Drug-Induced Liver Injury

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ABSTRACT

Drug-induced liver injury (DILI) can result from both idiosyncratic and intrinsic mechanisms. This article discusses the clinical impact of DILI from a broad range of medications as well as herbal and dietary supplements. Risk factors for idiosyncratic DILI (IDILI) are the result of multiple host, environmental, and compound factors. Some triggers of IDILI often seen in critical care include antibiotics, antiepileptic medications, statins, novel anticoagulants, proton pump inhibitors, inhaled anesthetics, nonsteroidal anti-inflammatory agents, methotrexate, sulfasalazine, and azathioprine. The mechanism of IDILI due to these medications varies, and the resulting damage can be cholestatic, hepatocellular, or mixed. The primary treatment of IDILI is to discontinue the causative agent. DILI due to acetaminophen is intrinsic because the liver damage is predictably aligned with the dose ingested. Acute acetaminophen ingestion can be treated with activated charcoal or N-acetylcysteine. Future areas of research include identification of mitochondrial stress biomarkers and of the patients at highest risk for DILI.

Keywords: drug-induced liver injury, clinical practice guidelines, adverse drug reactions, herbal and dietary supplements

Patients with drug-induced liver injury (DILI) display a continuum of diverse signs and symptoms of hepatic injury after taking a xenobiotic.1 Xenobiotics encompass “pharmacologically, endocrinologically, or toxicologically active substances.”2 Types of xenobiotics associated with DILI in critical care include antibiotics, antiepileptic medications, statins, novel anticoagulants, proton pump inhibitors, inhaled anesthetics, nonsteroidal anti-inflammatory agents, methotrexate, sulfasalazine, and azathioprine. The mechanism of IDILI due to these medications varies, and the resulting damage can be cholestatic, hepatocellular, or mixed. The primary treatment of IDILI is to discontinue the causative agent. DILI due to acetaminophen is intrinsic because the liver damage is predictably aligned with the dose ingested. Acute acetaminophen ingestion can be treated with activated charcoal or N-acetylcysteine. Future areas of research include identification of mitochondrial stress biomarkers and of the patients at highest risk for DILI.

Incidence of DILI is estimated to range from 1 to 10 in every 10 000 exposed persons.3 The incidence of liver injury caused by HDSs has been reported to be 0.9% in a Korean cohort of patients with DILI4 and up to 10% in a US cohort of patients with DILI.5,6 Prescription medications and HDSs typically cause idiosyncratic DILI (IDILI). Dose-dependent DILI, also known as intrinsic DILI, is

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associated with medications that, because of their chemical design and dosage toxicity, accrue recognized patterns of hepatocellular injury. Acetaminophen is an example of a medication with an intrinsic dose-linked injury manifestation of DILI and is the most common cause of DILI. About 46% of all persons with acute liver failure in the United States have liver damage associated with acetaminophen. Acetaminophen is combined with many over-the-counter medications and multiple oral prescription pain medications, making it easier for patients to unknowingly take higher dosages of acetaminophen than they realize. The most common causes of DILI due to acetaminophen are long-term dosage above recommended levels and dosage of acetaminophen greater than 150 mg/kg as a short-term intake. Patients with both types of DILI can experience a clinical course characterized as mild, moderate, or severe requiring liver transplant, with some patients rapidly progressing to severe encephalopathy and death.

Evaluation and treatment of DILI are based on guidelines targeted specifically to either IDILI or DILI due to acetaminophen. This article discusses both the unpredictable clinical course of IDILI and the predictable clinical course of DILI caused by acetaminophen. This article delineates the risk factors for DILI, diagnosis and management of DILI, and selected DILI-associated xenobiotics that are often used in critical care.

Risk Factors for DILI
Risk factors that predispose people to development of DILI can be grouped into 3 categories: host-related factors, environmental factors, and compound-related factors. Determining which patients are most susceptible to toxic effects on the liver is an excellent primary prevention for DILI development.

