WELCOME TO
AK LIVER DISEASE ECHO

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

NPAIHB
Indian Leadership for Indian Health

This project is supported by a grant from the Northwest Portland Area Indian Health Board and funding is provided from the HHS Secretary's Minority HIV/AIDS Fund.

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What brings you to the LD ECHO today

WHAT WE DO

- Didactic Presentations pertaining to ECHO topics
- We're accepting **case presentations and questions pertaining to:**
  - Elevated Liver Function Tests
  - Cirrhosis
  - Managing Complications of Decompensated Cirrhosis – Ascites, encephalopathy, esophageal varices
  - Alcohol-related liver disease, including Alcohol Hepatitis
  - Autoimmune liver disease – Autoimmune Hepatitis, Primary Biliary Cholangitis, Overlap
  - Nonalcoholic fatty liver disease/Nonalcoholic steatohepatitis
  - Hepatocellular carcinoma
- Provide Expert Panelists

CONSULTANT TEAM

- Brian McMahon, MD Hepatologist
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- Lisa Townshend, ANP Hepatology Provider
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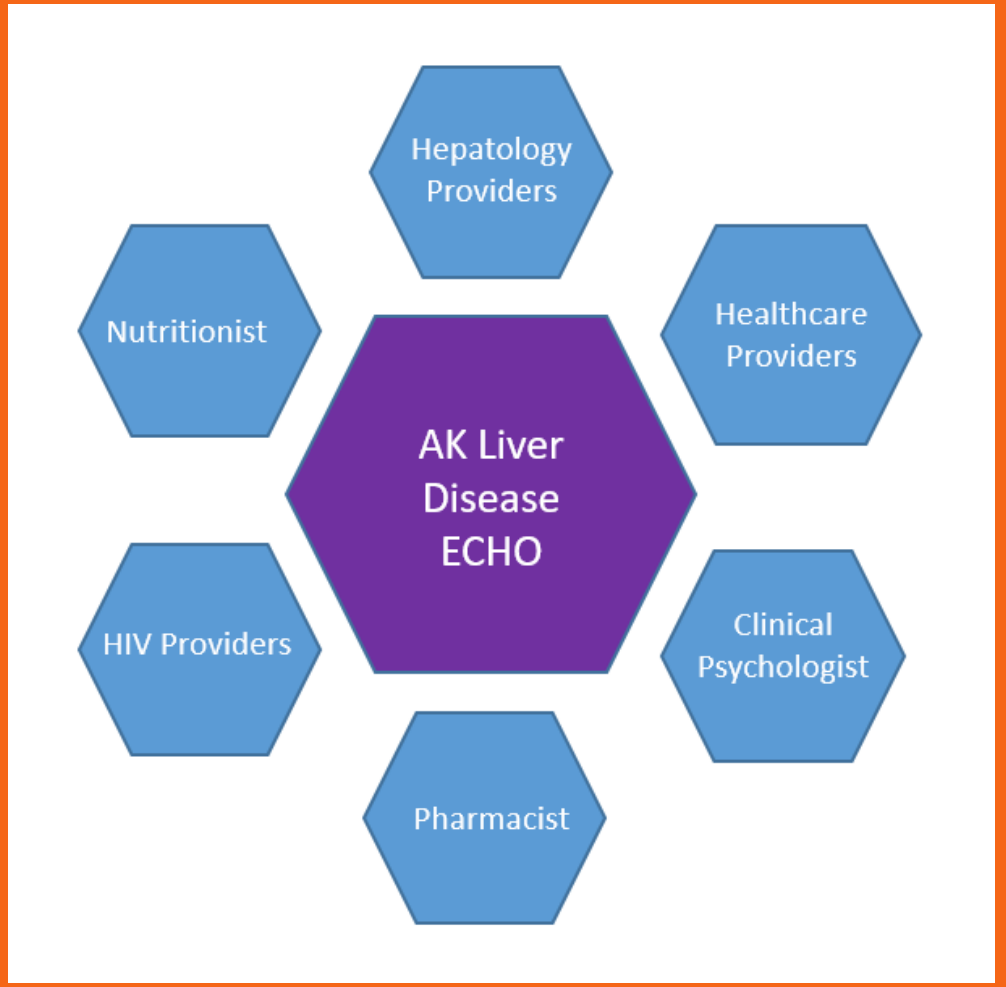

Welcome to Alaska Liver Disease ECHO

Approved Provider Statements:

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In support of improving patient care, Alaska Native Medical Center (ANMC) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Contact Hours:

ANMC designates this activity for a maximum of 12 contact hours, including 3 total pharmacotherapeutics contact hours, commensurate with participation.

Financial Disclosures:

Youssef Barbour, MD & Lisa Townshend-Bulson, APRN / faculty for this educational event, are primary investigators in an ANTHC sponsored hepatitis C study funded in part by Gilead Sciences. All of the relevant financial relationships listed have been mitigated.

Requirements for Successful Completion:

To receive CE credit please make sure you have actively engaged in the entire activity, your attendance is recorded by the facilitator, and complete the course evaluation form found here: https://forms.gle/R8vibUZgMbRcoScw9.

For more information contact
jlfielder@anthc.org or (907) 729-1387

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

LIVER DISEASE ECHO SCHEDULE AT A GLANCE

- **August 18th – Most Common Liver Toxic Drugs**
- September 15th – Trauma Informed Care and Liver Disease
- October 20th – Screening for Alcohol Use Disorder
- November 17 - Medication Assisted Treatment
- December 15 - HCC Surveillance – Are We Doing Enough?

LAND ACKNOWLEDGEMENT

Out of great respect, we acknowledge the Creator of all living things and the original inhabitants upon whose traditional lands we respectively now gather or reside.

Let us, forever, remember the benefits and bounty of the vast resources that stem from these traditional lands, and thank the original inhabitants for their past and present stewardship of the resources (i.e., waters, plants, animals), and the spiritual practices which they cherish on the lands we now call home.

Liver Toxic Drugs and LiverTox Website

ALASKA LIVER DISEASE ECHO AUGUST 18, 2022

BRITTANY L. KEENER, PHARMD, MPH, BCPS
CDR, UNITED STATES PUBLIC HEALTH SERVICE
ANTHC INTERNAL MEDICINE/SPECIALTY CLINICS PHARMACY MANAGER

- I have no conflicts of interest to disclose

Objectives

- Review common liver toxic drugs
- Review LiverTox website
- Review examples from LiverTox website

Pre-Test

TRUE/FALSE

1. AMOXICILLIN/CLAVULANATE (AUGMENTIN) IS THE MOST COMMON ANTIBIOTIC TO CAUSE LIVER INJURY
2. THE PURPOSE OF THE LIVERTOX WEBSITE IS TO PROVIDE CLEAR AND UNBIASED INFORMATION ON DRUG INDUCED LIVER INJURY TO SUPPORT CLINICAL MANAGEMENT OF PATIENTS AND TO STIMULATE INTEREST AND RESEARCH DIRECTED AT THE PREVENTION OR TREATMENT OF THIS IMPORTANT FORM OF LIVER DISEASE
3. CATEGORY X IS EQUIVALENT TO LIKELIHOOD OF FATALITY

Background

- The probability of an individual drug causing liver injury ranges from 1 in 10,000 to 100,000
- Some drugs report an incidence of 100 in 100,000
- Over 1,000 medications and herbal products have been implicated in the development of liver injury
- Drugs may cause injury in a dose-dependent, predictable way or in an unpredictable fashion, and may be immune-mediated or metabolic
- The injury can be from the parent drug or its metabolites
- The liver is exposed to nearly all drugs absorbed from the intestinal tract and is the predominant site of drug metabolism

UpToDate Drug Induced Liver Injury. 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. Accessed July 14, 2022.
UpToDate. Drugs and the liver: Metabolism and mechanisms of injury. https://www.uptodate.com/contents/drugs-and-the-liver-metabolism-and-mechanisms-of-injury?sectionName=MECHANISMS%20OF%20DRUG-INDUCED%20HEPATOTOXICITY&search=drug%20induced%20liver%20injury&topicRef=3571&anchor=H14&source=see_link#H14. Accessed July 14, 2022.

