

DRUG INDUCED LIVER INJURY

Alaska Liver Disease ECHO

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Brittany L. Keener, PharmD, MPH, BCPS

CDR, United States Public Health Service

ANTHC Internal Medicine/Specialty Clinics Pharmacy Manager

- ▶ I have no conflict of interest to disclose



- ▶ Epidemiology
- ▶ Associated Drugs
- ▶ Mechanism
- ▶ Classification
- ▶ Clinical Manifestations

- ▶ Diagnosis
- ▶ Management
- ▶ Prognosis
- ▶ Prevention

OBJECTIVES

True or False:

1. Acetaminophen is the only medication that can cause DILI and be reversed with a medication.
2. Stopping the offending medication is usually enough to reverse DILI in most patients.
3. All DILI occur within the first 6 months of exposure.
4. DILI frequently occurs during drug trials.

PRE-TEST

- ▶ Occurrence of Drug-induced Liver Injury (DILI)
 - ▶ 10 to 15 out of 10,000 to 100,000 of all people exposed to medication may develop
 - ▶ Especially concerning in newly-approved medications.
- ▶ Seriousness
 - ▶ Responsible for 10% of all hepatitis cases in the US each year
 - ▶ Most common cause of liver failure in the US

BACKGROUND

▶ Age

- ▶ Adults usually more at risk than children
 - ▶ Exception: valproate, aspirin (Reye syndrome), propylthiouracil (PTU)
- ▶ Increased risk with advanced age (especially antimicrobials)

▶ Women

- ▶ Not at overall higher risk of DILI
- ▶ Higher risk of liver injury resembling autoimmune hepatitis (AIH) with some medications
 - ▶ Minocycline, methyldopa, diclofenac, nitrofurantoin, and nevirapine

EPIDEMIOLOGY

Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR. Practice Parameters Committee of the American College of Gastroenterology ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. *Am. J. Gastroent.* 2021; 116(5): 878-898 doi: 10.14309/ajg.0000000000001259

Drug Induced Liver Injury. In: UpToDate [database online]. Wolters Kluwer. https://www.uptodate.com/contents/drug-induced-liver-injury?search=drug%20induced%20liver%20injury&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Updated March 31, 2021. Accessed July 23, 2021.

- ▶ Pregnancy
 - ▶ No inherent increase in DILI except with tetracycline use
- ▶ Diabetes
 - ▶ Animal studies show a link, but no human studies show an association
- ▶ Alcohol use disorder (AUD)
 - ▶ Alcohol use not an inherent risk factor, but heavy drinking with certain medications (isoniazid, acetaminophen, and methotrexate) increases risk
 - ▶ Anabolic steroids highest risk drug in heavy alcohol consumers

ADDITIONAL EPIDEMIOLOGY

- ▶ Acetaminophen most common medication cause
- ▶ Antibiotics and antiepileptic drugs >60% DILI in US
- ▶ Illicit drugs can cause acute liver failure (methylenedioxymethamphetamine)
- ▶ Most drugs cause DILI within 6 months of onset

ASSOCIATED DRUGS

Intrinsic	Idiosyncratic	
Acetaminophen	Allopurinol	Lapatinib
Amiodarone [§]	Amiodarone [§]	Methyldopa
Anabolic steroids	Amoxicillin-clavulanate	Minocycline
Antimetabolites	Bosentan	Nitrofurantoin
Cholestyramine**	Dantrolene	Pazopanib
Cyclosporine	Diclofenac	Phenytoin
Valproic acid	Disulfiram	Pyrazinamide
HAART drugs	Felbamate	PTU
Heparins**	Fenofibrate	Statins [§]
Nicotinic acid	Flucloxacillin	Sulfonamides
Statins [§]	Flutamide	Terbinafine
Tacrine**	Halothane	Ticlopidine
	Isoniazid	Tolvaptan
	Ketoconazole	Tolcapone
	Leflunomide	Trovafloxacin
	Lisinopril	

ASSOCIATED DRUGS

**Mild ALT elevations without jaundice
 §Both intrinsic and idiosyncratic

Antimicrobials: Short - moderate onset

- Fluoroquinolones
- Macrolides
- Nitrofurantoin (rarely)
- Trimethoprim/sulfamethoxazole