Host-Related Factors
The susceptibility of a host to DILI is believed to be genetic. Multiple genes control immunological and liver processes that set the stage for DILI development. Cheek-swab DNA tests are currently available to provide analysis of selected cytochrome P-450 pathways that affect drug metabolism. This information can be helpful, for example, before prescription of more than 150 behavioral and seizure medications that are associated with IDILI. Clinical utility and interpretation of individual DNA analyses to predict adverse drug reactions with liver injury is not a current clinical practice recommendation nor is its cost reimbursed by insurance. Genome-wide association studies suggest that the human leukocyte antigen (HLA) gene 6 coding may play an important role.

Another observed host factor is that most patients with idiosyncratic DILI are women. In 4 prospective cohorts, the incidence of IDILI in women from the United States, Iceland, Spain, and France was 49% to 60%. The reason for this gender predominance is unknown. In addition, the Drug Induced Liver Injury Network registries noted that Asian race was an independent risk factor for IDILI patients who required transplant, and African American race was associated with chronic liver dysfunction after IDILI.

Environmental Factors
Environmental risk factors discussed in the literature with IDILI are alcohol consumption and associated infection. Alcohol consumption may have a synergistic effect, predisposing the patient to greater hepatotoxic effects with antitubercular medications, antivirals, and antibiotics. Infection is believed to change the dose response of the liver through immunomodulation that sets the stage for the inflammatory aspects of IDILI.

Compound-Related Factors
Compound-related factors have been identified from study of substances that trigger IDILI. Lipophilia is a predominating characteristic of medications that trigger IDILI. Hepatic conversion of a lipophilic medication to a hydrophilic form requires multiple metabolic degradation pathways so that the kidneys can excrete the metabolites. Additional characteristics of compounds that are associated with liver damage are formation of reactive metabolites, molecular weight, induction of oxidative stress, and inhibition of hepatic transporters (Figure 1).

Idiosyncratic DILI
When drugs are tested in Food and Drug Administration (FDA) trials, IDILI often goes unrecognized. This problem is a matter of numeracy. A clinical trial that has fewer than 3000 patients will not detect the population risk for an adverse drug reaction with an
expected incidence of 1 in 10,000 patients.3,4 HDSs are not considered drugs and do not undergo rigorous testing and scrutiny before marketing; therefore, liver-associated adverse drug reactions are even more difficult to anticipate and predict with use of these xenobiotics. FDA-mandated recalls for HDSs occur only after adverse drug reactions are identified in the postmarketing period. Because of its low frequency of occurrence and the total number of xenobiotics that can trigger liver injury, IDILI is a diagnostic conundrum.6 Research is currently focusing on using prospective data from digital registries with the hope of earlier identification of hepatotoxic medications and HDSs.1 Big data registries are also helpful for identification of subpopulations at higher risk for IDILI.

Diagnosis and Management of IDILI

The American College of Gastroenterologists’ clinical practice document for the care of patients with IDILI is the compass document to direct the processes of diagnosis and management needed for these patients.8 Two online resources are available to provide guidance through the diagnostic and management process. One is the Livertox database at http://livertox.nih.gov.12 The other is the Drug Induced Liver Injury Network, which is available for consultation and provides a data registry for cases at http://www.dilin.org.13 Critical to IDILI diagnosis is meticulous collection of a medical history focused on time intervals between each suspected xenobiotic administration, onset of signs and symptoms, and total dosage interval. One difficulty with obtaining an accurate history is that patients do not consistently report HDS use. It has been reported that 50% of persons in the United States and greater than 60% to 70% of military personnel use HDSs.14,15 Data from analyses of electronic medical records show that only approximately 40% of patients are reporting this information.14,16

As the patient’s medical history unfolds, the health care provider should listen attentively...
for a history of allergy and sensitivity to medication classifications, particularly antibiotics and antiepileptic medications. History of prior liver disease, especially viral hepatitis or co-infection with Epstein-Barr virus, with increased fatigue are common findings.8,12 The clinical signs and symptoms of IDILI mirror those of hepatitis, so ruling out an infectious origin is critical.