Drug Induced Liver Injury Rank (DILIrank) Dataset

- Largest reference drug list ranked by the risk for developing DILI in humans
- Consists of 1,036 FDA-approved drugs
  - Divided into four classes: most-DILI-concern, less-DILI-concern, no-DILI-concern, or ambiguous-DILI-concern
  - Derived from hepatotoxic descriptions presented in FDA-approved drug labeling documents and assessing causality evidence in literature
- 192 most-DILI-concern
- 278 less-DILI-concern
- 312 no-DILI-concern
- 254 ambiguous-DILI-concern

The Food and Drug Administration. Drug Induced Liver Injury Rank (DILIrank) Dataset. https://www.fda.gov/science-research/liver-toxicity-knowledge-base-ltkb/drug-induced-liver-injury-rank-dilirank-dataset. Content current as of March 11, 2022. Accessed July 14, 2022.

Drug Induced Liver Injury Rank (DILIrank) Dataset

- DILIscore: > 6, high risk; 3-6, moderate risk; < 3, low risk
- Of 1,036 drugs included in the dataset:
  - 221 are considered high risk
  - 428 are considered moderate risk
  - 387 are considered low risk
- Of the 192 ranked most-DILI-concern:
  - 165 are considered high risk
  - 27 are considered moderate risk

The Food and Drug Administration. Drug Induced Liver Injury Rank (DILIrank) Dataset. https://www.fda.gov/science-research/liver-toxicity-knowledge-base-ltkb/drug-induced-liver-injury-rank-dilirank-dataset. Content current as of March 11, 2022. Accessed July 14, 2022.

Drug Induced Liver Injury Rank (DILIrank) Dataset

Drug Name	Severity Class	Drug Name	Severity Class	Drug Name	Severity Class	Drug Name	Severity Class	Drug Name	Severity Class
mercaptopurine	8	clarithromycin	8	pipamazine	8	nialamide	8	bosentan	7
indomethacin	8	testosterone	8	pralnacasan	8	nilutamide	8	micafungin	7
phenytoin	8	etodolac	8	sulfacarbamide	8	niperotidine	8	bortezomib	7
rifampin	8	pemoline	8	triacetyldiphenolisatin	8	nomifensine	8	milnacipran	7
abacavir	8	nevirapine	8	fiduxosin	8	nortriptyline	8	asparaginase	7
allopurinol	8	benzbromarone	8	pafuraidine	8	pirprofen	8	efavirenz	7
amineptine	8	busulfan	8	phenoxypropazine	8	riluzole	8	interferon beta-1b	7
amiodarone	8	disulfiram	8	oxandrolone	8	ritonavir	8	interferon beta-1a	7
bicalutamide	8	isoniazid	8	acarbose	8	sulcotidil	8	interferon alfacon-1	7
chlorzoxazone	8	nimesulide	8	alpidem	8	tolrestat	8	lamotrigine	7
dactinomycin	8	minocycline	8	bexarotene	8	fenclozic acid	8	nandrolone decanoate	7
dantrolene	8	alatrofloxacin mesylate	8	voriconazole	8	ebrotidine	8	dacarbazine	6
diclofenac	8	gemtuzumab ozogamicin	8	bendazac	8	nitrefazole	8	acetaminophen	5
diflunisal	8	acetazolamide	8	benzarone	8	tetrabamate	8	azathioprine	5
fenoprofen	8	benoxaprofen	8	benziodarone	8	xenazoic acid	8	erythromycin	5
flutamide	8	bromfenac	8	atomoxetine	8	zafirlukast	8	sulfasalazine	5
hydroxyurea	8	danazol	8	chlormezanone	8	falnidamol	8	isotretinoin	5
imatinib	8	febuxostat	8	erlotinib	8	zimelidine	8	atorvastatin	5
iproniazid	8	griseofulvin	8	cinchophen	8	telithromycin	8	clozapine	5
ketoconazole	8	ibufenac	8	tipranavir	8	ximelagatran	8	4-aminosalicylic acid	5
labetalol	8	sunitinib	8	clometacin	8	duloxetine	8	zileuton	5
leflunomide	8	methimazole	8	sorafenib	8	glafenine	8	acitretin	5
mefenamic acid	8	sulfathiazole	8	darunavir	8	mepazine	8	natalizumab	5
methyldopa	8	terbinafine	8	cyclofenil	8	lapatinib	8	papaverine	5
nefazodone	8	ticrynafen	8	didanosine	8	alaproclate	8	gemfibrozil	4
nitrofurantoin	8	trovafloxacin	8	interferon alfa-2b	8	orlistat	8	ticlopidine	4
perhexiline	8	etravirine	8	interferon alfa-2a, recombinant	8	sitaxsentan	8	exemestane	4
propylthiouracil	8	tolvaptan	8	droxicam	8	carbamazepine	7	gefitinib	4
stavudine	8	pazopanib	8	ethambutol	8	felbamate	7	eltrombopag olamine	4
sulindac	8	divalproex sodium	8	infliximab	8	ciprofloxacin	7	oxaliplatin	4
tamoxifen	8	lumiracoxib	8	exifone	8	oxymetholone	7	diltiazem	4
tizanidine	8	tasosartan	8	fialuridine	8	niacin	7	estramustine	4
tolcapone	8	oxyphenisatin	8	fipexide	8	cyclosporine	7	peginterferon alfa-2b	4
valproic acid	8	tilbroquinol	8	fosphenytoin	8	albendazole	7	methotrexate	3
zidovudine	8	alclofenac	8	gemcitabine	8	deferasirox	7	cytarabine	3
troglitazone	8	aplaviroc	8	levofloxacin	8	thiabendazole	7	maraviroc	3
fluconazole	8	clomacran	8	mebanazine	8	raltegravir	7	mexiletine	3
itraconazole	8	dermatan	8	moxisylyte	8	dronedarone	7	pentostatin	3
clomipramine	8	isaxonine	8						

The Food and Drug Administration. Drug Induced Liver Injury Rank (DILIrank) Dataset. https://www.fda.gov/science-research/liver-toxicity-knowledge-base-ltkb/drug-induced-liver-injury-rank-dilirank-dataset. Content current as of March 11, 2022. Accessed July 14, 2022.

