
Concurrent drug/herb more likely?	Positive Rechallenge	−3	Validated Test	−3
Risk Factor: Drinks/day Alcohol > 2 (female) > 3 (male)	Yes	+1	No	0
Risk Factor: Pregnant?	Yes	+1	No	0
Risk Factor: Age > 55 years old	Yes	+1	No	0
Alternatives to Rule Out				
Group I Alternative: Hepatitis A Virus via + Anti-HAV-IgM				
Group I Alternative: Hepatitis B Virus via + Anti-HBV-IgM or + HBV-DNA				
Group I Alternative: Hepatitis C Virus via + Anti-HCV-IgM or + HCV-RNA				
Group I Alternative: Hepatitis E Virus via + Anti-HEV-IgM, + Anti-HEV-IgG or + HEV-RNA				
Group I Alternative: Other positive test for other liver diseases or disorders, such as Hepatobiliary Sonography, Color Doppler Sonography, Endosonography, Liver CT Scan, Liver MRI				
Group I Alternative: Diagnosis of Alcoholism with elevated AST of ALT > 2				
Group I Alternative: Recent hypotensive history (particularly with underlying heart disease)				
Group II Alternatives: Autoimmune Hepatitis, Chronic Viral Hepatitis, Biliary or Sclerosing Cholangitis				
Group II Alternatives: Complications of Sepsis, Metastatic Malignancy, Genetic Liver Diseases				
Group II Alternatives: Positive Test for Infection Cytomegaly, Epstein-Bar, Herpes Simplex, Varicella-Zoster Viruses				
All Alternatives Ruled Out	Groups I and II	+2	Group I only	+1
Some Alternatives Ruled Out	5-6 of Group I	0	<5 of Group I	−2
An Alternative Cause is…	Highly Likely	−3	Somewhat Likely	0

Total Score ≤ 0 – means the drug or herb is not a likely cause; ≤ 2 – means it is unlikely to be the cause; ≤ 5 – means the drug or herb possibly may have caused this reaction; ≤ 8 - means the drug or herb is a probable cause of the reactions and > 8 – means the drug or herb is highly probable to be the cause. (2×N = Two Times the Normal Upper Limit)

Data from Reference 43.

Most hepatocellular injuries occur within 1 year of starting drug therapy. Hepatocellular injury can lead to fulminant hepatitis with a corresponding 20% survival rate with supportive care.[37] For those patients who present with the combination of hepatocellular injury and jaundice, there is a 10% mortality rate.[40] Acarbose, allopurinol, fluoxetine, and *losartan* are capable of causing hepatocellular injury.[42]

Autoimmune hepatocellular injury is often accompanied by fever and elevations in ANA, ASMA, LKM-1, and gamma globulins. Typically, this type of DILI is more rapid in onset (less than 2 months from start of therapy) and fulminant.[45] If identified early, autoimmune hepatocellular injury may respond to high-dose glucocorticoid treatment. This treatment must be carefully targeted, since glucocorticoid treatment can worsen underlying fatty liver disease.[20]

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 biopsy results.[46]

Cholestatic Injury

Cholestatic disease is more often seen in patients over the age of 60 and is slightly more common in males.[9] In cholestatic disease, disturbance of the subcellular actin filaments around the canaliculi prevents the movement of bile through the canalicular system.[21] Mutations in hepatic transporter genes can result in slower function prior to toxin exposure.[47] The inability of the liver to remove bile causes intrahepatic accumulation of toxins and waste products.[21,47]

Alkaline phosphatase is the dominant enzyme with cholestatic injury.[3] Cholestatic injury is defined by an Alk Phos > 3 UNL plus TBL > UNL plus and R ≤ 2. Erythromycin-associated DILI is the prototype for this injury, along with amoxicillin–clavulanic acid, and carbamazepine.[37] An IV form of vitamin E, α-tocopheryl acetate, causes cholestatic jaundice, primarily involving the canalicular duct in premature infants. The incidence of this reaction in those receiving this formulation was high (more than 10%) and the mortality even higher (more than 50%).[48]

Cholestatic injury is also known as cholestatic jaundice or cholestasis and can be further classified by the area of the bile canalicular or ductal system that is impaired. Canalicular cholestasis is often associated with long-term, high-dose estrogen therapy. These patients are often asymptomatic and present with mild-to-moderate elevations of serum bilirubin.[49]

A subtype of cholestatic injury, often associated with antibiotic usage, is “vanishing bile duct syndrome” occurring in 7% of all cases reported to the Drug Induced Liver Injury Network (DILI-Net) between 2004 and 2014.[50] The finding on biopsy of bile duct loss appears to be associated with progression to severe cholestatic disease in most cases, even if the loss is minimal or early.[51]

Mixed Hepatocellular and Cholestatic Injury

This pattern, as the name implies, is the result of both hepatocytes and bile canalicular cells bearing damage at approximately the same time.

ASSESSMENT: THE PATTERN OF HISTOLOGIC CHANGES

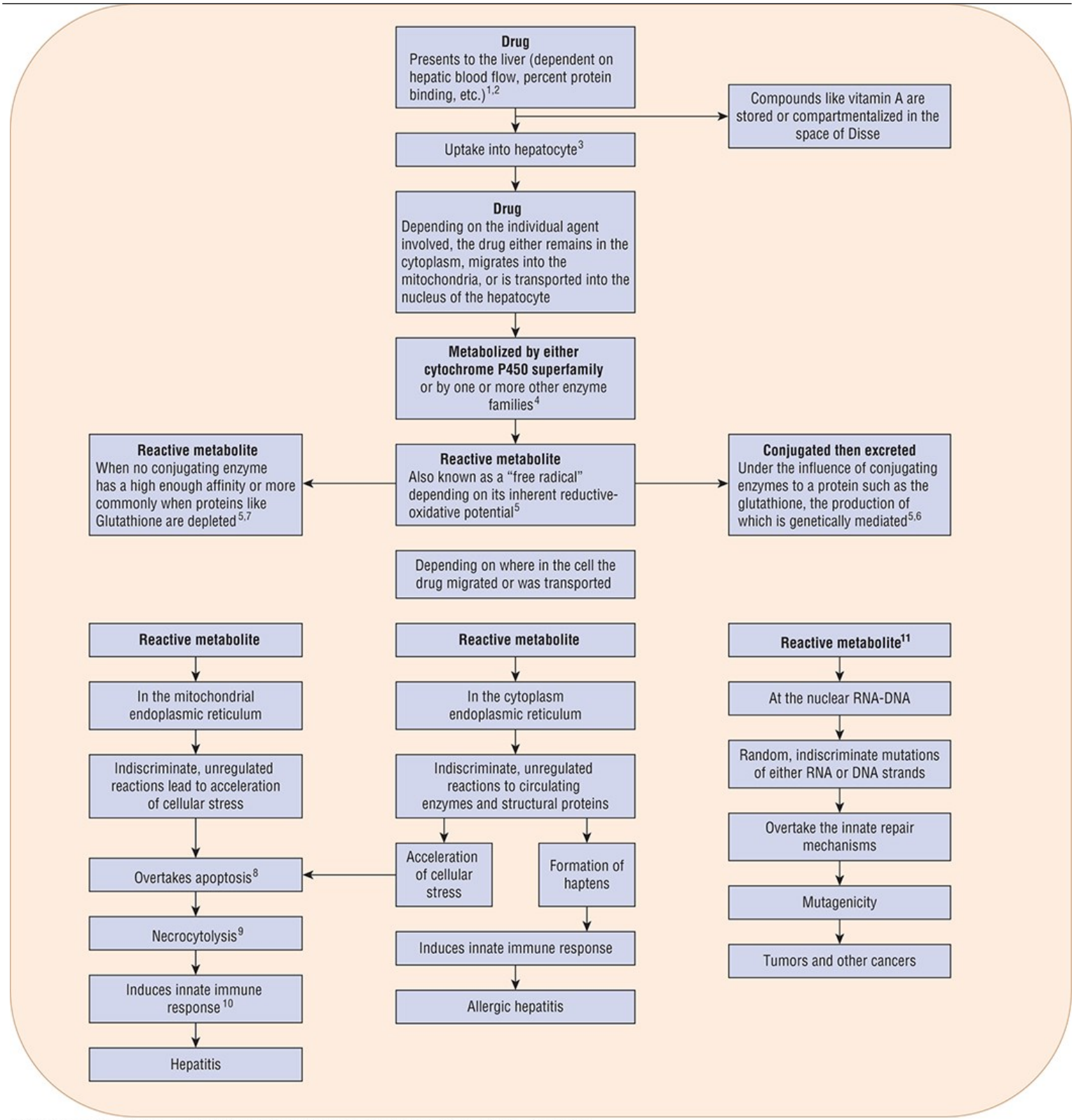
Samples of tissue obtained through biopsy are the best and most reliable identification technique in determining the impact of DILI. Evermore sophisticated magnetic resonance imaging, CT-scans, and ultrasonography are slowly replacing liver biopsy as the first choice in determining the pattern of histological changes clinically. Important anatomical features of the liver are illustrated in Fig. e56-1.

