

An Update on Treatment of Drug-Induced Liver Injury

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Abstract

Drug-induced liver injury (DILI) has been linked to more than 1,000 medications and remains the most common cause of acute liver failure in the United States. Here, we review the most current literature regarding treatment and make recommendations for the management of this relatively common disease. Since treatment of DILI remains largely elusive, recent studies have attempted to define new management strategies for these difficult patients. Early diagnosis and withdrawal of the suspected medication is the mainstay of treatment of DILI. For acetaminophen and Amanita mushroom poisoning, there are specific therapies in use. Finally, there are other possible management modalities for DILI, including corticosteroids and ursodeoxycholic acid.

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Introduction

Drug-induced liver injury (DILI) is defined as a liver injury due to xenobiotics, herbs, or medications that leads to either liver dysfunction or abnormal liver serology, in the setting of no other identifiable cause. Unlike idiosyncratic drug induced liver injury (IDILI), DILI seems to be dose-dependent, predictable, and reproducible. DILI has been associated with more than 1,000 medications and is the most common cause of acute liver failure in the United States, accounting for approximately 50% of fulminant cases.^{1-5,6} While retrospective studies have shown acetaminophen to be the most common cause of DILI, studies in liver transplant patients have demonstrated antibiotics and immunosuppressive agents, such as tacrolimus and azathioprine, as the top causes.^{7,8} Björnsson et al. performed a prospective study and found that amoxicillin-clavulanate was the most commonly implicated antibiotic. The incidence was approximately 19 cases per 100,000.⁹ In addition to the typical suspects stated above, herbal and dietary supplements have been a rising

cause of DILI, now accounting for up to 9% of all cases.¹⁰ In fact, one study based in China, which spanned eight years, found that nearly half of all cases were secondary to medicinal herbs.¹¹ While DILI is most commonly due to only one drug, a prospective study demonstrated that nearly 10% of cases were attributable to more than one medication.⁹

DILI has several clinical manifestations ranging from asymptomatic elevations in liver enzymes to fulminant liver failure. Hepatic, or cytochrome P450, metabolism of a drug has been strongly linked to DILI, and one study demonstrated that those medications that rely on more than 50% hepatic metabolism have a greater risk for alanine transferase (ALT) elevation, liver failure, and mortality.¹² Other proposed mechanisms for DILI include autoimmunity and hypersensitivity.^{2,13} Despite the possible mechanisms, treatment options all follow the same principles. The most important, and first, step is early diagnosis followed by discontinuation of the offending agent.²

Diagnosis

The most common presenting symptom in most cases of DILI is jaundice, although many cases are asymptomatic or have elevated enzymes incidentally detected.¹¹ However, DILI can present as cholestatic, hepatocellular, and mixed; and proper diagnosis will direct the treatment of a particular case. Cholestatic liver injury is defined by predominant elevations of alkaline phosphatase (ALP), whereas hepatocellular liver injury is defined as predominant elevations of aspartate transferase (AST) and ALT, and mixed has elevations in both ALP and transaminases.¹⁴ It is important to note that ALT is liver-specific, whereas elevations in AST may be associated with damage to skeletal or cardiac muscle or in conditions such as myocardial infarction and rhabdomyolysis. Hepatocellular injury remains the most common presentation and is correlated with a worse outcome.^{15,16} Table 1 provides specific definitions for both cholestatic and hepatocellular injury, which may aid in the identification of the patient's clinical diagnosis.