Common Liver Toxic Drugs

- Drugs that have been associated with more than 100 cases of DILI
- 92% of these drugs had documented positive rechallenge
- 98% had at least one convincing case that was associated with fatal outcome
- The most common types of drugs were antimicrobials (33%), followed by drugs acting on the central nervous system (12.5%), cardiovascular (12.5%), rheumatologic (12.5%), antineoplastic (10%), endocrine (6%) and other types of drugs (13%)

Drug Name	*Class/Indication*	Drug Name	*Class/Indication*	Drug Name	*Class/Indication*
Allopurinol	*Gout prophylaxis*	**Floxuridine**	*Antineoplastic*	**Nimesulide**	*NSAID*
Amiodarone	*Arrhythmia*	**Flucloxacillin**	*Antimicrobial*	**Nitrofurantoin**	*Antibiotic*
Amoxicillin-clavulanate	*Antibiotic*	**Flutamide**	*Antineoplastic*	**Phenytoin**	*Antiepileptic*
Anabolic steroids	*Body building*	**Gold salts**	*Immunosuppressive agent*	**Propylthiouracil**	*Antithyroid*
Atorvastatin	*Lipid lowering agent*	**Halothane**	*Anaesthetic*	**Quinidine**	*Arrhythmia*
Azathioprine/6-Mercaptopurine	*Immunosuppressive agent*	**Hydralazine**	*Antihypertensive*	**Pyrazinamide**	*Antituberculosis*
Busulfan	*Malignancy*	**Ibuprofen**	*NSAID*	**Rifampin**	*Antituberculosis*
Carbamazepine	*Antiepileptic*	**Infliximab**	*Immunosuppressive agent*	**Simvastatin**	*Lipid lowering agent*
Chlorpromazine	*Psychosis*	**Interferon alpha/ Peginterferon**	*Antimicrobial*	**Sulfamethoxazole/ Trimethoprim**	*Antibiotic*
Contraceptives	*Birth control*	**Interferon beta**	*Multiple Sclerosis*	**Sulfonamides**	*Antibiotic*
Dantrolene	*Muscle relaxant*	**Isoniazid**	*Antituberculosis*	**Sulindac**	*NSAID*
Diclofenac	*NSAID*	**Ketoconazole**	*Antifungal*	**Telithromycin**	*Antibioitic*
Didanosine	*Antimicrobial*	**Methotrexate**	*Immunosuppressive agent*	**Thioguanine**	*Antineoplastic*
Disulfiram	*Substance abuse agent*	**Methyldopa**	*Antihypertensive*	**Nimesulide**	*NSAID*
Efavirenz	*Antimicrobial*	**Minocycline**	*Antibiotic*	**Ticlopidine**	*Platelet inhibitor*
Erythromycin	*Antimicrobial*	**Nevirapine**	*Antimicrobial*	**Valproate**	*Antiepileptic*

Björnsson ES. Hepatotoxicity by Drugs: The Most Common Implicated Agents. Int J Mol Sci. 2016 Feb 6;17(2):224. doi: 10.3390/ijms17020224. PMID: 26861310; PMCID: PMC4783956.

Common Liver Toxic Drugs

Drug Name	*Class/Indication*
Amodiaquine	*Antimicrobial*
Azithromycin	*Antimicrobial*
Chlorzoxazone	*Muscle relaxant*
Cyproterone	*Antineoplastic*
Heparin	*Anticoagulant*
Imatinib	*Antineoplastic*
Irinotecan	*Antineoplastic*
Levofloxacin/Ofloxacin	*Antimicrobial*
Oxacillin	*Antimicrobial*
Phenobarbital	*Antiepileptic*
Stavudine	*Antimicrobial*
Tamoxifen	*Antineoplastic*
Terbinafine	*Antifungal*

- These drugs have been associated with >30 published case reports of DILI
- 38% have documented positive rechallenge
- 50% associated with a fatal outcome

Björnsson ES. Hepatotoxicity by Drugs: The Most Common Implicated Agents. Int J Mol Sci. 2016 Feb 6;17(2):224. doi: 10.3390/ijms17020224. PMID: 26861310; PMCID: PMC4783956.

Common Liver Toxic Drugs

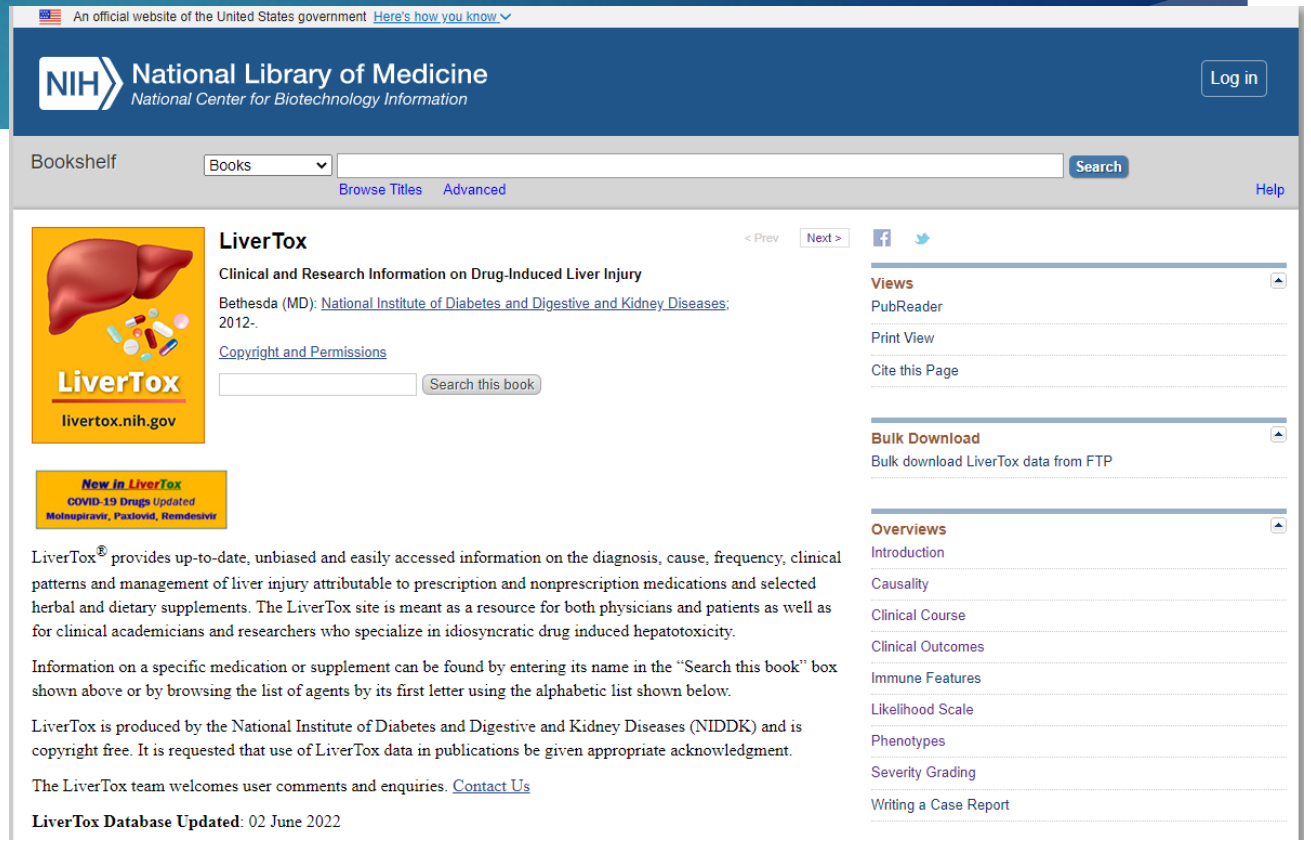
- The top 5 implicated drugs in three prospective studies on DILI
- RIP + INH + PIZ: Rifampin, Isoniazid and Pyrazinamide; SMZ/TMP: Sulfamethoxazole/Trimethoprim

Spanish Registry	DILIN Study (US)	Icelandic Study
Amoxicillin-clavulanate	**Amoxicillin-clavulanate**	**Amoxicillin-clavulanate**
Isoniazid	**Isoniazid**	Diclofenac
RIP + **INH** + PIZ	**Nitrofurantoin**	Azathioprine
Flutamide	SMZ/TMP	Infliximab
Ibuprofen	Minocycline	**Nitrofurantoin**

Björnsson ES. Hepatotoxicity by Drugs: The Most Common Implicated Agents. Int J Mol Sci. 2016 Feb 6;17(2):224. doi: 10.3390/ijms17020224. PMID: 26861310; PMCID: PMC4783956.