Centrilobular Necrosis

Centrilobular necrosis describes a pattern of cell damage that originates in the hepatocytes located nearest the central vein of the liver. Centrolobular necrosis is often the result of the production of a toxic metabolite (Fig. e56-2). The damage spreads outward from the middle of a lobe of the liver.

Figure e56-2

A general diagram of biotransformation. (1) Hepatic blood flow, which changes proportionately with changes in cardiac output, delivers the drug to the liver. (2) Protein binding is most affected by nutritional status and competing drugs. (3) The drug is actively transported into the hepatocyte by the organic anion transport pump, a transmembrane protein. (4) The metabolite (drug) interacts with one of a number of enzymes, the most common being CYP2C9, CYP2C19, CYP2D6, and CYP3A4. 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. (5) 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. (6) 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. (7) If unable to form a conjugate, the unstable metabolite can participate in oxidative reactions that damage lipids, proteins, or even DNA. (8) The normal process of cellular aging, death, and reabsorption by surrounding cells. (9) Widespread, rapid cellular death with the creation of multiple antigens. (10) Activation of 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 are mediated by genetic polymorphism. (11) 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.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

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.[10,52]

These reactions are predictable, often dose-related effects in the liver caused by specific agents. When taken in overdose, acetaminophen becomes bioactivated to a toxic intermediate known as *N*-acetyl-*p*-benzoquinone imine (NAPQI). NAPQI is highly reactive, with a high affinity for sulfhydryl groups. The tripeptide 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. The depletion of glutathione changes the mitochondrial oxidized to reduced glutathione ratio resulting in catastrophic shifts in mitochondrial function, accelerating cell necrocytolysis.[53] Continuing mitochondrial damage leading to fragmentation of mitochondrial DNA leads directly to necrosis.[54] Replenishing the liver's sulfhydryl capacity through the administration of *N*-acetylcysteine early after ingestion of the overdose halts this process.[48] 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.[55] Circulating cell-free mRNA (liver-specific mR-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 injuries in the future.[56]

Nonalcoholic Steatohepatitis

2 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 Fig. e56-2). 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 infiltration of polymorphonuclear leukocytes, degeneration of the hepatocytes, and Mallory bodies.[57]

Alcohol is the drug that most commonly produces steatonecrotic changes in the liver. When alcohol is converted into acetaldehyde, the synthesis of fatty acids is increased.[58,59] The hepatocyte can become completely engorged with microvesicular fat, resulting in alcoholic fatty liver. Metabolically this type of de novo free 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. Because of the pervasive nature it begins to react directly with the hepatocyte (see Fig. e38-1). It is commonly referred to separately as alcoholic liver disease (analogous to NAFLD) and alcoholic hepatitis (analogous to NASH).

In NAFLD, the same endpoint is often achieved through oxidation of lipid peroxidases.[60] 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. NAFLD is a common result of certain subtypes of type 2 diabetes mellitus. Here the cause is related to aberrant carbohydrate and liver metabolic rates and is strongly associated with insulin resistance.

3 Tetracycline produces NAFLD and NASH.[56] 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. Sodium valproate also can produce steatonecrosis through the process of bioactivation. Cytochrome P450 converts valproate to Δ-4-valproic acid, a potent inducer of microvesicular fat accumulation.[61,62]

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

2 6 Phospholipidosis is the accumulation of phospholipids instead of fatty acids. The phospholipids usually engorge the lysosomal bodies of the hepatocyte.[58] 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*-desethylamiodarone ratios, indicating a greater accumulation of the parent compound. Amiodarone and its major metabolite *N*-desethylamiodarone remain stored in the stellate cells (Fig. e56-1) of patients for 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.[13,57]

Generalized Hepatocellular Necrosis

2 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 haptens, which serve as neoantigens and induce the innate immune response (see Fig. e56-1).[63,64]

3 The rate of bioactivation can vary between individuals.[65,66] 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 subspecies 2C9, 2C19, 2D6, 3A4, and 4F8 are regulated by the highly inducible xenobiotic receptor on 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.[67]

3 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.[68] The *N*-acetyltransferase-2 (NAT2) genotype appears to play a role in determining a patient's relative risk. Seventy percent of patients who developed elevated liver enzymes (defined as at least 2.5 times upper normal) or jaundice were slow acetylators.[69] Isoniazid is metabolized by several pathways, acetylation being the major pathway. It is acetylated to acetylisoniazid, which, in turn, is hydrolyzed to acetylhydrazine.[70] Acetylhydrazine, and to a lesser extent the acetylisoniazid, is directly toxic to the cellular proteins in the hepatocyte, but rapid acetylators detoxify acetylhydrazine rapidly, converting it to diacetylhydrazine (a nontoxic metabolite). The rate and efficiency of this reaction sequence ultimately determines if hepatocellular damage will ensue.