Antimicrobials: Moderate-long onset

- Isoniazid
- Minocycline
- Nitrofurantoin

Antiepileptics

- Carbamazepine
- Lamotrigine
- Phenytoin (short onset)
- Valproate

Miscellaneous: Short-moderate onset

- Allopurinol
- Immune-checkpoint inhibitors (<12 weeks)
- Inhaled anesthetics
- Proton Pump Inhibitors (rare)
- Sulfasalazine

Miscellaneous: Moderate – long

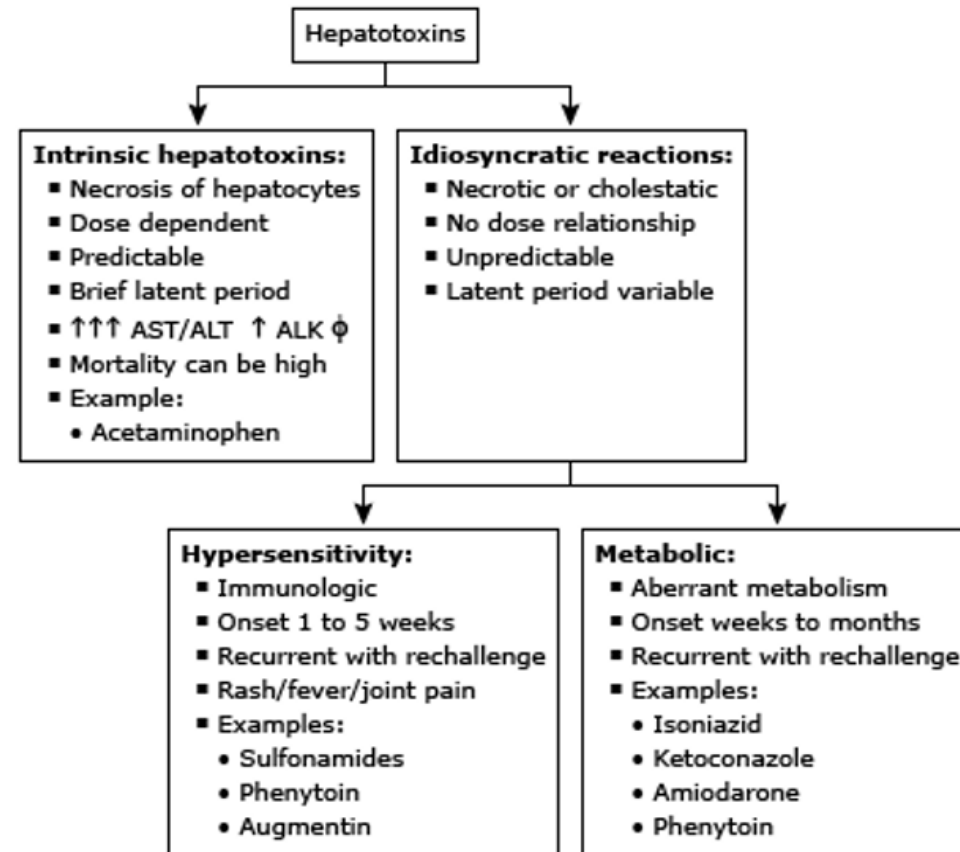
- Amiodarone (oral)
- Analgesics (NSAIDs and diclofenac)
- Androgen-containing steroids
- Methotrexate

DRUGS BY ONSET TIME

- ▶ Parent drug
- ▶ Metabolites
- ▶ Host immune system

MECHANISM

Mechanisms of drug-induced liver injury



AST: aspartate aminotransferase; ALT: alanine transaminase; ALK: alkaline phosphatase.