Once liver injury has been established, the next step is to determine the underlying cause. Risk factors for DILI have been difficult to determine with many studies because of conflicting results in regard to sex and age-related occurrences. However, a recent study found that older age and female sex was associated with a cholestatic type injury, while younger age and male sex was associated with hepatocellular type injury. Genetic polymorphisms have been consistently found to be a risk factor for DILI but are not typically tested for in patients prior to receiving a medication.^{17,18} Finally, liver transplant patients where the reason for transplant was primary sclerosing cholangitis are at

Keywords: Drug-induced liver injury; Hepatotoxicity; Acetaminophen toxicity.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transferase; AST, aspartate transferase; CDS, clinical diagnostic scale; DDW-J, digestive disease week-Japan; DILI, drug-induced liver injury; IDILI, idiosyncratic drug induced liver injury; INR, international normalized ratio; IV, intravenous; NAC, N-acetylcysteine; PT, prothrombin; M&V, Maria and Victorino; PT, prothrombin time; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal.
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Table 1. Definitions of DILI^{20,23,24}

Cholestatic Liver Injury	Elevations of ALP \geq 2X the upper limit of normal (ULN) OR ALT/ALP ratio of < 2 with both ALT and ALP $>$ ULN
Hepatocellular Liver Injury	ALT \geq 5X ULN AND Total bilirubin \geq 2X ULN

greater risk for developing DILI.⁸ Chronic liver disease is a risk factor but only for certain medications, including methotrexate, isoniazid, and HIV antiretroviral therapy.² When diagnosing DILI, several established criteria can be used, none of which is considered to be a gold standard. Hy's law is specific but not sensitive, whereas the Roussel Uclaf Causality Assessment Method (RUCAM) is more sensitive but more difficult to administer in its truest form as it is complicated and requires rechallenging patients once they have recovered.^{19–21} One modification is the Digestive Disease Week-Japan (DDW-J) scale, which includes lymphocyte stimulation testing, although this test has not been validated.²² Yet another modification is the Clinical Diagnostic Scale (CDS) or Maria and Victorino (M&V) scale, which is more simple to administer but less predictive in patients who have had a prolonged period of time between drug use and development of symptoms or in those patients who have developed chronic liver injury.^{23–24} When examining these scales, common features, which make them specific and sensitive tests, include temporal relationship, exclusion of other causes, and prior reports of hepatotoxicity of the suspected medication. While specific criteria may be used, at a minimum the above three commonalities should be investigated. For reference, Wang et al found in China that the majority of cases occurred between 5 and 90 days of the initiation of the drug.¹¹ As an aid for the clinician, Table 2 provides medications and their typical liver injury presentation.

Once a specific drug has been identified as the cause of DILI, it must be discontinued.² Following withdrawal of the suspected agent, therapy is largely supportive with a few notable exceptions for acetaminophen and Amanita mushroom poisoning. All patients' laboratory values, including AST, ALT, ALP, bilirubin, and international normalized ratio (INR) and mental statuses should be monitored for changes. It is important to note that measuring only AST and ALT is insufficient when monitoring liver function in DILI. Damage to hepatocytes causes elevation of AST and ALT levels, and once sufficient damage has occurred, there are less hepatocytes and AST and ALT levels begin to decrease.¹⁴ Therefore, bilirubin and INR must also be monitored. With discontinuation of the drug, most cases resolve without further sequelae, with one prospective study reporting a median duration from diagnosis to normalization of laboratory values of 64 days.⁹

Lee et al. performed an eight year prospective, double-blind, placebo control trial of *N*-acetylcysteine (NAC) for patients with acute liver failure not secondary to acetaminophen overdose. While overall survival was similar in the populations (70% vs. 66%), transplant-free survival was significantly better for those who received NAC (40% vs. 27%).²⁵ At this time, NAC therapy can and should be considered for patients who are presenting with acute liver failure.

In addition, a small uncontrolled study performed by Wree et al. compared steroid pulse therapy with steroid step down

therapy, both in combination with ursodeoxycholic acid, in the treatment of drug-induced liver injury, including patients with hepatocellular and/or cholestatic injury. Both therapies demonstrated a decrease in time to normalization of bilirubin, AST, and ALT values.²⁶ However, since this was an uncontrolled study, it is uncertain if the observed improvement in their patient population actually reflected the natural history of DILI.