3 6 6 Isoniazid simultaneously is an example of the potential predictability of DILI based on SNP and a lesson in the limitations of our current understanding. There are definite links to NAT2 genotype and toxicity.[71] In particular the polymorphic forms of NAT2 *5, NAT2 *6, NAT2 *7, and NAT2 *14 encode for slow acetylation.[72] The risk for this reaction is also influenced heavily by the age, which is a stronger risk factor than phenotype.[68,69,71] Females, patients with low BMI, patients diagnosed with alcohol misuse, AIDS, hepatitis B, hepatitis C, and those with previous hepatic injuries are reported more often to have suffered injury than the general population.[71,72] In one prospective series focused on DILI, 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.[8]

Ketoconazole produces generalized hepatocellular necrosis or milder forms of hepatic dysfunction in up to 2% of patients treated for fungal infections. The onset is usually early in therapy. In immunocompromised patients in whom ketoconazole is used, special care should be taken to watch for changes in liver function.[73]

Toxic Cirrhosis or Fibrosis

2 The scarring effect of hepatitis in the liver leads to the development of cirrhosis through a process known as fibrosis. 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. The loss of cytoglobin, a stellate cell-specific protein complex, may mark the beginnings of this process.[33]

6 Methotrexate causes periportal fibrosis in most patients who experience hepatotoxicity. The lesion results from the action of a bioactivated metabolite produced by CYP450.[74] 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.[53,75] Vitamin A is normally stored in liver cells, and causes significant hypertrophy and fibrosis when taken for long periods in high doses. Hepatomegaly is a common finding, along with ascites and portal hypertension. In patients with vitamin A toxicity, gingivitis and dry skin are also very common. This is accelerated by ethanol, which competes with retinol for aldehyde dehydrogenase.[58]

Liver Vascular Disorders

2 Focal lesions in hepatic venules, sinusoids, and portal veins occur with various drugs. Commonly associated drugs include the cytotoxic agents used to treat cancer, the pyrrolizidine alkaloids, and the sex hormones. A centralized necrosis often follows the vasculitis and can result in cirrhosis. Azathioprine and herbal teas that contain comfrey (a source of pyrrolizidine alkaloids) are associated with venoocclusive disease. The exact incidence is rare and may be

dose related.[57] 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 cavities within the parenchyma. Rupture of the lacunae can lead to severe peritoneal hemorrhage. Peliosis hepatitis is associated with 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.[76]

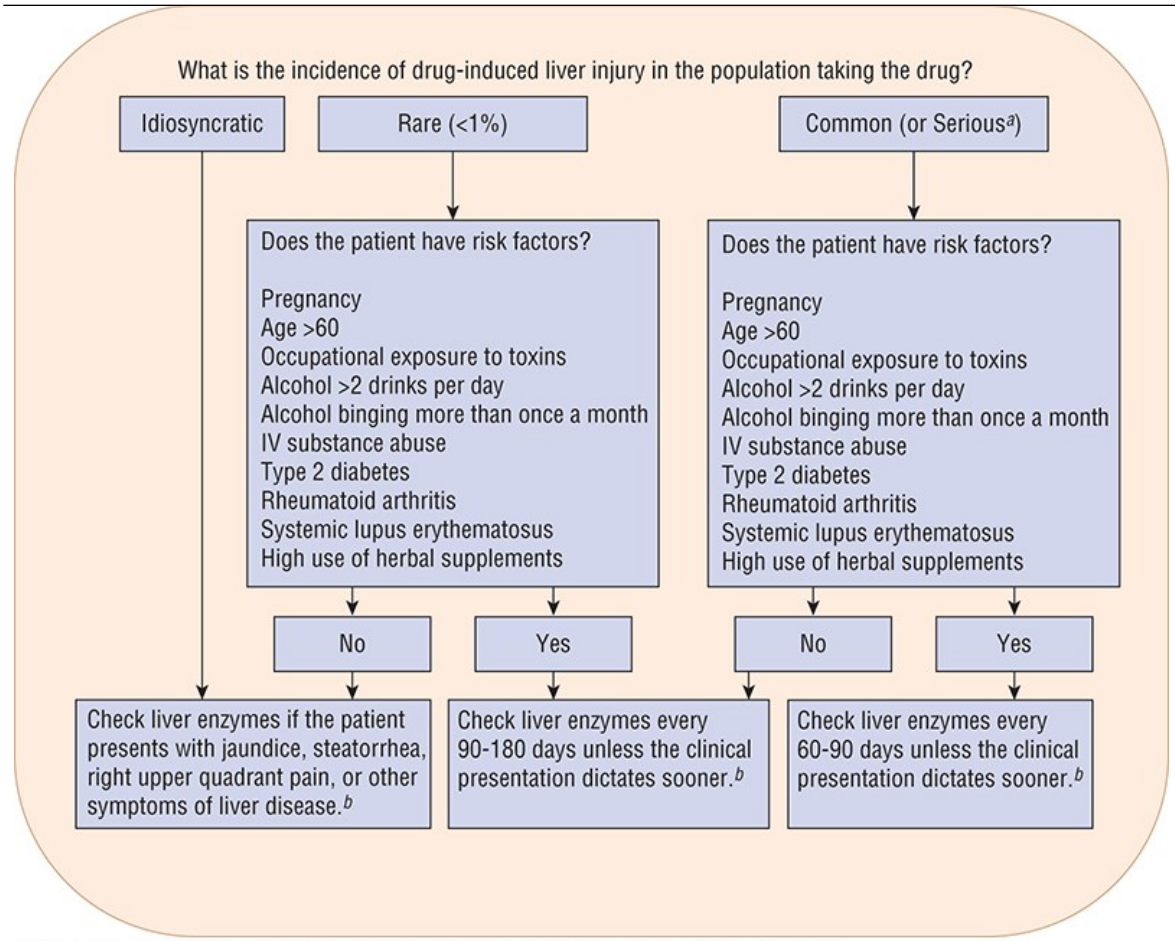
ASSESSMENT: DETERMINING THE MEDICATION-RELATED PROBLEM

4 It is important to document the pattern of liver enzyme changes, the pattern of histologic changes if known to assess the medication-related problem. Key information also comes from the patient's history. Confirming DILI requires the exclusion of common causes of liver injury, the timing of drug exposure to injury onset, along with supporting laboratory and clinical features. 4 Causality assessment tools include the Roussel Uclaf Causality Assessment Method (RUCAM), Clinical Diagnostic Scale, and Digestive Disease Week Japan system.[44] RUCAM was the first causality assessment method that defined criteria of liver injury by using liver test thresholds based upon multiples of upper limits of normal of liver function tests as a diagnostic criterion.[2,3,44]

6 A patient's history of drug use is essential to consider (Fig. e56-3).[72-75] Drugs used for recreational purposes must not be overlooked. Cocaine has been directly linked to liver disease.[80,81] Methylenedioxymethamphetamine (MDMA or Ecstasy) has induced deadly fulminant hepatitis as have various combinations of the so-called synthetic marijuana or Spice.[82,83] The more pervasive but harder to detect impact of street drugs on the incidence of hepatic disease is the concomitant injection or ingestion of adulterants. Talc, heavy metals, and various solvents are used. Many of these adulterants are either directly toxic or serve to enhance the toxicity of the drug (see Table e56-2).

Figure e56-3

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.