The next step is to evaluate the laboratory test results relevant to liver biochemistries and eosinophil activation. A useful determination for treatment is to determine the $R$ value, calculated as follows: upper limit of normal for alanine transaminase divided by the upper limit of normal for alkaline phosphatase. This number is used clinically to categorize injury patterns into 3 types: hepatocellular ($R > 5$), mixed ($2 < R < 5$), and cholestatic ($R < 2$).8,12 The diagnostic workup then proceeds by the decision tree arms determined by the $R$ score. The American College of Gastroenterologists has developed a diagnostic clinical decision tree (Figure 2, Table 1).8 This useful clinical reasoning tool aids in data collection for this diagnosis of exclusion.

![Figure 2: An algorithm to evaluate suspected idiosyncratic drug-induced liver injury (DILI). The $R$-value cutoff numbers of 2 and 5 serve only as a guideline. Which tests and their order must be based on the overall clinical picture, including risk factors for competing diagnosis (eg, recent travel to hepatitis E virus [HEV] endemic area), associated symptoms (eg, abdominal pain, fever), and timing of laboratory tests (ie, the $R$ value may change as the DILI evolves). Abbreviations: ALT, alanine aminotransferase; Alk P, alkaline phosphatase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HSV, herpes simplex virus; MR, magnetic resonance; ULN, upper limit of normal. Reprinted from Chalasani et al.8 Used with permission from the American Journal of Gastroenterology.](http://acc.aacnjournals.org/Downloaded from)

Abnormal liver enzymes

Thorough history and physical
Complete review of medications and
herbals and dietary supplements

Calculate $R$ value*

$R$ value = Serum (ALT/ALT ULN) ÷ (Alk P/Alk P ULN)

- $R$ value ≥ 5 (Hepatocellular)
  1st-line tests: Acute viral hepatitis serologies, HCV RNA & autoimmune hepatitis serologies; imaging studies (eg, abdominal ultrasound)
  2nd-line tests on a case by case basis: ceruloplasmin, serologies for less common viruses (HEV, CMV, and EBV), liver biopsy

- $2 < R$ value < 5 (Mixed)
  1st-line tests: Acute viral hepatitis serologies, HCV RNA & autoimmune hepatitis serologies; imaging studies (eg, abdominal ultrasound)
  2nd-line tests on a case by case basis: ceruloplasmin, serologies for less common viruses (HEV, CMV, and EBV), liver biopsy

- $R$ value ≤ 2 (Cholestatic)
  1st-line test: imaging studies (abdominal ultrasound)
  2nd-line tests on a case by case basis: cholangiography (either endoscopic or MR based), serologies for primary biliary cirrhosis, liver biopsy

**Figure 2:** An algorithm to evaluate suspected idiosyncratic drug-induced liver injury (DILI). The $R$-value cutoff numbers of 2 and 5 serve only as a guideline. Which tests and their order must be based on the overall clinical picture, including risk factors for competing diagnosis (eg, recent travel to hepatitis E virus [HEV] endemic area), associated symptoms (eg, abdominal pain, fever), and timing of laboratory tests (ie, the $R$ value may change as the DILI evolves). Abbreviations: ALT, alanine aminotransferase; Alk P, alkaline phosphatase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HSV, herpes simplex virus; MR, magnetic resonance; ULN, upper limit of normal. Reprinted from Chalasani et al.8 Used with permission from the American Journal of Gastroenterology.
Specific Triggering Medications and IDILI

Knowing which types of medications are associated with IDILI assists critical care health professionals to assess patterns of injury associated with these prescription and over-the-counter medications. Discussed next are some of the prescription medications, HDSs, and over-the-counter medications that are often associated with IDILI reports.