LiverTox Website

- 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.
- https://www.ncbi.nlm.nih.gov/books/NBK547852/



LiverTox: Likelihood of DILI

- **Category A** .The drug is **well known**, well described and well reported to cause either direct or idiosyncratic liver injury, and has a characteristic signature; more than 50 cases including case series have been described.
- **Category B**. The drug is reported and **known** or **highly likely** to cause idiosyncratic liver injury and has a characteristic signature; between 12 and 50 cases including small case series have been described.
- **Category C**. The drug is **probably** linked to idiosyncratic liver injury, but has been reported uncommonly and no characteristic signature has been identified; the number of identified cases is less than 12 without significant case series.
- **Category D**. Single case reports have appeared implicating the drug, but fewer than 3 cases have been reported in the literature, no characteristic signature has been identified, and the case reports may not have been very convincing. Thus, the agent can only be said to be a **possible** hepatotoxin and only a rare cause of liver injury.
- **Category E**. Despite extensive use, no evidence that the drug has caused liver injury. Single case reports may have been published, but they were largely unconvincing. The agent is **not believed** or is **unlikely** to cause liver injury.
- **Category E***. The drug is suspected to be capable of causing liver injury or idiosyncratic acute liver injury but there have been no convincing cases in the medical literature. In some situations cases of acute liver injury have been reported to regulatory agencies or mentioned in large clinical studies of the drug, but the specifics and details supportive of causality assessment are not available. The agent is **unproven, but suspected** to cause liver injury.
- **Category X**. Finally, for medications recently introduced into or rarely used in clinical medicine, there may be inadequate information on the risks of developing liver injury to place it in any of the five categories, and the category is characterized as "**unknown**."

LiverTox: Causality Assessment

- **Definite** (>95% assurance) implies that the association is "beyond a reasonable doubt"; that the agent is known to cause liver injury; the drug causes a specific clinical pattern of liver injury; and, that other possible competing diagnoses have been adequately and convincingly ruled out.
- **Very likely** (75% to 95% assurance) suggests that the association is "clear and convincing"; that the agent is known to cause liver injury; and, that most, but perhaps not all, competing diagnoses have been excluded or the pattern of injury is not completely typical.
- **Probable** (50% to 75% assurance) suggests that "the predominance of the evidence" supports the association. The agent may not have been previously linked to liver disease; and/or the pattern of injury may be atypical; and/or not all competing diagnoses have been completely excluded. Nevertheless, the reviewer believes that the weight of the evidence is in favor of the drug having caused the liver injury.
- **Possible** (25% to 50% assurance) suggests that the association is weak but cannot be ruled out completely. Perhaps the agent has not been clearly linked to liver injury; or, the pattern of injury is unusual for the medication; or, another cause of liver injury is present.
- **Unlikely** (<25% assurance) suggests that the liver injury is clearly due to another condition or its association with the medication is not at all convincing.

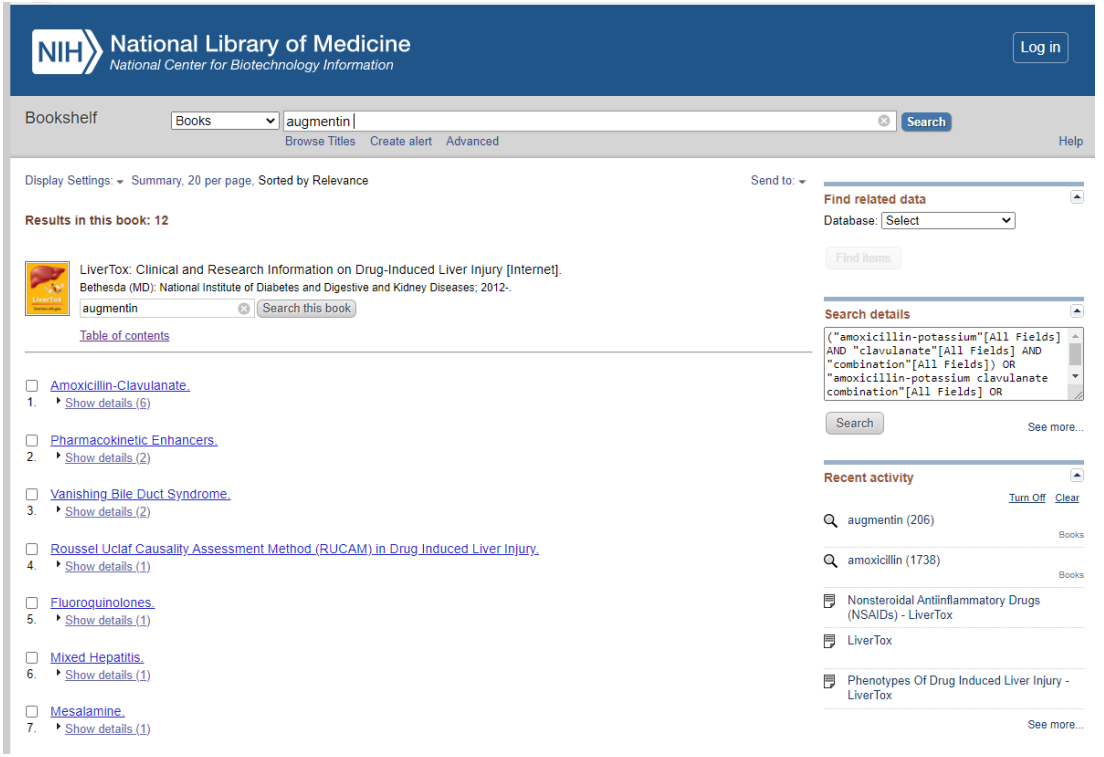
LiverTox:
Severity Grading In DILI

- 1+ = Mild
- 2+ = Moderate
- 3+ = Moderate to Severe
- 4+ = Severe
- 5+ = Fatal

LiverTox: Severity Grading in DILI

- **1+, Mild:** Raised serum aminotransferase or alkaline phosphatase levels or both, but total serum bilirubin <2.5 mg/dL and no coagulopathy (INR <1.5)
- **2+, Moderate:** Raised serum aminotransferase or alkaline phosphatase levels or both and total serum bilirubin level ≥2.5 mg/dL or coagulopathy (INR ≥1.5) without hyperbilirubinemia
- **3+, Moderate to Severe:** Raised serum aminotransferase or alkaline phosphatase levels and total serum bilirubin level ≥2.5 mg/dL and hospitalization (or preexisting hospitalization is prolonged) because of the drug induced liver injury
- **4+, Severe:** Raised serum aminotransferase or alkaline phosphatase levels and serum bilirubin ≥2.5 mg/dL and at least one of the following:
  - Prolonged jaundice and symptoms beyond 3 months, or
  - Signs of hepatic decompensation (INR ≥1.5, ascites, encephalopathy), or
  - Other organ failure believed to be related to drug induced liver injury
- **5+, Fatal:** Death or liver transplantation for drug induced liver injury

LiverTox: Examples



LiverTox: Examples

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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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   - CITED REFERENCES.
   - ANNOTATED BIBLIOGRAPHY.

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].
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Drug Records

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Amoxicillin-Clavulanate

Last Update: October 20, 2020.

OVERVIEW

Introduction

The **combination** of amoxicillin and **clavulanate** is an oral antibiotic widely used in the treatment of mild-to-moderate bacterial infections including sinusitis, bronchitis, otitis media, cellulitis and community acquired pneumonia. Amoxicillin-**clavulanate** is currently the most common cause of clinically apparent, drug induced acute liver injury both in the United States and Europe.