4 It is also important to determine nondrug hepatic disease risk from occupational or environmental exposure. Arsenic is known to induce both acute and chronic hepatic reactions.[77] 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.[77-80] Table e56-3 lists some of the more common hepatic toxins found in occupational or environmental exposures that can add to the risk for developing a hepatic lesion.[79] Immune-mediated chronic liver diseases can often be tracked to geographic clusters that correspond to known toxic waste sites around the world.[84]

TABLE e56-3

Environmental Hepatotoxins and Associated Occupations at Risk for Exposure

Hepatotoxin	Associated Occupations at Risk for Exposure
Arsenic	Chemical plant, agricultural workers
Carbon tetrachloride	Chemical plant workers, laboratory technicians
Copper	Plumbers, sculpture artists, foundry workers
Dimethylformamide	Chemical plant workers, laboratory technicians
2,4-Dichlorophenoxyacetic acid	Horticulturists
Fluorine	Chemical plant workers, laboratory technicians
Toluene	Chemical plant, agricultural workers, laboratory tech
Trichloroethylene	Printers, dye workers, cleaners, laboratory technicians
Vinyl chloride	Plastics plant workers; also found as a river pollutant

46 The history of a person's use of alternative medicines must be solicited. As traditional medicine usage is commonplace, herbal remedies and other traditional medicines accounted for 14 of 132 cases of DILI.[8] Comfrey tea is a common cause of hepatocellular damage. The Chinese remedy *jinbuhuan*, or the more elegantly presented chaparral capsules containing grease wood leaves, may occasionally cause severe disability or death from fulminant hepatic failure.[80] Pennyroyal oil, margosa oil (also *Neem Ka Tel* in India), and clove oil cause a dose-related hepatotoxicity.[85]

Patients with liver dysfunction are typically unable to identify a specific component in the dietary supplement being consumed. In a report covering 132 cases of herbal or supplement-related liver injury reported to the DILI-Net (https://dilin.org); 45 cases were related or caused by body building agents, likely an anabolic steroid in the supplement. Weight loss products were the next most frequently reported agents.[86] Products for depression, sexual performance, gastrointestinal upset, immune support, and joint care often combined with Chinese herbs made up another third of the reports.[86]

44 The nutritional status of a patient can be as important to the development of a DILI as the hepatotoxin itself.[77-80] Patients who are malnourished because of illness or long-term alcohol misuse make up the most highest risk group.[87] Low serum levels of vitamins E and C along with lutein and the α- and β-carotenes are associated with asymptomatic elevations in transaminases. High serum iron, transferrin, and selenium levels are also associated with asymptomatic elevations of transaminases.[88]

When the drug in question is stopped the patient should be closely observed. It is also important to keep in mind that most elevations in liver enzymes will not be associated with a drug. In 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.[13] In all cases of patients with elevated liver enzymes, titers of serum antibodies to hepatitis A, B, and C should be determined. Even in cases in which the drug is absolutely targeted as the cause, viral hepatitis may be a complication.[77-80]

ASSESSMENT: SEVERITY OF THE MEDICATION-RELATED PROBLEM

55 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 (Table e56-4). 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.[89]

TABLE e56-4

Relative Patterns of Hepatic Enzyme Elevation versus Type of Hepatic Lesion

Enzyme	Abbreviations	Necrotic	Cholestatic	Chronic
Alkaline phosphatase	Alk Phos, AP	↑	↑↑↑	↑
5′-Nucleotidase	5-NC, 5NC	↑	↑↑↑	↑
γ-Glutamyltransferase	GGT, GGTP	↑	↑↑↑	↑↑
Aspartate aminotransferase	AST, SGOT	↑↑↑	↑	↑↑
Alanine aminotransferase	ALT, SGPT	↑↑↑	↑	↑↑
Lactate dehydrogenase	LDH	↑↑↑	↑	↑

Bilirubin concentrations and serum enzyme elevations give a static picture of the liver's condition and are not good indicators of hepatic function. Serum protein (albumin or transferrin) measurement can be used to assess hepatic function. As hepatic function decreases, serum protein concentrations decrease. Overhydration and starvation can also decrease serum protein concentrations. Albumin levels less than 2.8 g/dL (28 g/L) were associated with significant mortality following the onset of DILI.[90]

Elevations in blood monocyte counts appear to occur early and dramatically in acute hepatic injuries evolving into hepatitis.[37] Changes in the prothrombin time as reported as the international normalized ratio (INR) often occur earlier than the changes in albumin or transferrin. INR is a good predictor of liver function in acute liver failure.[91] The response of the INR to the administration of 10 mg of parenteral vitamin K has been used to differentiate between hepatic and extrahepatic disease.[91]

Novel Biomarkers for Drug-Induced Liver Injury

Because liver enzymes are released into circulation following most hepatocyte damage they do not provide insight into the mechanism of the underlying injury.[92,93] Some of the novel biomarkers that may allow early detection and insight into underlying mechanisms include sorbitol dehydrogenase (SDH), micro-RNA 122, glutamate dehydrogenase (GLDH), cytokeratin 18 (CK 18), and high mobility group box 1 protein (HMGB1).[92,94]

SDH has been studied in various forms of liver injury and shows promise in the early detection of DILI.[93] The new biomarkers, micro-RNA 122, CK18, and HMGB1 are potentially useful in DILI as prognostic makers.[92,95] Likewise, GLDH, CK18, and HMGB1 have potential as mechanistic biomarkers. Elevated levels of serum GLDH are indicative of mitochondrial dysfunction and loss of mitochondrial integrity. The Apoptic Index, which is a measure of the ratio of CK18 to ccK18 levels in the serum, estimates the contribution of apoptosis and necrosis in the face of liver injury. The HMGB1 is also a marker of tissue necrosis and its acetylated form is a marker of activation of the innate immune system.[92,94]

In cases where either the cause or the severity of a liver injury is still in question, consultation with LiverTox is suggested. LiverTox (https://livertox.nih.gov/) provides information about drug-induced liver injury caused by drugs, herbals, and supplements. LiverTox also provides guidance on the diagnosis and management of DILI.

Documentation of Liver Injury

Once liver injury from a drug is diagnosed, it is important to share that information with other healthcare practitioners. Liver injury that is new or poorly established from a drug or herbal product should be reported to the FDA through MedWatch (https://www.fda.gov/safety/medwatch/default.htm).[96] For any severe drug-induced liver injury, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has established the Drug-Induced Liver Injury DILI-Net at http://www.dilin.org/ to collect and analyze cases of severe liver injury caused by drugs, and alternative medicines.[97]

ABBREVIATIONS

ABC	ATP binding cassette
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ASMA	antismooth muscle antibodies
AST	aspartate aminotransferase
BMI	body mass index (BMI = [Weight (lb)/2.205] / [(Height (in)/39.37)^2] or [Weight (kg)]/[Height (m)]^2)
CYP450	cytochrome P450 liver enzyme family
DILI	drug-induced liver injury
GGTP	gamma (γ)-glutamyltransferase
HLA	human leukocyte antigen
HSC	hepatic stellate cells
IL-9	interleukin-9, prevents apoptosis
IL-19	interleukin-19, induces apoptosis
INR	international normalized ratio
LDH	lactic dehydrogenase
LKM-1	liver kidney microsomal autoantibodies
miRNA-122	circulating micro-RNA–number 122
MDMA	methylenedioxymethamphetamine
NAFLD	nonalcoholic fatty liver disease
NAPQI	*N*-acetyl-*p*-benzoquinone imine
NASH	nonalcoholic steatohepatitis
NAT2	*N*-acetyltransferase 2 genotype
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
SER	smooth endoplasmic reticulum
SNP	single nucleotide polymorphism