Antibiotic-Associated IDILI

Some of the most frequent causes of IDILI stem from the use of antibiotics and antiviral agents. In a recent Icelandic study by Björnsson et al., amoxicillin-clavulanate was the most commonly implicated agent in IDILI, causing liver damage in 22% of patients studied. The type of damage inflicted by amoxicillin-clavulanate is usually cholestatic, but the damage can also occur as a mixed type of liver injury, especially if amoxicillin-clavulanate is combined with another agent that is known to cause IDILI. Liver damage caused by amoxicillin-clavulanate is more likely to be caused by the clavulanate portion of the agent, as the incidence of IDILI is much lower when amoxicillin is used as a single

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Table 1: Terminology and Definitions

<table>
<thead>
<tr>
<th>Term or Concept</th>
<th>Technique</th>
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<tbody>
<tr>
<td>Intrinsic DILI</td>
<td>Hepatotoxicity with potential to affect all individuals to varying degrees. Reaction typically stereotypic and dose dependent (eg, acetaminophen).</td>
</tr>
<tr>
<td>Idiosyncratic DILI</td>
<td>Hepatotoxicity affecting only rare susceptible individuals. Reaction less dose dependent and more varied in latency, presentation, and course.</td>
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<tr>
<td>Chronic DILI</td>
<td>Failure of return of liver enzymes or bilirubin to pre-DILI baseline, and/or other signs or symptoms of ongoing liver disease (eg, ascites, encephalopathy, portal hypertension, coagulopathy) 6 months after DILI onset</td>
</tr>
<tr>
<td>Latency</td>
<td>Time from medication (or HDS) start to onset of DILI</td>
</tr>
<tr>
<td>Washout, resolution, or dechallenge</td>
<td>Time from DILI onset to return of enzymes and/or bilirubin to pre-DILI baseline levels</td>
</tr>
<tr>
<td>Rechallenge</td>
<td>Readministration of medication or HDS to a patient who already had a DILI to the same agent</td>
</tr>
<tr>
<td>Hy’s law</td>
<td>Observation made by late Hyman Zimmerman suggesting a 1 in 10 mortality risk of DILI if the following 3 criteria are met: 1. Serum ALT or AST &gt; 3 × ULN 2. Serum total bilirubin elevated to &gt;2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) 3. No other reason can be found to explain the combination of increased aminotransferases and bilirubin, such as viral hepatitis A, B, C, or other preexisting or acute liver disease</td>
</tr>
<tr>
<td>Temple’s corollary</td>
<td>An imbalance in the frequency of ALT &gt; 3 × ULN between active treatment and control arms in a randomized controlled trial. This is used to assess for hepatotoxic potential of a drug from premarketing clinical trials</td>
</tr>
<tr>
<td>R value</td>
<td>ALT/ULN ÷ AP/ULN. Used to defined hepatotoxicity injury patterns: hepatocellular (R &gt; 5), mixed (R = 2–5), and cholestatic (R &lt; 2)</td>
</tr>
<tr>
<td>RUCAM</td>
<td>Diagnostic algorithm that uses a scoring system based on clinical data, preexisting hepatotoxicity literature on the suspected agent and rechallenge</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; HDS, herbal and dietary supplement; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal.

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agent.19 In a study by García Rodríguez et al,19 the incidence of IDILI for amoxicillin-clavulanate per 10 000 prescriptions was 1.7 (95% CI, 1.1-2.7) cases compared with 0.3 (95% CI, 0.2-0.5) cases for amoxicillin alone. Because prescriptions for amoxicillin-clavulanate are usually short-term, the onset of IDILI is commonly diagnosed after the course of the agent has been completed.20

Another antibiotic that has often been implicated in IDILI is sulfamethoxazole-trimethoprim, with the sulfonamide component serving as the main culprit.21 As with amoxicillin-clavulanate, IDILI caused by sulfamethoxazole-trimethoprim is usually cholestatic, but hepatocellular injury has occurred.17 In a study by Björnsson,17 a small number of patients who had IDILI develop after intake of sulfamethoxazole-trimethoprim either died or required a liver transplant. Liver injury caused by sulfamethoxazole-trimethoprim is often accompanied by fever, rash, and eosinophilia.8