UpToDate®

- ▶ Direct hepatotoxicity
 - ▶ Acute hepatitis
 - ▶ Nodular regenerative hyperplasia
 - ▶ Sinusoidal obstructive syndrome (SOS)
 - ▶ Idiosyncratic hepatotoxicity
- ▶ Nonimmune
 - ▶ Immune-mediated
 - ▶ Drug-induced autoimmune-like hepatitis (DI-AIH)
 - ▶ Indirect hepatotoxicity

MECHANISM

Clinical presentation

- Hepatocellular (cytotoxic) injury
 - Cholestatic injury
 - Mixed injury

Hepatotoxicity Mechanism

- Predictable
- Idiosyncratic

Histological Findings

- Hepatitis
- Cholestasis
- Steatostasis

CLASSIFICATION

- ▶ R-values are serum alanine aminotransferase (ALT)/upper limit of normal (ULN) divided by alkaline phosphatase (Alk P)/ULN
 - ▶ $R > 5$ = hepatocellular DILI
 - ▶ $R < 2$ = cholestatic DILI
 - ▶ $2 < R < 5$ = mixed DILI

R-VALUES

Heptocellular Injury (Hepatitis)

- Serum aminotransferase >> compared to alkaline phosphatase
- $R > 5$

Cholestatic Injury

- Alkaline phosphatase >> compared to serum aminotransferases
- $R < 2$

Similar etiologies in both injury types

- Possible increases in serum bilirubin
- Abnormal synthetic function tests possible

CLINICAL PRESENTATION

- ▶ Acute hepatitis C and hepatitis E infections can appear as DILI
 - ▶ 1.5% of HCV cases appeared as DILI with negative antibody tests
 - ▶ Exclude HCV using RNA testing
 - ▶ 3% of people with a tentative DILI diagnosis were positive for HEV
 - ▶ Exclude HEV from differential by testing serology for patients at highest risk for exposure (traveled to endemic area)

CLINICAL CONFOUNDERS

- ▶ Acute DILI
 - ▶ Usually asymptomatic, but abnormal liver tests
 - ▶ Symptomatic patients: N/V, low-grade fever, anorexia, RUQ pain, jaundice, discolored stools/urine with hepatomegaly
 - ▶ Cholestasis accompanied by pruritus
 - ▶ Acute jaundice-like illness resembling viral hepatitis
 - ▶ Acute liver failure (hepatic encephalopathy and coagulopathy)
- ▶ Chronic injury
 - ▶ Resembles autoimmune hepatitis (elevated antinuclear antibody)
 - ▶ Symptomatic patients have symptoms resembling Alcohol-induced liver disease, cirrhosis, fibrosis, or hepatic decompensation (jaundice, ascites, palmar erythema, etc.)

CLINICAL MANIFESTATIONS

- ▶ Nonspecific symptoms after starting a new drug regimen
 - ▶ Nausea, anorexia, fatigue, RUQ pain, pruritus, or malaise)
- ▶ Obtain drug history and blood tests
- ▶ Exclude liver disease
- ▶ Drug has clinical reports of causing DILI in other patients
- ▶ Multiple scales to try to classify exposure to drug with DILI, but none used routinely in clinical practice because none of them include all patient risk factors
- ▶ Histology may help rule out other causes of liver injury and etiologic clues, but not diagnostic for cause of DILI

DIAGNOSIS

- ▶ Primary treatment: discontinue agent that caused DILI and do not re-challenge
- ▶ Treatment for overdoses
 - ▶ Acetaminophen: treated with N-acetylcysteine
 - ▶ Valproic acid: treated with L-carnitine
- ▶ Glucocorticoids have limited place in treatment
 - ▶ Hypersensitivity reactions with progressive cholestasis despite removal of drug
 - ▶ Biopsy resembles autoimmune hepatitis
 - ▶ Pulmonary exacerbation in drug reaction with eosinophilia and systemic symptoms (DRESS)
- ▶ Bile acid sequestrant for cholestatic liver disease with pruritus

MANAGEMENT

- ▶ Usually complete recovery within 6 months once agent removed
- ▶ Poor prognosis in hepatocellular injury
 - ▶ Jaundice (bilirubin > 2x ULN) with ALT > 3x ULN – progressive chronic liver disease possible
 - ▶ Acute liver failure in children from antiepileptic agents
 - ▶ APAP toxicity requiring hemodialysis
 - ▶ Increased SCr
 - ▶ Pre-existing liver disease