TBL	total bilirubin
TNF	tumor necrosis factor
UNL	upper normal limit for the particular laboratory test

REFERENCES

1. Grant LM, Rickey DC. Drug-induced liver injury. *Curr Opin Gastroenterol.* 2012;28:198–202. [PubMed: 22450893]

2. Leise MD, Poterucha JJ, Talwalker JA. Drug-induced liver injury. *Mayo Clin Proc.* 2014;89(1):95–106. [PubMed: 24388027]

3. Murray KF. Drug-related hepatotoxicity and acute liver failure. *J Pediatr Gastroenterol Nutr.* 2008;47:395–405. [PubMed: 18852631]

4. Lee W. Drug-induced hepatotoxicity. *N Engl J Med.* 2003;349:474–485. [PubMed: 12890847]

5. Mindikoglu AL, Magder LS, Regev A. Outcome of liver transplantation for drug-induced acute liver failure in the United States: Analysis of the United Network for Organ Sharing Database. *Liver Transpl.* 2009;15:675–676, 719–729. [PubMed: 19562694]

6. Beuers U, Boberg KM, Chapman RW, et al. Clinical Practice Guidelines Panel. EASL Clinical practice guidelines: Management of cholestatic liver diseases. *J Hepatol.* 2009;51:237–267. [PubMed: 19501929]

7. Chang C, Schiano T. Review article: drug hepatoxicity. *Aliment Pharmacol Ther.* 2007;25:1135–1151. [PubMed: 17451560]

8. Mandana K, Burman B. Liver disease. In Hammer GD, McPhee SJ, eds. *Pathophysiology of Disease: An Introduction to Clinical Medicine*. 7th ed. McGraw-Hill Education; 2014:chap.14.

9. Reuben A, Koch DG, Lee WM. Acute liver failure (ALF) secondary to drug induced liver injury (DILI): causes & consequences. *Hepatology*. 2009;50:347A.

10. Lucena MI, Adrarde RJ, Kaplowitz N, et al. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and sex. *Hepatology*. 2009;49:2001–2009. [PubMed: 19475693]

11. Fernandes NF, Martin RR, Schenker S. Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. Am J Gastroenterol. 2000;95:532–535. [PubMed: 10685763]

12. Fisher K, Vuppalanchi R, Ramil S. Drug-induced liver injury. *Arch Pathol Lab Med.* 2015;139:876–887. [PubMed: 26125428]

13. Chang CC, Petrelli M, Tomashefski JF Jr, McCullough AJJ. Severe intrahepatic cholestasis caused by amiodarone toxicity after withdrawal of the drug: a case report and review of the literature. *Arch Pathol Lab Med.* 1999;123:251–256. [PubMed: 10086516]

14. Komori A. Recent updates on the management of autoimmune hepatitis. *Clinical and Molecular Hepatology*. 2021;27(1):58–69. doi: 10.3350/cmh.2020.0189.

15. Nicoletti P, Aithal GP, Bjornsson ES, Andrade RJ, Sawle A, et al. Association of liver injury from specific drugs, or groups of drugs, with polymorphisms in HLA and other genes in a genome-wide association study. *Gastroenterology*. 2017;152(5):1078–1089. [PubMed: 28043905]

16. Hoofnagle JH, Bonkovsky HL, Phillips EJ, et al. HLA-B*35:01 and green tea-induced liver injury. *Hepatology (Baltimore, Md)*. 2021;73(6):2484–2493. 10.1002/hep.31538.

17. Monshi MM, Faulkner L, Gibson A. Human leukocyte antigen (HLA)-B*5701-restricted activation of drug-specific T cells provides the immunologic basis for flucloxacillin-induced liver injury. *Hepatology*. 2013;57:727–739. [PubMed: 22987284]

18. Barbarino JM, Kroetz DL, Altman RB, Klein TE. PharmGKB summary: abacavir pathway. *Pharmacogenet Genomics*. 2014;24(5):276–282. doi: 10.1097/FPC.0000000000000040.

19. Teschke R, Uetrecht J. Mechanism of idiosyncratic drug induced liver injury (DILI): unresolved basic issues. *Ann Transl Med.* 2021;9(8):730. [PubMed: 33987428]

20. Benesic A, Rotter I, Dragoi D, Weber S, et al. Development and validation of a test to identify drugs that cause idiosyncratic drug-induced liver disease. *Clin Gastroenterol Hepatol.* 2018;16:1488–1494. ClinicalTrials.gov NCT 02353455. [PubMed: 29723689]

21. Norman B. Drug induced liver injury (DILI): mechanisms and medicinal chemistry avoidance/mitigation strategies. *J Med Chem.* 2020;63:11397–11419. [PubMed: 32511920]

22. Jee A, Sernoskie S, Uetrecht J. Idiosyncratic drug-induced liver injury: mechanistic and clinical challenges. *Int J Mol Sci.* 2021;22:954. [PubMed: 33477998]

23. Wu F, Liu W, Zheng M, et al. Targeting endoplasmic reticulum stress in liver disease. *Expert Rev Gastroenterol Hepatol.* 2016;10(9):1041–1052. [PubMed: 27093595]

24. Tirona RG, Leake BF, Merino, G, Kim, RB. Polymorphisms in OATP-C: Identification of multiple allelic variants associated with altered transport activity among European- and African-Americans. *J Biol Chem.* 2001;276(38):35669–35675. [PubMed: 11477075]

25. Michalski C, Cui Y, Nies AT, et al. A naturally occurring mutation in the SLC21A6 gene causing impaired membrane localization of the hepatocyte uptake transporter. *J Biol Chem.* 2002;277(45):43058–43063. [PubMed: 12196548]

26. Niemi M, Pasanen MK, Neuvonen PJ. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol Rev.* 2011;63(1):157–181. [PubMed: 21245207]

27. Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol.* 2009;158(3):693–705. [PubMed: 19785645]

28. Bachmakov I, Glaeser H, Fromm MF, et al. Interaction of oral antidiabetic drugs with hepatic uptake transporters: focus on organic anion transporting polypeptides and organic cation transporter 1. *Diabetes*. 2008;57(6):1463–1469. [PubMed: 18314419]

29. Stanca C, Jung D, Meier PJ, Kullak-Ublick GA. Hepatocellular transport proteins and their role in liver disease. *World J Gastroenterol.* 2001;7(2):157–169. doi: 10.3748/wjg.v7.i2.157.

30. Nayagam JS, Williamson C, Joshi D, Thompson RJ. Review article: liver disease in adults with variants in the cholestasis-related genes ABCB11, ABCB4 and ATP8B1. Alimentary pharmacology & therapeutics. 2020;52(11-12):1628–1639. doi: 10.1111/apt.16118.