Specific treatment

Treatment for acetaminophen toxicity largely consists of NAC therapy. Studies have conflicted between whether oral or intravenous (IV) therapy should be given. Yarema et al. compared IV to oral administration and found that hepatotoxicity occurred less often in patients who received IV therapy within 12 hours of ingestion.²⁷ However, a recent study performed using a simulation system demonstrated that for those patients presenting within 24 hours of acetaminophen ingestion, the oral protocol is superior to the 21-hour intravenous protocol in persevering hepatocytes. These authors argued that Yarema's study contained two differing treatment groups.²⁸ Regardless, NAC therapy should be started if there is an elevation in AST, a detectable acetaminophen level, or if the level is above the treatment line on the Rumack-Matthew nomogram.²⁹ A computer simulation suggested that International Normalized Ratio (INR) did not undertreat patients but did lead to overtreatment, whereas treating until ALT peaked did not undertreat and rarely overtreated patients.²⁸ Current recommendations are to treat according to the protocol and to recheck AST and the acetaminophen level. At this point, AST should be less than 100 IU/L and acetaminophen level should be less than 10 mcg/mL. If not, therapy should be continued using the normalization of INR as a marker of resolution.³⁰

Amanita mushroom ingestion can lead to liver injury via the amatoxin, which inhibits RNA polymerase II and leads to hepatocyte necrosis. Presentation consists of a gastrointestinal phase followed by a hepatic phase. The gastrointestinal phase is characterized by nausea, vomiting, and abdominal pain. This is followed by symptomatic improvement but an elevation in AST and ALT followed by the development of jaundice. Since the hepatic phase is preceded by a gastrointestinal phase where dehydration and metabolic derangements may have developed, it is important to treat any dehydration and electrolyte abnormalities.³¹ While it has no proven efficacy for long-term survival, repeated activated charcoal administration is often recommended, which will prevent reabsorption of the amatoxin. While amatoxin may cause metabolic acidosis on its own, activated charcoal, which contains propylene glycol, can also cause a high anion gap metabolic acidosis. While clinicians should be aware of this potential complication, it should not preclude treatment with activated charcoal.³² Silibinin is universally accepted as a treatment modality for amatoxin poisoning because it

Table 2. Common biochemical presentation in DILI and associated medications / environmental exposure

Biochemical presentation	Associated medications / exposure
Cholestatic <i>(ALP > 2 × ULN or ALP/ALT <2)</i> <i>with both ALP and ALT > 1 × ULN</i>	Antimicrobials: <ul style="list-style-type: none"> Amoxicillin-clavulanate acid, Erythromycin, Trimethoprim-sulfamethoxazole Cardiovascular: <ul style="list-style-type: none"> Clopidogrel, ACE inhibitors Endocrine: <ul style="list-style-type: none"> Anabolic steroids Immunosuppressive: <ul style="list-style-type: none"> Azathioprine Gynecology: <ul style="list-style-type: none"> Oral contraceptives Neuropsychiatric: <ul style="list-style-type: none"> Carbamazepine, Chlorpromazine, Tricyclic antidepressants Anti-inflammatory: <ul style="list-style-type: none"> Sulindac
Hepatocellular <i>(ALT >5 × ULN and Bilirubin >2 × ULN)</i>	Anti-inflammatory: <ul style="list-style-type: none"> Acetaminophen, Bromfenac, Diclofenac, Ibuprofen, Naproxen Antimicrobials: <ul style="list-style-type: none"> Ciprofloxacin, Isoniazid, Ketoconazole, Nitrofurantoin, Protease inhibitors, Pyrazinamide, Rifampin, Tetracycline, Trimethoprim-sulfamethoxazole Cardiovascular: <ul style="list-style-type: none"> Amiodarone, Lisinopril, Quinidine, Statins Endocrine: <ul style="list-style-type: none"> Acarbose, Troglitazone Gastrointestinal: <ul style="list-style-type: none"> Cimetidine, Omeprazole Immunosuppressive: <ul style="list-style-type: none"> Allopurinol Neuropsychiatric: <ul style="list-style-type: none"> Bupropion fluoxetine, Methyldopa, Nefazodone, Paroxetine, Risperidone, Sertraline, Trazodone, Valproic acid Environmental exposures: <ul style="list-style-type: none"> Amatoxin Other: <ul style="list-style-type: none"> Halothane
Mixed <i>(ALT >5 × ULN or Bilirubin >2 × ULN) and (ALP >2 × ULN or ALP/ALT <2 with both ALP and ALT >1 × ULN)</i>	Antimicrobials: <ul style="list-style-type: none"> Clindamycin, Protease inhibitors, Reverse transcriptase inhibitors, Sulfonamides Cardiovascular: <ul style="list-style-type: none"> ACE inhibitors, Statins Immunosuppressive: <ul style="list-style-type: none"> Azathioprine Neuropsychiatric: <ul style="list-style-type: none"> Amitriptyline, Phenytoin,
Steatohepatitis	Antineoplastic: <ul style="list-style-type: none"> Tamoxifen Cardiovascular: <ul style="list-style-type: none"> Amiodarone
Veno-occlusive	Antineoplastic: <ul style="list-style-type: none"> Busulfan, Cyclophosphamide Environmental exposures: <ul style="list-style-type: none"> Arsenic, Thorium dioxide, Vinyl chloride, Other: <ul style="list-style-type: none"> Vitamin A