Nitrofurantoin is regularly listed as a common cause of IDILI and can cause an acute or chronic hepatocellular injury that can resemble hepatitis.8 Risk factors associated with nitrofurantoin-induced liver injury include older age, female sex, and prolonged exposure to the agent.21 DILI from short-term use of nitrofurantoin can be accompanied by fever, rash, or eosinophilia.8 Nitrofurantoin is regularly listed as a common cause of IDILI and can cause an acute or chronic hepatocellular injury that can resemble hepatitis.8 Risk factors associated with nitrofurantoin-induced liver injury include older age, female sex, and prolonged exposure to the agent.21 DILI from short-term use of nitrofurantoin can be accompanied by fever, rash, or eosinophilia.8

Isoniazid is a commonly used agent in the treatment of tuberculosis and has been associated with hepatocellular injury that resembles viral hepatitis. Because of the protracted course of isoniazid required to treat tuberculosis, exposure to this agent occurs over an extended period of time.8 Elevations in aminotransferase levels are often seen and signs and symptoms of the onset of injury are often delayed.22 Interestingly, pharmacogenetic implications have been reported in isoniazid-induced liver injury, especially in those patients who are slow acetylators of isoniazid.22

Antiepileptic Agents
Valproic acid is the antiepileptic agent most commonly associated with IDILI.8 A black-box warning is placed in the package insert of valproic acid, warning of potential fatal hepatic failure in all patients and recommending extreme caution with the use of valproic acid in children less than 2 years of age.10 Recent studies have shown associations with a higher risk of liver injury induced by valproic acid in patients with genetic metabolic mutations or a carnitine deficiency.10 Valproic acid is unique in that it has multiple mechanisms by which it can cause DILI. One of the first aberrations seen with valproic acid is hyperammonemia, which manifests in patients as encephalopathy or coma. Discontinuing valproic acid allows ammonia levels to normalize.8 Valproic acid can also cause acute hepatocellular damage that is associated with jaundice. In addition, in children, valproic acid can cause a Reye’s-like syndrome with symptoms of fever and lethargy and elevated aminotransferase and ammonia levels.8 Carbamazepine is also commonly associated with IDILI and can cause transiently elevated aminotransferase levels in up to 61% of patients.23 Hypersensitivity to carbamazepine can occur and is associated with fever and eosinophilia; it can even lead to Stevens-Johnson syndrome. Carbamazepine is linked with anticonvulsant hypersensitivity syndrome and can result in hepatocellular or cholestatic injury.23 Like carbamazepine, lamotrigine is also connected with anticonvulsant hypersensitivity syndrome associated with fever, eosinophilia, and Stevens-Johnson syndrome.8 Rapid dose titration and younger age are risk factors for the development of IDILI from lamotrigine.23

Statins
Idiosyncratic DILI from statins has been reported, although it is rare.17 With most statins, patients may see a mild elevation in aminotransferase level that is usually transient.23 However, patients with hepatocellular damage or cholestatic injury after taking statins have been reported.24 Because of the rare incidence of IDILI from statins, routine monitoring of aminotransferase levels in patients on long-term statin therapy is not recommended unless signs or symptoms of liver injury are apparent.24

Novel Anticoagulants
The novel anticoagulants include rivaroxaban, dabigatran, apixaban, and edoxaban.
These medications are indicated for use in many different diagnoses owing to updates in many clinical practice guidelines and profiles of fewer adverse effects compared with traditional anticoagulants. These drugs act by directly inhibiting clotting factors as opposed to traditional oral anticoagulants such as warfarin, which inhibits clotting factor synthesis. All novel anticoagulants have shown some incidence of hepatotoxic effects, but only limited data are available for apixaban and edoxaban. The mechanism of IDILI with these drugs is not well understood but has not been determined to be exclusively dose related. Animal models and postmarket evaluation have shown immune-mediated IDILI as well as IDILI resulting from potentially toxic metabolites. Most reported cases of IDILI have been at therapeutic doses of all agents.

Evaluation of recent studies has shown rivaroxaban to have the highest incidence of IDILI, but the incidence is not significantly greater than the incidence seen with warfarin. The majority of IDILI cases had asymptomatic elevations in levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin. Patients often recover rapidly after discontinuation of drug therapy without further intervention or long-term damage. Although the risk of IDILI with novel anticoagulants is minimal, further postmarketing evaluations are needed to determine the risk accurately.