31. Malarkey D, Johnson K, Ryan L, Boorman G, Maronpot R. New insights into functional aspects of liver morphology. *Toxicol Pathol.* 2005;33(1):27–34. [PubMed: 15805053]

32. Natarajan V, Harris E, Kidambi S. SECs (sinusoidal endothelial cells), liver microenvironment, and fibrosis. *Biomed Res Int.* 2017;2017:4097205. [PubMed: 28293634]

33. Thuy LTT, Hai H, Kawada N. Role of cytoglobin, a novel radical scavenger, in stellate cell activation and hepatic fibrosis. *Clinical and Molecular Hepatology*. 2020;26(3):280–293. doi: 10.3350/cmh.2020.0037.

34. Zhao Q, Qin C, Zhao Z, Fan Y, Wang K. Epigenetic modifications in hepatic stellate cells contribute to liver fibrosis. *Tohoku J Exper Med.* 2013;229(1):35–43.

35. Moore JK, MacKinnon AC, Man TY, Manning JR, Forbes SJ, Simpson KJ. Patients with the worst outcomes after paracetamol (acetaminophen)-induced liver failure have an early monocytopenia. *Aliment Pharmacol Ther.* 2017;45(3):443–454. Epub 2016 Nov 28. doi: 10.1111/apt.13878.

36. Ye H, Nelson L, de Moral M, Martinez-Naves E, Cubero F. Dissecting the molecular pathophysiology of drug-induced liver injury. *World J Gastroenterol.* 2018;24(13):1373–1385. [PubMed: 29632419]

37. Ramachandran R, Kakar S. Histological patterns in drug-induced liver disease. *J Clin Pathol.* 2009;62:481–492. [PubMed: 19474352]

38. Fromenty B. Alteration of mitochondrial DNA homeostasis in drug-induced liver injury. *Food and Chemical Toxicology*. 2020;135:110916. [PubMed: 31669601]

39. Lee FI, Smith PM, Bennett B, Williams DMJ. Occupationally related angiosarcoma of the liver in the United Kingdom 1972-1994. *Gut.* 1996;39:312–318. [PubMed: 8977349]

40. Anonymous. Epidemiologic notes and reports: Angiosarcoma of the liver among polyvinyl chloride workers—Kentucky. *MMWR Morb Mortal Wkly Rep.* 1997;46:99–101.

41. Navarro V, Senior J. Drug-related hepatotoxicity. *N Engl J Med.* 2006;354:731–739. [PubMed: 16481640]

42. Robles-Diaz M, Lucena MI, Kaplowitz N, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. *Gastroenterology*. 2014;147:109–118. Available at http://dx.doi.org/10.1053/j.gastro.2014.03.050. Accessed August 2016. [PubMed: 24704526]

43. Danan G, Teschke R. RUCAM in Drug and Herb Induced Liver Injury: The Update. *International Journal of Molecular Sciences*. 2015;17(1). doi: 10.3390/ijms17010014.

44. Bjonsson E. Drug-induced liver injury: Hy's rule revisited. *Clin Pharmacol Ther.* 2006;79:521–528. [PubMed: 16765139]

45. Bjomsson E, Talwalker J, Treeprasertsuk S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. *Hepatology*. 2010;51(6):2040–2048. [PubMed: 20512992]

46. Trauner M, Fickert P, Zollner G. Genetic disorders and molecular mechanisms in cholestatic liver disease—a clinical approach. *Semin Gastrointest Dis.* 2001;12(2):66–88. [PubMed: 11352122]

47. Lorch V, Murphy D, Hoersten L, et al. Unusual syndrome among premature infants: associated with a new intravenous vitamin E product. *Pediatrics*. 1985;75:598–601. [PubMed: 3975131]

48. Foitl DR, Hyman G, Leftowitch JH. Jaundice and intrahepatic cholestasis following high-dose megestrol acetate for breast cancer. *Cancer*. 1989;63:438–439. [PubMed: 2912522]

49. Zhao Z, Bao L, Yu X, et al. Acute vanishing bile duct syndrome after therapy with cephalosporin, metronidazole, and clotrimazole: a case report. *Medicine*. 2017;96(36):e8009. [PubMed: 28885366]

50. Bonkovsky HL, Kleiner DE, Gu J, et al. U.S. Drug Induced Liver Injury Network Investigators. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. *Hepatology*. 2017;65(4):1267–1277. [PubMed: 27981596]

51. Fontana RJ, McCashland TM, Benner KG, et al. Acute liver failure associated with prolonged use of bromfenac leading to liver transplantation. The Acute Liver Failure Study Group. *Liver Transpl Surg.* 1999;5:480–484. [PubMed: 10545534]

52. Riemer J, Bulleid N, Herrmann JM. Disulfide formation in the ER and mitochondria: two solutions to a common process. *Science*. 2009;324:1284–1287. [PubMed: 19498160]

53. McGill MR, Sharpe MR, Williams CD, Taha M, Curry SC, Jaeschke H. The mechanism underlying acetaminophen induced hepatotoxicity in humans and mice involves mitochondrial damage and nuclear DNA fragmentation. *J Clin Invest.* 2012;122(4):1574–1583. [PubMed: 22378043]

54. Tan H, Chang CY, Martin P. Acetaminophen hepatotoxicity: Current management. *Mt Sinai J Med.* 2009;76:75–83. [PubMed: 19170221]

55. Wang K, Lee I, Carlson G, Hood L, Galas D. Systems biology and the discovery of diagnostic biomarkers. *Dis Markers*. 2010;28:199–207. [PubMed: 20534905]

56. Björnsson E. Review article: drug-induced liver injury in clinical practice. *Aliment Pharmacol Ther.* 2010;32:3–13. [PubMed: 20374223]

57. Leo MA, Lieber CSJ. Alcohol, vitamin A, and beta-carotene: adverse interactions, including hepatotoxicity and carcinogenicity. *Am J Clin Nutr.* 1999;69:1071–1085. [PubMed: 10357725]

58. Agarwal DP, Goedde HW. Human aldehyde dehydrogenases: their role in alcoholism. *Alcohol.* 1989;6:517–523. [PubMed: 2688685]

59. Bohan A, Boyer J. Mechanisms of hepatic transport of drugs: implications for cholestatic drug reactions. *Semin Liver Dis.* 2002;22:123–136. [PubMed: 12016544]

60. Lee WM. Acute hepatic failure. *N Engl J Med.* 1993;329:1862–1872. [PubMed: 8305063]

61. Konig SA, Schenk M, Sick C, et al. Fatal liver failure associated with valproate therapy in a patient with Friedreich's disease: review of valproate hepatotoxicity in adults. *Epilepsia*. 1999;40:1036–1040. [PubMed: 10403231]

62. Gasmi B, Kleiner D. Liver histology diagnostic and prognostic features. *Clin Liver Dis.* 2020;24(1):61–74. [PubMed: 31753251]

63. Beane PH, Bourdi M. Autoantibodies against cytochrome P450 in drug-induced autoimmune hepatitis. *Ann NY Acad Sci.* 1993;685:641–645.

64. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science*. 1999;286:487–491. [PubMed: 10521338]

65. Hunt CM, Westerkam WR, Stave GM. Effect of age and gender on the activity of human hepatic CYP3A. *Biochem Pharmacol.* 1992;44:275–283. [PubMed: 1642641]

66. Liddle C, Goodwin B. Regulation of hepatic drug metabolism: role of nuclear receptors PXR and CAR. *Semin Liver Dis.* 2002;22:115–122. [PubMed: 12016543]

67. Tsagaropoou-Stinga H, Mataki-Emmanouilidon R, Karida-Kavalioti S, et al. Hepatotoxic reactions in children with severe tuberculosis treated with isoniazid-rifampin. *Pediatr Infect Dis.* 1985;4:270–273. [PubMed: 4000989]

68. Bose PD, Sarma MP, Medhi S, Das BC, Husain SA, Kar P. Role of polymorphic N-acetyl transferase2 and cytochrome P4502E1 gene in antituberculosis treatment-induced hepatitis. *J Gastroenterol Hepatol.* 2011;(26):312–318. [PubMed: 21261721]

69. Kergueris MF, Bourin M, Larousse C. Pharmacokinetics of isoniazid: Influence of age. *Eur J Clin Pharm.* 1986;30:335–340.

70. Vuilleumier N, Rossier MF, Chiappe A, et al. CYP2E1 genotype and isoniazid-induced hepatotoxicity in patients treated for latent tuberculosis. *Eur J Clin Pharmacol.* 2006;62:423–429. [PubMed: 16770646]

71. Klien DJ, Boukouvaia S, McDonagh EM, Shuldiner SR, et al. PharmGKB summary: isoniazid pathway, pharmacokinetics (PK). *Pharmacogenet Genomics*. 2016;26(9):436–444. 10.1097/FPC.0000000000000232.

72. Van Puijenbroek EP, Metselaar HJ, Berghuis PH, Zondervan PE, Stricker BH. Acute hepatocytic necrosis during ketoconazole therapy for treatment of onychomycosis. National Foundation for Registry and Evaluation of Adverse Effects. *Ned Tijdschr Geneeskd.* 1998;142:2416–2418. [PubMed: 9864540]

73. Gunawan B, Kaplowitz N. Mechanisms of drug-induced liver disease. *Clin Liver Dis.* 2007;11:459–475. [PubMed: 17723915]

74. Aithal GP, Haugk B, Das S, Card T, Burt AD, Record CO. Monitoring methotrexate-induced hepatic fibrosis in patients with psoriasis: are serial liver biopsies justified? *Aliment Pharmacol Ther.* 2004;19:391–399. [PubMed: 14871278]

75. Soe KL, Soe M, Gluud CN. Liver pathology associated with anabolic androgenic steroids. *Ugeskr Laeger*. 1994;156:2585–2588. [PubMed: 8016966]

76. Lee WM. Assessing causality in drug-induced liver injury. *J Hepatol.* 2000;33:1003–1005. [PubMed: 11131436]

77. Lucena MI, Garcia-Cortes M, Cueto R, Lopez-Duran J, Andrade RJ. Assessment of drug-induced liver injury in clinical practice. *Fundam Clin Pharmacol.* 2008;22:141–158. [PubMed: 18353109]

78. Shapiro M, Lewis J. Causality assessment of drug-induced hepatotoxicity: promises and pitfalls. *Clin Liver Dis.* 2007;11:477–505. [PubMed: 17723916]

79. Davern T. Drug-induced liver disease. *Clin Liver Dis.* 2012;16:231–245. [PubMed: 22541696]

80. Graziani M, Antonilli L, Togna AR, Grassi MC, Badiani A, Saso L. Cardiovascular and hepatic toxicity of cocaine: potential beneficial effects of modulators of oxidative stress. *Oxid Med Cell Longev.* 2016;2016:8408479. 10.1155/2016/8408479.

81. Jones AL, Simpson KJJ. Review article: mechanisms and management of hepatotoxicity in ecstasy (MDMA) and amphetamine intoxications. *Aliment Pharmacol Ther.* 1999;13:129–133. [PubMed: 10102941]

82. Senior J. Evolution of the Food and Drug Administration approach to liver safety assessment for new drugs: current status and challenges. *Drug Saf.* 2014;37(suppl 1):S9–S17.

83. Stanca CM, Babar J, Singal V. Pathogenic role of environmental toxins in immune-mediated liver diseases. *J Immunotoxicol.* 2008;5:59–68. [PubMed: 18382859]

84. Steadman C. Herbal hepatotoxicity. *Semin Liver Dis.* 2002;22:195–206. [PubMed: 12016550]

85. Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. *Hepatology*. 2017;65(1):363–373. [PubMed: 27677775]

86. Seef LB, Cuccherin BA, Zimmerman HJ, et al. Acetaminophen hepatotoxicity in alcoholics: a therapeutic misadventure. *Ann Intern Med.* 1986;104:399–404. [PubMed: 3511825]

87. Ruhl CE, Everhart JE. Relation of elevated serum alanine aminotransferase activity with iron and antioxidant levels in the United States. *Gastroenterology*. 2003;124:1821–1829. [PubMed: 12806616]

88. Grant LM, Rickey DC. Drug-induced liver injury. *Curr Opin Gastroenterol.* 2012;28:198–202. [PubMed: 22450893]

89. Bjomsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. *Hepatology*. 2005;42(2):481–489. [PubMed: 16025496]

90. Steuerwald NM, Foureau DM, Norton HJ, et al. Profiles of serum cytokines in acute drug-induced liver injury and their prognostic significance. *PLoS One*. 2013;8(12):e81974. doi: 10.1371/journal.pone.0081974.

91. Takikawa Y, Harada M, Wang T, Suzuki K. Usefulness and accuracy of the international normalized ratio and activity percent of prothrombin time in patients with liver disease. *Hepatol Res.* 2014;44:92–101. [PubMed: 23521497]

92. Fu S, Wu D, Jang W, Long J, Chengyao J, Zhou T. Molecular biomarkers in drug-induced liver injury: challenges and future perspectives. *Front Pharmacol.* 2020;10:1667. [PubMed: 32082163]

93. Danjuma M, Sajid J, Haajra F, Elzouki A. Novel biomarkers for potential risk stratification of drug induced liver injury (DILI). *Medicine*. 2019;98:50.

94. Meunier L, Larrey D. Drug-induced liver injury: biomarkers, requirements, candidates, and validation. *Front Pharmacol.* 2019;10:1482. [PubMed: 31920666]

95. Church R, Watkins P. Serum biomarkers of drug-induced liver injury: current status and future directions. *J Dig Dis.* 2019;20:1–10.

96. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. US Food and Drug Administration. Available at

https://www.fda.gov/safety/medwatch/.

97. The Drug Induced Liver Injury Network. What is DILIN? Available at http://www.dilin.org/. Accessed August 2018.

SELF-ASSESSMENT QUESTIONS

1. Which of the following mechanisms of drug-induced liver injury are devoid of hypersensitivity features, have a long latency period, and are not associated with rapid re-injury with rechallenge?