PROGNOSIS FOR ACUTE HEPATOCELLULAR LIVER INJURY

Chalasan NP, Maddur H, Russo MW, Wong RJ, Reddy KR . Practice Parameters Committee of the American College of Gastroenterology ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. *Am. J. Gastroent.* 2021; 116(5): 878-898 doi: 10.14309/ajg.000000000001259

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- ▶ Usually better prognosis
- ▶ Acute steatosis (fatty degeneration) → usually mild jaundice and less ALT increase
 - ▶ Usually good outcomes
 - ▶ If a severe case develops, high mortality rate

PROGNOSIS FOR ACUTE CHOLESTATIC INJURY

- ▶ Chronic injury, like acute injury, usually resolves when drug that caused the injury is removed
- ▶ Chronic disease develops in 5-10% of patients who experience ADEs
 - ▶ More common in cholestasis
 - ▶ Cholestasis more prolonged liver recovery (> 3 months)
- ▶ Possible to progress to cirrhosis without symptoms
- ▶ Vanishing bile duct syndrome
 - ▶ Chronic cholestasis damages liver and causes bile ducts to stop working and results in overt ductopenia = may result in cirrhosis and liver failure

PROGNOSIS FOR CHRONIC INJURY

- ▶ Patient education
 - ▶ Do not exceed dose of hepatotoxic drugs (APAP)
 - ▶ Avoid interactions with other drugs or alcohol
 - ▶ Signs and symptoms of hepatic injury
- ▶ Benefit of monitoring DILI using ALT screening unclear
 - ▶ Acute liver failure cases have occurred with patients being monitored
 - ▶ Slight ALT elevation doesn't always indicate early DILI
 - ▶ Most benefit by monitoring patients on high risk medications (isoniazid and methotrexate)

PREVENTION

▶ LiverTox

- ▶ <https://livertox.nih.gov>
- ▶ Clinical database with medications, recommended dosing, type of liver injury for common medications
- ▶ Database managers
 - ▶ National Institute of Diabetes and Digestive and Kidney Diseases
 - ▶ National Library of Medicine
 - ▶ Drug-Induced Liver Injury Network (DILIN) study group

CLINICAL RESOURCES



LiverTox < Prev Next >

Clinical and Research Information on Drug-Induced Liver Injury

Bethesda (MD): [National Institute of Diabetes and Digestive and Kidney Diseases](#); 2012-.

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New in LiverTox
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LiverTox[®] provides up-to-date, unbiased and easily accessed information on the diagnosis, cause, frequency, clinical patterns and management of liver injury attributable to prescription and nonprescription medications and selected herbal and dietary supplements. The LiverTox site is meant as a resource for both physicians and patients as well as for clinical academicians and researchers who specialize in idiosyncratic drug induced hepatotoxicity.

Information on a specific medication or supplement can be found by entering its name in the “Search this book” box shown above or by browsing the list of agents by its first letter using the alphabetic list shown below.

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The LiverTox team welcomes user comments and enquiries. [Contact Us](#)

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LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-
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Hepatotoxicity

Amoxicillin-**clavulanate** has been implicated in hundreds of cases of clinically apparent acute liver injury and this **combination** is currently the most common cause of drug induced liver disease in most large case series from the United States and Europe. The onset of injury is typically a few days to as long as 8 weeks (average ~3 weeks) after initiation of therapy and often occurs after the course of antibiotic is completed, the delay being a few days to as long as six weeks. The onset is typically with fatigue, low grade fever, nausea and abdominal pain, followed by pruritus and jaundice. The pattern of liver enzyme elevations is typically cholestatic with marked elevations in alkaline phosphatase and gamma glutamyl transpeptidase (Case 1). In some instances, aminotransferase levels are markedly elevated giving a mixed (Case 2) or hepatocellular pattern (Case 3), particularly in younger patients with earlier onset of injury. In children, amoxicillin-**clavulanate** hepatotoxicity is typically anicteric and presents with nausea, vomiting and abdominal pain rather than jaundice and itching. The pattern of serum enzyme elevations is also much more likely to be hepatocellular in children, but the course of illness is typically benign. Because the liver injury may present days or weeks after stopping therapy, the association of the liver injury with receipt of amoxicillin-**clavulanate** may be missed. Immunoallergic features (fever, rash, eosinophilia) can occur, but are not invariably present and are usually not prominent. Autoantibody formation is not common. The hepatic injury is idiosyncratic and is estimated to occur after ~1 in 2,500 prescriptions. The injury is more common in men than women, in the elderly and after multiple courses. Genetic studies indicate a link with HLA types, particularly the extended haplotype: DRB1*15:01-DRB5*01:01-DQB1*06:02.