Proton Pump Inhibitors

Although proton pump inhibitors (PPIs) have a warning of hepatotoxicity, evidence for liver injury due to PPI therapy is extremely limited. The majority of case reports have noted elevated serum levels of aminotransferases due to pantoprazole therapy specifically. Most PPIs, including pantoprazole, are metabolized in the liver by various cytochrome enzymes, and that may be the mechanism by which IDILI occurs. The highest incidence of IDILI with PPI therapy has been seen when a PPI is combined with azathioprine. IDILI due to PPI therapy resolves quickly upon discontinuation of the drug.

Inhaled Anesthetics

Inhaled anesthetics such as isoflurane, desflurane, and sevoflurane have shown some potential for hepatotoxicity. These agents are metabolized by the liver and often have highly reactive metabolites that can potentially cause hepatic injury. Inhaled anesthetics also can stimulate an immune response that can result in damaging inflammation in the liver and other organs. Because inhaled anesthetics are used during surgery and trauma, it can be difficult to differentiate if liver injury is the result of these agents or is the result of injury or surgery. Isoflurane in particular has been associated with hepatotoxic effects after repeat exposures. Two types of hepatotoxic effects are seen: mild dysfunction and life-threatening hepatitis. The mild dysfunction is characterized by elevations in serum levels of aminotransferases in patients who are otherwise asymptomatic; patients with mild dysfunction experience complete recovery. Fulminant liver failure characterized by extensive hepatocellular necrosis leads to a need for urgent transplant.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a large class of analgesics available as prescription and over-the-counter medications. These medications include ibuprofen, naproxen, meloxicam, diclofenac, etodolac, and ketorolac as well as others. Several NSAIDs (eg, bromfenac, ibufenac, and benoxaprofen) have been withdrawn from the market because of the increased risk of hepatotoxic effects associated with them.

NSAIDs have long been associated with hepatotoxic effects, although such effects occur in less than 0.1% of the population of patients. The precise mechanism of NSAID-induced liver injury is not well understood. The most widely accepted explanation is that the injury is due to the electrophilicity of the chemical structure of most NSAIDs. The electrophilic structure results in reactive metabolites that can cause hepatotoxic effects and cellular necrosis. One of the additional proposed mechanisms is the suppression of inflammatory cytokines and decreased immune response that can potentiate hepatocellular injury. The incidence of IDILI varies depending on the specific NSAID used. In a recent prospective study, Schmeltzer et al determined that diclofenac therapy resulted in the most cases of acute liver failure when compared with several other prescription NSAIDs. Ibuprofen and naproxen have shown the lowest incidence of IDILI and are considered to be the most

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frequently used NSAIDs thanks to their availability without a prescription.34

Methotrexate

Methotrexate is an immunosuppressive agent that acts by inhibiting folate metabolism and can be used for a variety of different indications. Methotrexate IDILI occurs in more than 10% of patients receiving methotrexate and varies from elevated aminotransferase levels to fibrosis and cirrhosis that can be life-threatening.35 The mechanism of methotrexate’s hepatotoxic effects is linked to the depletion of folate stores in the liver.36 Folate plays a vital role in cellular reproduction, and its depletion causes improper DNA replication within hepatocytes. The hepatocytes that develop are unable to function effectively, resulting in a buildup of toxins and elevated aminotransferase levels.35 Although higher doses over longer duration have a higher risk of IDILI, injury can occur with both short- and long-term therapy.

Hepatotoxic effects of methotrexate are treated by discontinuation of the drug and administration of folic acid to replenish the nutrient necessary for the liver to function and repair.36 Unfortunately, if IDILI is not identified before cirrhosis or fibrosis develops, it can cause permanent damage and require a liver transplant.35 Patients with transient elevations of aminotransferase levels while undergoing methotrexate therapy usually do not suffer long-term hepatic damage.35 Serum aminotransferase levels should be monitored frequently throughout methotrexate therapy to identify potential IDILI and take preventative measures such as folic acid supplementation or methotrexate dose adjustment.