   A. Stimulation of autoimmunity

   B. Disruption of calcium homeostasis

   C. Non-allergic idiosyncratic reaction

   D. Mitochondrial injury

2. Which drug is associated with liver vascular disorder?

   A. Amiodarone

   B. Ketoconazole

   C. Isoniazid

   D. Azathioprine

3. Which condition has a pattern of damage that originates in the hepatocytes located nearest the central vein of the liver and occurs as a result of the production of a toxic metabolite?

   A. Centrilobular necrosis

   B. Nonalcoholic steatohepatitis

   C. Toxic cirrhosis

   D. Phospholipidosis

4. Which environmental toxin has been shown to produce acute and chronic hepatic reactions?

   A. Copper

   B. Arsenic

   C. Toluene

   D. Fluorine

5. Which serum marker is a sensitive indicator for most hepatic lesions and also has significant prognostic value?

   A. Alanine aminotransferase

   B. Aspartate aminotransferase

   C. Alkaline phosphatase

   D. Bilirubin

6. Which of the following signs or symptoms are commonly associated with a dysfunctioning liver?

   A. Hyperglycemia

   B. Hypertension

   C. Abdominal Pain

   D. Arthralgia

7. To assess for drug, herbal or alternative causes; which of the following is the most important question?

   A. Does the patient smoke?

   B. Has the patient ever been diagnosed with or suspected of alcohol misuse?

   C. Does the patient have high blood pressure?

   D. Does the patient have type 1 diabetes mellitus?

8. What set of laboratory values are going to be the most useful in determining hepatocellular damage (direct damage to the hepatocytes)?

   A. AST, ALT

   B. γ-GTP (GGTP), Alk Phos

   C. Bilirubin

   D. INR, Ammonia, Transferrin

9. What set of laboratory values are going to be the most useful in determining cholestatic liver damage (direct damage to the bile canicular system)?

   A. AST, ALT

   B. γ-GTP (GGTP), Alk Phos

   C. Bilirubin

   D. INR, Ammonia, Transferrin

10. What set of laboratory values are going to be the most useful in determining a decrease in liver function during or after the injury?

    A. AST, ALT

    B. γ-GTP (GGTP), Alk Phos

    C. Bilirubin

    D. INR, Ammonia, Transferrin

11. How do individual genetic differences in cytochrome P450 phenotypes effect the susceptibility of a person to drug-induced liver injury? Patient's with (____fill in the blank____)

    A. any variant slow or fast will react about the same, since cytochrome P450 is rarely involved with drug metabolism.

    B. those with slow variants will be at greater risk from bioactivated free radicals.

    C. those with fast variants will be at a reduced risk since they will clear the drugs out of the hepatocytes faster

    D. slow-reacting variants will react differently than patients with very fast-reacting variants.

12. Inhibiting bile acid transport proteins can put a patient at risk for what type of liver injury, sometimes seen during pregnancy?

    A. Hepatocellular Hepatitis

    B. Cholestatic Hepatitis

    C. Venoocclusive Disease

    D. Nonalcoholic Steatosis

13. Hepatic neoplastic disorders are most strongly associated with which of the following agents?

    A. Levothyroxine

    B. Amoxicillin

    C. Polyvinyl Chloride

    D. Ritonavir

14. Hy's Law defines hepatocellular injury as a rise in ALT that is how many times above the upper limit of normal?

    A. 2

    B. 3

    C. 4

    D. 5

15. Autoimmune hepatocellular injury is often accompanied by which of the following?

    A. Gouty Pain

    B. ANA

    C. Micro-RNA

    D. Dysgeusia

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** These reactions are unpredictable with our current ability to assess for vulnerable phenotypes. Antibiotics dominate as causative agents. Please refer to the section on Mechanisms of Drug-Induced Liver Injury and idiosyncratic reactions for additional information.

2. **D.** Azathioprine and herbal teas that contain comfrey (a source of pyrrolizidine alkaloids) and are associated with venoocclusive disease. Please refer to the section on the Patterns of Histologic Changes for additional information.

3. **A.** The damage in centrilobular necrosis spreads outward from the middle of a lobe of the liver. Please refer to the section on Patterns of Histologic Changes for additional information.

4. **B.** Arsenic is used in limited industrial applications and in the past as an insecticide. Its damage is cumulative in most cases. Please refer to the section on Assessment: Determining the Medication-Related Problem for additional information.

5. **D.** Higher peak bilirubin concentrations are associated with poorer survival and a greater likelihood that the patient will eventually require a liver transplant. Please refer to the section on Assessment: Severity of the Medication-Related Problem for additional information.

6. **C.** Nausea, vomiting, diarrhea (often steaorrhea), abdominal pain, pruritis, jaundice, severe fatigue are common. Hypertension would be rare; Hyperglycemia is not helpful given its many other causes. Arthralgia would only be a common symptom during an autoimmune hepatitis. Please refer to

the section on Assessment: Determining the Medication-Related Problem for additional information.

7. **B.** Smoking is not protective against liver injury, but it is not a strong risk factor. Alcohol misuse and moderate to heavy drinking is a distinct and powerful risk factor. Hypertension does not impact the risk for a liver injury. Type 2 diabetes mellitus is often associated with nonalcoholic fatty liver disorder which is a risk factor for more severe liver injury, type 1 diabetes mellitus is not associated with increased risk. Please refer to the section on Assessment: Determining the Medication-Related Problem for additional information.

8. **A.** AST, ALT are liver enzymes released as the hepatocytes are damaged.

9. **B.** γ-GTP (GGTP), Alk Phos are liver enzymes primarily associated with the bile canicular system. Please refer to the section on Assessment: Determining the Medication-Related Problem for additional information.

10. **D.** INR, ammonia, transferrin along with albumin and to some extent bilirubin are products or substrates of the liver and indicate liver function. Please refer to the section on Assessment: Determining the Medication-Related Problem for additional information.

11. **D.** Cytochrome P450 enzymes often create bioactivated, highly reactive compounds. Patients with faster reacting variants of these enzyme when coupled with higher doses of drug can overwhelm detoxifying conjugating peptides, such as glutathione. Please refer to the section on Assessment: Determining the Medication-Related Problem for additional information.

12. **B.** Selected SNPs that code for various bile salt export pumps (BSEP) are associated with rare congenital liver diseases and cholestasis during pregnancy. These patients may have a higher risk for cholestatic liver injury.

13. **C.** The most documented xenobiotic-induced hepatic cancer agent is polyvinyl chloride exposure. Used in the production of many types of plastic products, a high-quality exposure polyvinyl chloride induces angiosarcoma in exposed workers in as few as 3 years.

14. **B.** Hy's law defines hepatocellular injury as an increase in ALT that is at least three times above the upper limit of normal (UNL) with concurrent rise in TBL to a point at least 2 UNL without a significant rise in the Alk Phos. Please refer to the section on Assessment: Determining the Medication-Related Problem for additional information.

15. **B.** Autoimmune liver injuries are mediated by the immune sys tem and are associated with elevations in ANA, IgG, ASMA, LKM-1 and associated with other immune-mediated symptoms like fever, chills, arthralgia, malaise, fatigue and vague myalgia.