Background

The **combination** of amoxicillin and **clavulanate** is a commonly used antibiotic which is active against many bacterial organisms that cause sinusitis, bronchitis, otitis media, skin and tissue infections and community acquired pneumonia. The **combination** consists of amoxicillin which is a semisynthetic, third generation penicillin and **clavulanate** which is a beta lactam that acts as an inhibitor of beta lactamase, the major bacterial enzyme responsible for penicillin resistance. Amoxicillin-**clavulanate** was approved for use in the United States in 1984 and, currently, approximately 6 million prescriptions are filled yearly, making it one of the most common antibiotic regimens used. Current indications are for mild-to-moderate bacterial infections due to known or suspected penicillinase resistant gram positive or gram negative organisms. This **combination** is provided in multiple dose combinations, typically as 250 to 875 mg amoxicillin with 125 mg of **clavulanate**, given two to three times daily for 7 to 10 days. Amoxicillin-**clavulanate** is available in multiple generic formulations and under the brand name **Augmentin**. Side effects are usually mild and self-limited and can include diarrhea, nausea and vomiting, fatigue, headache, and rash. Rare but potentially serious adverse events include hypersensitivity reactions, anaphylaxis, severe skin rash, Stevens Johnson syndrome, C. difficile diarrhea, interstitial nephritis, neutropenia, aplastic anemia and thrombocytopenic purpura.

LiverTox: Examples

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 safe and does not cause recurrence of liver injury except in the rare instance in which the penicillin rather than **clavulanate** is responsible for the liver injury.

Drug Class: Antiinfective Agents, Aminopenicillins

Other Drugs in the Subclass, Aminopenicillins: Ampicillin, Ampicillin-Sulbactam, Amoxicillin, Bacampicillin, Pivampicillin, Ticarcillin-**Clavulanate**

CASE REPORTS

Case 1. Cholestatic hepatitis from amoxicillin-clavulanate.(1)

A 75 year old man with a history of prostate cancer and regular alcohol use (2 to 3 drinks daily) was given amoxicillin-**clavulanate** (500 mg/125 mg) for chronic maxillary sinusitis. Because of persistent symptoms, the antibiotic was continued for 31 days. When seen in follow up two weeks later, he complained of jaundice and was admitted to the hospital for evaluation. He had symptoms of dark urine, weakness, and poor appetite. Blood test results showed a total bilirubin of 42.7 mg/dL, ALT 194 U/L, AST 107 U/L, and alkaline phosphatase 257 U/L. Tests for acute hepatitis A, B, C and E were negative. Ultrasound of the abdomen showed no evidence of biliary obstruction or gallstones. During the hospitalization he developed profound anemia and thrombocytopenia requiring blood and platelet transfusions, and was further treated with corticosteroids and cyclophosphamide. His serum bilirubin peaked at 48.8 mg/dL and remained elevated for several months while aminotransferase and alkaline phosphatase levels were only modestly elevated (Table). The prothrombin time was elevated (INR 1.4 to 1.6) transiently and he developed mild confusion that was believed to be due to hepatic encephalopathy; he was treated with lactulose. During the hospitalization he developed renal failure and required dialysis. A liver biopsy was performed and findings were consistent with amoxicillin-**clavulanate** hepatotoxicity. He was hospitalized for 2 months and required another several months to recover fully. However, when seen 4 months after onset of the jaundice, he was back to his usual state of health and had normal laboratory tests, including normal aminotransferase and alkaline phosphatase levels, normal serum bilirubin and creatinine, and normal hemoglobin and platelet counts.

LiverTox: Examples

Key Points

Medication:	Amoxicillin-**clavulanate** 500/125 mg thrice daily for 31 days
Pattern:	Cholestatic (R=1.9)
Severity:	4+ (jaundice, hospitalization, severe thrombocytopenia and acute renal failure)
Latency:	45 days, 14 days after stopping
Recovery:	Slowly over 4 months
Other medications:	Guaifenesin

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Comments
31 days	0	Amoxicillin-**clavulanate** stopped			
40 days	9 days	Jaundice			
6 weeks	2 weeks	126	195	43.8	Admission, platelets 2,000
7 weeks	3 weeks	58	165	48.6	
2 months	4 weeks	59	248	48.8	
	5 weeks	44	198	42.4	Acute renal failure
	7 weeks	40	195	19.4	Liver biopsy
3 months	8 weeks	40	267	7.4	
98	67	47	242	3.6	Discharged, platelets 376,000
158	127	11	81	0.6	Creatinine 2.5
Normal Values		**<42**	**<115**	**<1.2**	

Comment

This case is an example of severe amoxicillin-**clavulanate** hepatotoxicity. Liver histology showed central lobular retention of bile with mixed infiltrates of lymphocytes, neutrophils and eosinophils in portal areas and in areas of focal spotty necrosis in the parenchyma. There was minimal steatosis, no fibrosis and no biliary damage or peribiliary fibrosis or edema. The findings were consistent with a drug induced intrahepatic cholestasis. The case was typical of amoxicillin-**clavulanate** hepatotoxicity in its onset 1 to 2 weeks after stopping therapy in an elderly man without other history or risk factors for liver or biliary disease. The severe thrombocytopenia and anemia were atypical, but similar nonhepatic manifestations of immunoallergic injury have been reported. Important conditions to exclude were biliary obstruction due to malignancy or gallstone disease and viral hepatitis. Therapy should be limited to symptomatic management of pruritus and avoidance of further hepatic injury. Appropriate management calls for follow up documentation of resolution of liver injury. The patient should be warned to avoid any further exposure to amoxicillin-**clavulanate**. In view of the severity of the injury, use of amoxicillin alone might also be best avoided.

Case 2. Mixed cholestatic-hepatocellular injury due to amoxicillin-clavulanate.(1)

A 52 year old man without major medical illnesses developed an upper respiratory infection and was given a 14 day course of amoxicillin-**clavulanate**. One and two months later, because of similar symptoms of fever and congestion, he was given a 2nd and 3rd 14 day course along with antihistamines and decongestants. Two weeks after the 3rd course of antibiotics, he developed abdominal pain, nausea, poor appetite, and itching, followed soon after by jaundice and dark urine. He was seen and blood tests revealed total bilirubin of 3.9 mg/dL with marked elevations in both ALT and alkaline phosphatase (Table). He was managed as an outpatient, did not undergo liver biopsy, and recovered symptomatically over the next few weeks. When seen one year later, he was asymptomatic and laboratory tests had returned to normal.

Key Points

Medication:	Amoxicillin-**clavulanate** 500/125 mg twice daily for 42 days
Pattern:	Mixed cholestatic-hepatocellular (R=2.3)
Severity:	2+ (jaundice, never hospitalized)
Latency:	58 days, 16 days after stopping
Recovery:	Six months after stopping
Other medications:	None

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Comments
2 weeks	0	Amoxicillin-**clavulanate** stopped			
4 weeks	16 days	Nausea, jaundice, arthralgia			
	16 days	879	731	3.9	Albumin 4.3 g/dL
5 weeks	3 weeks	629	503	1.7	
7 weeks	5 weeks	141	182	0.8	
10 weeks	8 weeks	90	103	0.8	
14 weeks	3 months	88	95	0.6	INR 0.9
~1 year		57	76	0.7	Albumin 4.5 g/dL
Normal Values		**<65**	**<126**	**<1.2**	

LiverTox: Examples

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].

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Nitrofurantoin

Last Update: May 1, 2020.

OVERVIEW

Introduction

Nitrofurantoin is an oral antibiotic widely used either short term to treat acute urinary tract infections or long term as chronic prophylaxis against recurrent infections. **Nitrofurantoin** is one of the most common causes of drug induced liver disease and can cause either an acute or a chronic hepatitis-like syndrome that can be severe and lead to liver failure or cirrhosis.