Sulfasalazine

Sulfasalazine is primarily used to treat rheumatoid arthritis and Crohn disease. Although the mechanism is not well understood, treatment with sulfasalazine has been linked to hepatotoxic and nephrotoxic effects. A widely accepted mechanism of injury is the increased oxidative stress that sulfasalazine imposes on the liver during treatment.37 Case reports have shown that IDILI due to sulfasalazine therapy can occur over a wide range of doses and various durations of therapy.38 The primary treatment for sulfasalazine IDILI is drug discontinuation. Researchers in several recent studies have sought to determine the effects of use of antioxidants on the prevention and treatment of sulfasalazine IDILI, but evidence for use of this treatment is minimal at this time.38

Azathioprine

Azathioprine is widely used as an antirejection medication for patients who have undergone organ transplant or who have rheumatoid arthritis. It has been linked to mild hepatotoxic effects indicated by an asymptomatic increase in serum aminotransferase levels. The type of damage associated with moderate to severe hepatotoxic effects is mixed type including cholestatic hepatitis and hepatocellular injury.39 The hepatic metabolism of azathioprine results in the development of reactive oxygen species and mitochondrial dysfunction within the liver, which has been associated with IDILI.40

Herbal and Dietary Supplements

Liver transplant registries note that 5% of liver transplants are a consequence of HDS-induced ILIDI.10,41 In HDS-suspected injuries, the process of diagnosis is different. The same data are gathered and evaluated, but expert opinion and review of the literature for similar HDS case reports are used. Use of a Roussel Uclaf Causality Assessment Method (RUCAM) instrument to gauge the likelihood of HDS-triggered IDILI is also recommended.8,42,43 This tool is an algorithm that uses a scoring system based on clinical data, preexisting publications on the hepatotoxicity of the suspected agent, and rechallenge with the substance. Health care providers look for patterns of hepatic injury within matched host factors and xenobiotic exposure.

A good example of this diagnosis detective work was in Hawaii with the cluster of liver failure associated with the use of OxyElite Pro (USPLabs LLC).43 The health care providers used the RUCAM and expert opinion to diagnosis the cases. The Hawaii Department of Health and the Centers for Disease Control and Prevention carefully examined the cluster of IDILI cases, determining that the common factor was the use of the weight-loss supplement. The FDA issued a recall of the product with specific attention to one ingredient in the product, aegeline, which had not been tested for safety in humans. This HDS product highlights the difficulty for toxicologists who are trying to identify which component
or combination of components are the source of hepatic injury. Herbal formulas can vary in potency with every lot or dose because the soil, altitude, and season can change the potency of the herb.41-43

**Diagnosis, Management, and Treatment of Acetaminophen-Associated DILI**

Acetaminophen-associated DILI is a consequence of both the dosage of the drug and the metabolic pathways that take place in the microsomes within hepatocytes. Therefore, it is considered an intrinsic type of DILI because liver damage is predictably aligned with dosage. Acetaminophen-associated liver failure accounts for approximately half of the patients who have acute liver failure diagnosed each year.44,45 This situation is attributed to the excessive use of acetaminophen as an over-the-counter medication and in combination with prescription opioid medications. Acetaminophen metabolism requires 3 sets of metabolic detoxifications in the liver. Hepatotoxicity results from the breakdown of acetaminophen to a noxious metabolite N-acetyl-p-benzoquinone imine, which leads to mitochondrial dysfunction and diminishes levels of adenosine triphosphate within the hepatic cells.45 Additionally, peroxynitrite, a toxic free radical, is generated and structurally damages the mitochondria. Acetaminophen-triggered cell death is characterized by necrosis.