inhibits the transfer of amanitin into hepatocytes. It should be administered within 48 hours of mushroom ingestion. The current recommended dose is 20 to 50 mg/kg/day IV, which should be continued for 48–96 hours. High dose penicillin G is

also known to displace amatoxin and promote its excretion. The recommended dose is 1,000,000 IU/kg for first day and 500,000 IU/kg for next two days via continuous IV administration. Some studies suggest co-administration with NAC as

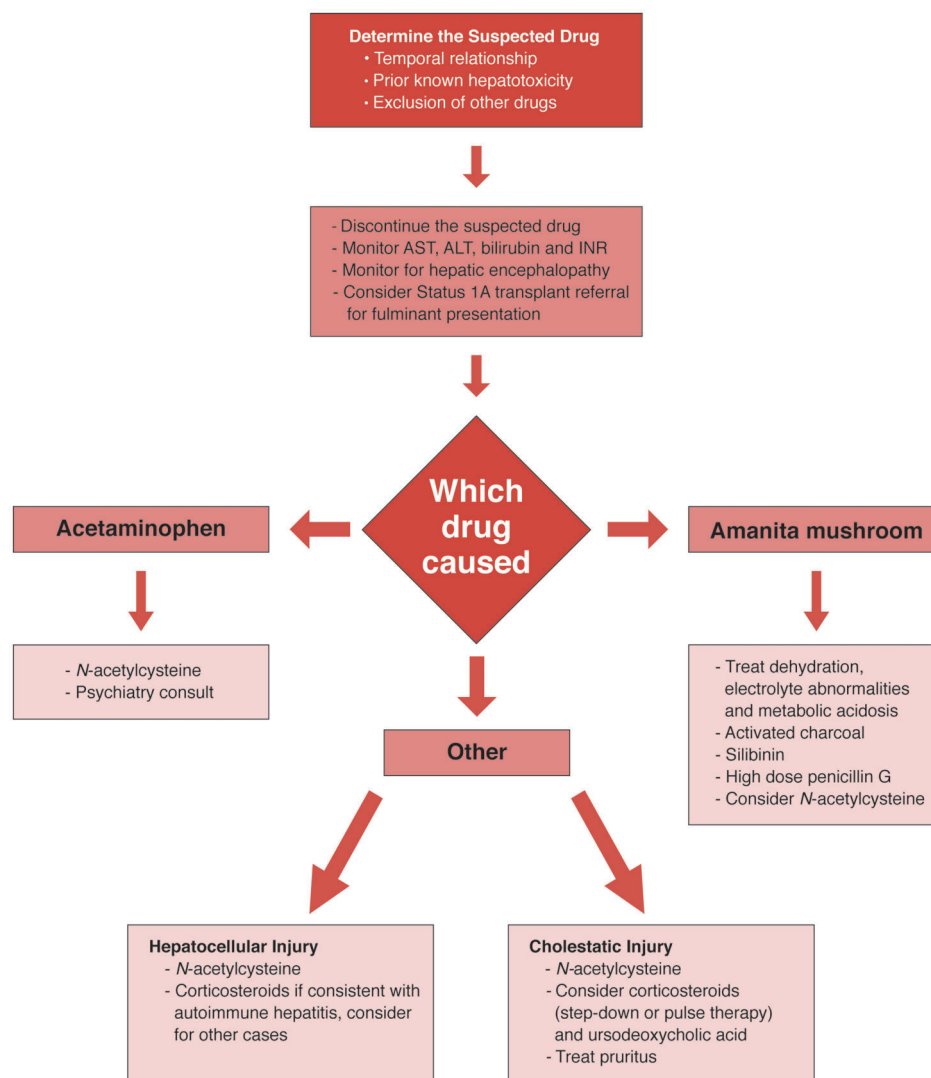


Fig. 1. Proposed treatment algorithm

well. Finally, if started early, the Molecular Adsorbent Recirculating System may be considered as it does improve liver function, although no specific studies have been done with Amanita mushroom poisoning.³¹

Patients who present with fever, rash, and eosinophilia should be considered for a diagnosis of drug-induced autoimmune hepatitis. If the DILI is severe, corticosteroid therapy should be considered as studies have demonstrated normalization of biochemical tests within six months.³³

Finally, patients who present with a cholestatic picture may complain of intense pruritus. Treatment options for these patients include emollients, hydroxyzine, diphenhydramine, bile acid resins, and rifampicin.³⁴

Potential role for liver assist devices

Extracorporeal systems have progressed through advances in genetically produced cell lines, stem cell-derived functional hepatocytes, immortalized human hepatocytes as well as improved techniques and methods for preserving the

hepatocytes. Demetriou et al. conducted the first prospective randomized trial using the HepatAssist Liver Support System. The system, composed of a hollow-fiber cartridge lined with porcine hepatocytes, was used in a multi-center trial showing survival benefit to those treated.³⁵ Advances in bioartificial livers continue with current trials being conducted by Vital Therapies and Hepa Wash GmbH (clinicaltrials.gov). These devices provide the potential for significant benefit to patients with DILI, subacute fulminate failure, and fulminate failure; and we are encouraged for the use of this technology in the future treatment of these patients.