Background

Structurally, **nitrofurantoin** (nye" troe fure an' toyn) is a nitrated 5-member furan ring with a side chain of hydantoin. **Nitrofurantoin** inhibits several bacterial enzyme systems and has broad antibacterial activity. Its precise mechanism of action is not known. Importantly, antibacterial resistance to **nitrofurantoin** is rare, which makes it an attractive choice for long term treatment. In addition, **nitrofurantoin** is well absorbed orally and is rapidly excreted in the urine so that drug levels in urine are high while serum levels are minimal, which makes it an appropriate agent to treat urinary tract but not systemic infections. **Nitrofurantoin** was first approved for use in the United States in 1953 and is still in wide use with more than 3 million prescriptions filled yearly. Current indications are treatment of acute and prophylaxis against chronic or recurrent urinary tract infections due to susceptible organisms. For treatment of acute infections, the recommended regimen is 50 to 100 mg orally four times daily for one week. For prophylaxis against chronic or recurrent infections, the recommended dose is 50 to 100 mg daily long term. Generic formulations are available (25, 50, and 100 mg); specific commercial names include Macrodantin, Macrobid and Furadantin, among others. Common side effects include nausea, diarrhea, dyspepsia, dizziness, drowsiness and rash. **Nitrofurantoin** has multiple rare, but potentially severe side effects that arise particularly with long term use and include interstitial pneumonitis, peripheral neuropathy, exfoliative dermatitis, hemolytic anemia, lupus-like syndromes and hepatotoxicity.

Hepatotoxicity

Nitrofurantoin is currently one of the most common causes of drug induced liver injury. Liver injury from **nitrofurantoin** can cause either an acute or chronic hepatitis-like syndrome. The acute form is typically associated with a 1 or 2 week course of treatment with **nitrofurantoin** and is rare (~0.3 cases per 100,000 prescriptions). Acute liver injury typically presents within a few weeks of starting **nitrofurantoin** and can arise up to a few weeks after stopping a defined course of treatment. The pattern of liver injury is usually hepatocellular with or without jaundice, and typically is accompanied by symptoms of fever and rash. The acute injury due to **nitrofurantoin** usually resolves rapidly once the medication is stopped, but severe and fatal instances have been reported. In some instances, autoimmune features are present, but these are more common with the chronic presentation of **nitrofurantoin** hepatotoxicity. The course and outcome of acute **nitrofurantoin** hepatotoxicity is variable, severe forms with acute liver failure can occur, and **nitrofurantoin** is regularly listed as one of the major causes of acute liver failure due to medications.

The chronic form of **nitrofurantoin** hepatotoxicity is more common than the acute form and typically presents months to years after initiation of long term prophylactic therapy. The estimated incidence of liver injury from **nitrofurantoin** is approximately 1 per 1500 persons exposed. The presentation is usually insidious and marked initially by fatigue and weakness followed by dark urine and jaundice. The clinical pattern and laboratory features can mimic autoimmune hepatitis with marked elevations in serum ALT levels, increases in gamma globulin levels, and the presence of antinuclear and anti-smooth muscle antibodies. In some instances, the onset is abrupt and resembles acute hepatitis. However, immunoallergic features of fever and rash are less common than with the acute form of **nitrofurantoin** hepatotoxicity. Liver histology typically demonstrates features of chronic hepatitis with inflammation, interface hepatitis, focal or centrilobular bridging necrosis and variable degrees of fibrosis. Cirrhosis as a result of **nitrofurantoin** hepatotoxicity has been reported and, if not recognized as due to the medication, can progress to end stage liver disease. There is a female preponderance and the risk of injury appears to increase with age particularly the chronic forms.

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

Mechanism of Injury

The mechanism of **nitrofurantoin** hepatotoxicity is not well known. Its nitro-reductive metabolism produces injurious oxidative free radicals which can damage hepatocytes. Many cases demonstrate evidence an autoimmune etiology and some studies have shown a linkage with HLA-DR6 and DR2.

LiverTox: Examples

Outcome and Management

The severity of **nitrofurantoin** induced liver injury ranges from mildly symptomatic elevations in serum aminotransferase levels (Cases 1 and 2), hepatitis with jaundice (Case 3) to fulminant liver failure and death (Case 4). Complete recovery is expected after stopping the drug, but recovery may be slow (2 to 6 months). In rare instances, evidence of chronic liver injury persists. Because of the autoimmune features of many cases of **nitrofurantoin** hepatotoxicity, corticosteroids are often used particularly in cases that are severe or slow to resolve. In many instances, corticosteroid therapy appears to lead to improvement. However, the ultimate benefit of immunosuppressive therapy remains to be proven and corticosteroids should be used cautiously and withdrawn as soon as possible, and with careful follow up to document lack of relapse after stopping. Rechallenge leads to recurrence and should be avoided. There does not appear to be cross reactivity to hepatic injury between **nitrofurantoin** and other commonly used antibiotics.

Drug Class: Antiinfective Agents

CASE REPORT

Case 1. Chronic hepatitis with hepatocellular pattern of serum enzyme elevations due to nitrofurantoin.(1)

A 68 year old woman was given **nitrofurantoin** (50 mg daily) for prophylaxis against recurrent urinary tract infections. She continued on therapy for 3 years at which time serum enzymes were found to be elevated. She had no symptoms that could be attributed to liver disease. **Nitrofurantoin** was stopped, but restarted one month later because of recurrence of urinary tract infections. Serum aminotransferase levels remained mildly elevated (2 to 3 times the upper limit of normal). Six months later she had the insidious onset of nausea, fatigue and weakness. Serum aminotransferase levels were still elevated, but alkaline phosphatase and bilirubin values were normal. Anti-smooth muscle antibody was present (1:80), but other autoantibodies were not detected. Tests for hepatitis A, B and C were negative. A liver biopsy showed chronic active hepatitis with moderate to severe inflammatory infiltrates and moderate fibrosis. The symptoms persisted for several months and the medication was discontinued again. Two months after stopping **nitrofurantoin** the patient had returned to her usual state of health and serum aminotransferase levels returned to normal.

Key Points

Medication:	**Nitrofurantoin**, 50 mg daily
Pattern:	Hepatocellular (aminotransferase elevations only)
Severity:	1+ (never jaundiced, never hospitalized)
Latency:	Several years, 6 months after restarting
Recovery:	Complete within 5 months
Other medications:	Sumatriptan, alendronate, clopidogrel, estrogen, verapamil

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Nitrofurantoin started					
1 month		79	62	0.4	
3 months		115			
4 months		88			Nausea, fatigue
5 months		255			Liver biopsy
6 months	0	176	99	0.5	SMA 1:80
Nitrofurantoin stopped					
9 months	3 months	52	101	0.7	
11 months	5 months	30	102	0.7	
Normal Values		**<42**	**<115**	**<1.2**	

Comment

Initially, the liver injury was believed to be caused by chronic hepatitis unrelated to medications. Because of appearance of symptoms and findings on liver biopsy, **nitrofurantoin** was subsequently suspected and discontinued. The resolution of liver test abnormalities and symptoms of fatigue after stopping **nitrofurantoin** supported the diagnosis of drug induced liver disease. While the clinical pattern resembles idiopathic chronic autoimmune hepatitis, the disease generally resolves once the medication is stopped with or without corticosteroid therapy. In any case, long term follow up to document resolution of hepatitis is warranted, particularly if corticosteroids were used initially.

LiverTox: Examples

Case 4. Acute liver failure due to nitrofurantoin.(1)

A 46 year old woman with history of spina bifida and neurogenic bladder was treated with **nitrofurantoin** in a dose of 50 mg per day for recurrent urinary tract infections. Therapy was effective in suppressing infections and she remained on the drug for 3 and a half years, when she was found to have jaundice, followed shortly thereafter by fatigue, nausea and vomiting. She was hospitalized for investigation. Serum aminotransferase and bilirubin levels were markedly elevated. Tests for hepatitis A, B and C were negative. Anti-nuclear and anti-smooth muscle antibody titers were elevated. CT of the abdomen showed no evidence of biliary obstruction or hepatic masses. Because of worsening hepatic failure, she was transferred to a liver transplant center, but she rapidly developed mental obtundation, coma and respiratory failure, followed by intractable cerebral edema and death five days later. Autopsy showed a small, shrunken liver weighing ~600 g.