Diagnosis is made by history of ingestion, time and doses of medication viewed within a weight calculation, and serum level of acetaminophen. Each toxicology center and acute care facility may follow an internal protocol for the use of activated charcoal and infusion of N-acetylcysteine. One of the tools most commonly used in the decision to use N-acetylcysteine is the Rumack-Matthew nomogram for acute overdose.45 This tool is a mathematical algorithm appropriately used for acute, single overdose ingestions of acetaminophen. This tool accounts for the variable that 4 hours after ingestion is typically the zenith of the level of toxic metabolites generated from a single overdose, allowing the clinician to predict the optimal dose of N-acetylcysteine. N-acetylcysteine works to replenish hepatic stores of cysteine, the element needed to detoxify the toxic metabolites of acetaminophen. Other descriptors of the action of N-acetylcysteine with acute acetaminophen overdose are immunological active, antioxidant, and antiapoptic functions. Prompt intervention with N-acetylcysteine has reduced mortality to 0.7% of patients who have overdosed on acetaminophen.45

The signs and symptoms of the 5 stages of acetaminophen overdose are summarized in Table 2.45 Each stage requires that the critical care team carefully evaluate the patient for resolution of the liver dysfunction or prompt transfer to an acute care liver transplant evaluation center. Research on acetaminophen-associated DILI focuses on the optimal dosing and duration of treatment with N-acetylcysteine and on identifying biomarkers that will predict excessive mitochondrial damage leading to acute liver failure.42

<table>
<thead>
<tr>
<th>Stage</th>
<th>Time Interval</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>24 h</td>
<td>Nausea, vomiting, diaphoresis, fatigue</td>
</tr>
<tr>
<td>II</td>
<td>24-72 h</td>
<td>Latent period, elevation in liver enzyme levels, possible for acute tubular necrosis to develop</td>
</tr>
<tr>
<td>III</td>
<td>72-96 h</td>
<td>Nausea, vomiting, fatigue, marked elevation in liver enzyme levels, jaundice, lactic acidosis, level of consciousness declines, cerebral edema, hypoglycemia, bleeding</td>
</tr>
<tr>
<td>IV</td>
<td>96 h to 2 weeks</td>
<td>Recovery of systems dependent on resolution of multiple organ failure associated with stage III</td>
</tr>
</tbody>
</table>

*a Based on information from Yoon et al.46*
Treatment of IDILI and Acetaminophen-Induced DILI

The treatment of DILI is guided by the degree of hepatic dysfunction and comorbid conditions. Consultations with a toxicologist are clinically helpful in both the immediate and follow-up phases of care because of toxicologists’ extensive knowledge of drug metabolism. The signs and symptoms are evaluated as mild, moderate, or severe. The majority of patients with mild and moderate signs and symptoms simply recover normal liver function after identification and discontinuation of the triggering substance. Treatment outcomes for acetaminophen-induced DILI are tied to the timing of the antidote N-acetylcysteine and the total ingested dose of acetaminophen. Severe DILI is characterized by jaundice at the onset with a rapid decline in level of consciousness and the presence of coagulopathies. Patients who quickly progress to acute liver failure will need evaluation for dialysis support and careful monitoring of acid-base balance to prevent progression to multisystem organ failure. If the liver function continues to decline, evaluation for liver transplant may be indicated. Encephalopathy is the most common process of death for these patients if the liver failure is not reversed.

Conclusion

A wide range of xenobiotic agents that use multiple pathological pathways can cause hepatotoxic effects. Diagnosing IDILI is a complex clinical challenge because exponential variables are in motion when xenobiotic agents interact with host factors. Because IDILI occurs infrequently and is also a disease of exclusion, timely recognition requires astute clinical judgment and expert validation. Acetaminophen-induced DILI is the largest contributor to acute liver failure and occurs frequently. Mortality is highly preventable, with well-described clinical signs and symptoms. Prognosis is dependent on recognition of the overdose and prompt treatment. DILI is a reminder to clinicians that the risks, benefits, and alternatives are important in every pharmacological decision. The hope for reducing the number of these events in the future is centered on recognizing patterns from big data on adverse drug reactions and biomarkers for mitochondrial distress when medications are metabolized.

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REFERENCES


Drug-Induced Liver Injury
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