Liver transplant referral considerations

The King's College criteria have been developed for both paracetamol and non-paracetamol causes in order to determine when a patient should be initially referred for transplantation. The criteria include a prothrombin time (PT) over 100 seconds or at least three of the following: PT over 50 seconds, bilirubin > 300 micromol/Liter, age below 10 or

over 40, an interval between jaundice and encephalopathy greater than seven days, or drug toxicity.³⁷ Other criteria that may be used include Clinchy's criteria and Escudie's criteria.

Patients with fulminant liver failure, defined as the presentation of hepatic encephalopathy within eight weeks of the development of symptoms related to liver disease, should be referred for transplant. In the United States, according to United Network for Organ Sharing (UNOS), a status 1A listing may be obtained if the patient has a life expectancy of seven days or less, does not have a pre-existing liver disease, and is in the intensive care unit requiring either ventilator assistance or dialysis or with an INR greater than two.³⁸ However, it is important to keep in mind the contraindications for transplant, which include significant comorbidities and active malignancy. Each patient should be considered on a case-by-case basis, and the guidelines should be consulted when considering a patient for transplant.

Conclusions

DILI remains an important cause of liver disease. Although it has a varied presentation and multiple possible drug causes, treatment for all cases requires discontinuation of the offending agent. If a patient has ingested acetaminophen or Amanita mushrooms, appropriate therapy should be administered. All patients can now be considered for NAC therapy and should be monitored for normalization of biochemical tests. Finally, early referral for liver transplant may be life saving for some patients.

Conflict of interest

None

Author contributions

Writing the manuscript and creating figures and tables (CG), performing literature searches (CG, XZ), and editing and revising the manuscript (XZ).

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