Key Points

Medication:	**Nitrofurantoin**
Pattern:	Hepatocellular (R=16)
Severity:	5+ (death)
Latency:	3.5 years
Recovery:	None
Other medications:	None

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Comments
Pre	Pre	23	152	0.7	
0		**Nitrofurantoin** started			
3.5 years		Jaundice, fatigue, nausea			
	-2 days	1988	338	28.9	Hospitalized: INR = 4.0
	-1 day	1676	296	27.7	INR = 5.0
	0	**Nitrofurantoin** stopped			
3.5 years	1 day	1525	285	31.5	INR = 6.0
	2 days	1325	260	26.6	INR = 11.0
	3 days	907	150	27.3	Transferred
	4 days	538	134	28	Respiratory failure,
	5 days	491	184	28.4	Cerebral edema, Death
Normal Values		**<42**	**<115**	**<1.2**	

Comment

The clinical pattern indicated an acute hepatitis-like picture, but the timing and gradual onset was more representative of chronic hepatitis with a severe unrelenting course. Nevertheless, autopsy revealed massive hepatic necrosis suggesting an acute process. In hepatocellular forms of drug induced liver disease, jaundice indicates severe injury with a mortality rate that is greater than 10%, a finding stressed by the late Dr. Hyman J. Zimmerman and familiarly known as "Hy's law".

LiverTox: Examples

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].

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Tamoxifen

Last Update: August 20, 2020.

OVERVIEW

Introduction

Tamoxifen is a nonsteroidal antiestrogen that is widely used in the treatment and prevention of breast cancer. Long term **tamoxifen** therapy has been associated with development of fatty liver, steatohepatitis, cirrhosis, and rare instances of clinically apparent acute liver injury.

Background

Tamoxifen (ta mox' i fen) is referred to as a selective estrogen receptor modulator with tissue specific actions, having estrogenic agonist effects on bone, brain and liver, but antagonist activity on breast tissue. **Tamoxifen** may also have other, as yet undefined, anticancer effects. Adjuvant therapy with **tamoxifen** has been shown to prolong survival in women with early stage breast cancer and to decrease the risk of de novo breast cancer as well as recurrence in women at high risk. **Tamoxifen** was approved for use in the United States in 1977 and is still widely used, being considered a first line adjuvant therapy for breast cancer. Current indications include both treatment of breast cancer and reduction of breast cancer risk in women at high risk. **Tamoxifen** is available in 10 and 20 mg tablets generically and under several trade names such as Nolvadex and Tamone. **Tamoxifen** is also available as an oral solution (10 mg/5 mL). The usual dose for treating breast cancer is 20 to 40 mg daily, and for secondary prevention is 20 mg once daily for five years. Common side effects include hot flashes, nausea, diarrhea, amenorrhea, altered menses, weight change and fluid retention. Rare but potentially severe adverse events include stroke, pulmonary embolus and venous thromboses, uterine cancer and other malignancies.

Hepatotoxicity

Tamoxifen has been associated with rare instances of idiosyncratic, clinically apparent liver injury, typically arising within the first six months of treatment and having variable presentations with cholestatic, mixed or hepatocellular pattern of enzyme elevations. Immunoallergic features (fever, rash, eosinophilia) are uncommon, as are autoantibodies. Some instances have been severe with signs of hepatic failure, but most cases are self-limited.

More commonly, long term **tamoxifen** therapy has been linked to the development of fatty liver and steatohepatitis. In some prospective studies, up to one third of women have developed fatty liver during 1 to 3 years of **tamoxifen** therapy, as shown by routine imaging using computerized tomography. Fatty liver usually becomes demonstrable within 1 to 2 years of starting **tamoxifen** but is usually not accompanied by symptoms, although serum aminotransferase levels may be elevated modestly in up to half of patients. Liver biopsy may demonstrate steatohepatitis and a proportion of women develop hepatic fibrosis. Several instances of cirrhosis have been described after therapy with **tamoxifen** for 3 to 5 years. Serum aminotransferase elevations and fatty liver generally improve once **tamoxifen** is stopped, but the improvement may be slow and in rare instances, signs and symptoms of portal hypertension persist. While the frequency of hepatic steatosis during **tamoxifen** therapy is higher in women with higher body weight and body mass index (BMI), the appearance of fatty liver is usually not accompanied by change in body weight and does not relate to alcohol use or receipt of adjuvant chemotherapy. Because steatohepatitis is usually (although not always) accompanied by minor serum aminotransferase elevations, monitoring of serum enzymes during long term **tamoxifen** therapy is often recommended.

In addition, long term **tamoxifen** therapy has also been linked to isolated cases of peliosis hepatis, hepatic cysts and several cases of hepatocellular carcinoma in women with no other risk factors for this tumor. However, in large retrospective analyses, no increase in hepatocellular carcinoma in women taking **tamoxifen** for 5 years has been demonstrated, although these same studies did show an increase in rates of endometrial carcinoma. **Tamoxifen** also been linked to an increased risk of venous thromboses, and instances of portal vein thrombosis with combinations of portal hypertension and esophageal variceal bleeding have been reported.

Finally, **tamoxifen** use has been associated with development of symptomatic porphyria cutanea tarda (PCT), presenting after 1 to 4 years of use with skin fragility, hypertrichosis and reddish urine and accompanied by elevations in urinary porphyrins and mild serum aminotransferase elevations. **Tamoxifen** related cases usually arise without other risk factors for PCT such as iron overload, alcohol abuse or hepatitis C virus infection. Stopping **tamoxifen** is followed by gradual improvement in symptoms, decrease in porphyrin excretion and improvement in liver enzymes.

Likelihood score: B (highly likely but rare cause of clinically apparent liver injury).

Mechanism of Injury

The acute form of liver injury attributed to **tamoxifen** use is probably due to an idiosyncratic reaction to a metabolite of the medication rather than its estrogenic effects. In contrast, the induction of fatty liver and triggering of porphyria cutanea tarda are likely due to estrogenic effects on the liver in the setting of a genetic predisposition to fatty liver disease or porphyria cutanea tarda.

LiverTox: Examples

Outcome and Management

While fatty liver arises in at least one third of women treated with **tamoxifen** for up to 5 years, clinically significant steatohepatitis is less common. Nevertheless, monitoring of serum aminotransferase levels during **tamoxifen** therapy is appropriate. In women with persistent elevations in ALT levels, the relative benefits and risks of continuing **tamoxifen** therapy must be weighed. Factors to help in the decision, include noninvasive tests for hepatic fibrosis (platelet count), imaging of the liver and, in some instances, liver biopsy. Switching to aromatase inhibitors such as anastrozole, letrozole or exemestane is another option. These agents may also cause or exacerbate fatty liver disease, but the risk appears far less than with **tamoxifen**. Other approaches short of stopping **tamoxifen** therapy include nutritional advice and weight loss, abstinence from alcohol, and possibly medical therapies for nonalcoholic steatohepatitis (which are currently investigational and have not been shown to be specifically helpful in **tamoxifen** induced fatty liver). The possible development of serious hepatic fibrosis and portal hypertension can be assessed noninvasively by serial determinations of platelet count, but may require liver biopsy to document.