Likelihood score: A (well established cause of clinically apparent liver injury).

Mechanism of Injury

The cause of amoxicillin-**clavulanate** hepatotoxicity is unknown, but is probably immunoallergic in origin. Allergic manifestations can occur and include rash, fever, arthralgias and eosinophilia. Several studies have reported an HLA Class II association with DRB1*15:01 and the extended haplotype DRB1*15:01-DRB1*01:01-DQB1*06:02. An independent HLA Class I association has also been made with HLA-A*02:01. The liver injury appears to be due to the **clavulanate** rather than amoxicillin, as reexposure to amoxicillin alone has not been associated with recurrence (Case 5), whereas reexposure to the **combination** is usually followed by a more rapid onset of a more severe hepatic injury, which can include prolonged cholestasis and development of cirrhosis. Other beta lactamase inhibitors (tazobactam and sulbactam) have not been reported to cause a similar hepatic injury, although it has been reported with other penicillins when combined with **clavulanate** (ticarcillin **clavulanate**).

Outcome and Management

The liver injury caused by amoxicillin-**clavulanate** is typically associated with jaundice and can be severe and prolonged (with jaundice lasting 4 to 24 weeks), but rarely results in lasting injury or death. Deaths due to amoxicillin-**clavulanate** hepatic injury have been described, but largely in patients with other comorbidities including cirrhosis or with multiple exposures. In addition, rare instances of prolonged cholestasis and vanishing bile duct syndrome have been reported after acute amoxicillin-**clavulanate** injury. Corticosteroids have been used in patients with marked or prolonged cholestasis, but their efficacy has not been shown and their use cannot be recommended routinely. Cholestyramine or ursodiol may help alleviate symptoms but probably do not speed recovery. **Rechallenge** with amoxicillin-**clavulanate** results in recurrence and should be avoided. Amoxicillin alone, on the other hand, is

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OTHER REFERENCE LINKS

- Recent References on Amoxicillin-Clavulanate: from PubMed.gov
- Trials on Amoxicillin-Clavulanate: from ClinicalTrials.gov

Related information

- PMC
- PubChem Substance
- PubMed

Similar articles in PubMed

- [Review](#) Augmentin (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tr [J Antimicrob Chemother. 2004]
- [Review](#) Amoxicillin/clavulanate potassium extended release tablets: a new antimicrobial for t [Expert Opin Pharmacother. 2003]
- Comparative effectiveness and safety of cefdinir and amoxicillin-clavulanate in treatment of acu [Antimicrob Agents Chemother. 1...]
- [Review](#) Amoxicillin-potassium clavulanate, a beta-lactamase-resistant antibiotic combination. [Clin Pharm. 1984]
- Double-blind, randomized study of the efficacy and safety of oral pharmacokinetically enhanced [Antimicrob Agents Chemother. 2...]

Recent Activity

- Amoxicillin-Clavulanate - LiverTox

CLINICAL RESOURCES

True or False:

1. Acetaminophen is the only medication that can cause DILI and be reversed with a medication.
2. Stopping the offending medication is usually enough to reverse DILI in most patients.
3. All DILI occur within the first 6 months of exposure.
4. DILI frequently occurs during drug trials.

POST-TEST

A decorative graphic consisting of several parallel white lines of varying lengths and orientations, located in the bottom right corner of the slide.

- ▶ DILI possible with multiple drug classes
- ▶ Patient education critical to alert providers of possible early toxicity
- ▶ Monitor patients closely on frequent offender drugs

CONCLUSIONS