Drug Class: Antineoplastic Agents, Antiestrogens

CASE REPORTS

Case 1. Clinically apparent, acute liver injury due to tamoxifen.(1)

A 75 year old woman developed nausea, vomiting and mild serum enzyme elevations 10 weeks after starting **tamoxifen** (10 mg twice daily) for metastatic breast cancer. She was treated with prednisolone (5 mg daily) and antiemetics, but continued to be symptomatic and serum enzymes and bilirubin continued to rise (Table). She had no history of liver disease, denied alcohol use and had no risk factors for viral hepatitis. Tests for hepatitis A and B were negative. Ultrasound of the abdomen showed no gallstones or evidence of biliary obstruction. A liver biopsy showed cholestasis and portal inflammation with minimal bile duct changes. All medications were stopped except for prednisolone, and liver test abnormalities began to decrease towards near normal levels. **Tamoxifen** was restarted for 12 days and she was monitored closely. Within 9 days she became symptomatic with nausea and vomiting and serum enzyme levels began to rise, peaking a few days after **tamoxifen** was stopped and then returning again towards normal. Shortly thereafter, she died of cerebral metastases. On autopsy, she had small hepatic metastases, but no evidence of biliary obstruction.

Key Points

Medication:	**Tamoxifen** (20 mg daily)
Pattern:	Mixed (alkaline phosphatase levels were raised, but no values given)
Severity:	3+ (jaundice, hospitalization)
Latency:	10 weeks
Recovery:	2-3 weeks
Other medications:	Prednisolone, antiemetics

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Bilirubin (mg/dL)	Other
0		38	0.7	**Tamoxifen** started
4 weeks		35	0.9	
10 weeks		54	0.9	Symptoms (nausea)
14 weeks	0	735	4.1	Worsening symptoms
15 weeks	1 week	670	5.3	
16 weeks	2 weeks	110	3.5	
19 weeks	5 weeks	54	1.0	Nausea resolved
21 weeks	7 weeks	50	1.4	
Time After restarting	**Time After Stopping**	**Tamoxifen** restarted		
1 week	0	79	1.1	Symptoms (nausea)
2 weeks	1 week	258	1.8	
3 weeks	2 weeks	180	1.3	
5 weeks	4 weeks	64	1.2	
Normal Values		**<45**	**<1.2**	

* Values estimated from Figure.

Comment

The clinical presentation of symptomatic liver injury 10 weeks after starting **tamoxifen** and recurrence of a similar pattern of injury within 2 weeks of restarting provides strong evidence for the role of **tamoxifen** in causing the liver injury. Cases of acute liver injury with jaundice due to **tamoxifen** have been reported, but are rare and represent an idiosyncratic reaction. More common is fatty liver disease which can be associated with significant steatohepatitis and result in cirrhosis. However, steatosis and steatohepatitis rarely cause jaundice and are usually minimally symptomatic and respond slowly to withdrawal of **tamoxifen**. Furthermore, in this patient, ultrasonography and ultimately autopsy did not demonstrate significant steatosis. While tests for hepatitis C and E were not available to exclude those diagnoses, the reappearance of injury on rechallenge makes it likely that **tamoxifen** was the primary cause of symptoms and liver test abnormalities.

LiverTox: Examples

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].

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Paxlovid

Last Update: January 31, 2022.

OVERVIEW

Introduction

Paxlovid is a co-packaged combination of **nirmatrelvir**, a second generation protease inhibitor, and ritonavir, a pharmacological enhancer, that is used to treated infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) , the cause of the novel and severe coronavirus disease, 2019 (COVID-19). Paxlovid is given orally for 5 days in patients early in the course of infection and has not been linked to serum aminotransferase elevations or to clinically apparent liver injury.

Background

Paxlovid consists of second generation protease inhibitor (**nirmatrelvir**) co-packaged with a pharmaceutical enhancer (ritonavir), which is used for oral treatment of recent-onset, mild-to-moderate COVID-19. **Nirmatrelvir** (ner mat" rel vir) is a peptidomimetic inhibitor of the main protease of SARS-CoV-2: M^{pro} and has antiviral activity in vitro against several coronaviruses including SARS-CoV-1 and -2. Ritonavir (ri toe' na vir) is a protease inhibitor and potent inhibitor of the enzyme (CYP 3A4) responsible for the metabolism of **nirmatrelvir**, which allows for higher peak levels and more prolonged half-life of the active antiviral metabolite. In preregistration trials, Paxlovid started within 5 days of symptom onset demonstrated a 89% reduction in subsequent hospitalizations for COVID-19 (1.0% vs 6.7%) and a significant reduction in 28-day mortality (none vs 1.6%). Based upon these results and the ongoing COVID-19 pandemic, Paxlovid was granted Emergency Use Authorization (EUA) in December 2021 as therapy of nonhospitalized patients (adults and children 12 years or older) with documented COVID-19 infection who are at high risk of complications. Paxlovid is available under the EUA as tablets of 150 mg of **nirmatrelvir** co-packaged with 100 mg tablets of ritonavir; the recommended dose being 2 tablets of **nirmatrelvir** and one tablet of ritonavir twice daily for 5 days. Longer term therapy is not recommended, nor is therapy recommended for hospitalized patients or patients who have had symptoms or signs for more than 5 days. Currently, Paxlovid is being actively evaluated for efficacy and safety in treating patients not at high risk for complications, for children, and for patients with known exposure to COVID-19 (post-exposure prophylaxis). Paxlovid appears to be generally well tolerated; mild adverse events may include headache, myalgia, gastrointestinal upset, nausea and diarrhea. The total clinical experience with Paxlovid has been limited and its safety not fully defined.

Hepatotoxicity

In preregistration clinical trials, serum aminotransferase elevations were uncommon and mild, and were no more frequent with Paxlovid than with placebo. Furthermore, among more than 1000 patients treated with Paxlovid (**nirmatrelvir** 300 mg with ritonavir 100 mg twice daily) for 5 days in prelicensure studies, there were no reported episodes of clinically apparent liver injury. Confounding the issue is that serum aminotransferase elevations are common during symptomatic SARS-CoV-2 infection, present in up to 70% of patients and are more frequent in patients with severe disease and in those with the known risk factors for COVID-19 severity such as male sex, older age, higher body mass index and diabetes. Thus, Paxlovid has not been shown to cause liver injury, but the total clinical experience with its use is limited.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The lack of adverse events and hepatic injury from Paxlovid may be due to its relatively short duration of therapy. Paxlovid is metabolized by the cytochrome P450 system (largely CYP 3A4) and is given with a CYP 3A4 inhibitor to prolong its half-life and achieve better plasma concentrations and prolong its half-life. However, as a consequence Paxlovid is likely to have significant drug-drug interactions with agents that are metabolized by the CYP 3A4 enzyme. Whether longer term Paxlovid is also without serious adverse events remains to be seen.

Drug Class: Antiviral Agents

Other Drugs in the Subclass: Molnupiravir

Conclusions

- Over 1,000 medications and herbal products have been implicated in the development of liver injury
- Hundreds of medications are considered high risk of causing liver injury
- Commonly used antibiotics have a high rate of reported liver injury
- The LiverTox website (https://www.ncbi.nlm.nih.gov/books/NBK547852/) is dedicated to providing up-to-date, comprehensive clinical information

Post-Test

TRUE/FALSE

1. AMOXICILLIN/CLAVULANATE (AUGMENTIN) IS THE MOST COMMON ANTIBIOTIC TO CAUSE LIVER INJURY
2. THE PURPOSE OF THE LIVERTOX WEBSITE IS TO PROVIDE CLEAR AND UNBIASED INFORMATION ON DRUG INDUCED LIVER INJURY TO SUPPORT CLINICAL MANAGEMENT OF PATIENTS AND TO STIMULATE INTEREST AND RESEARCH DIRECTED AT THE PREVENTION OR TREATMENT OF THIS IMPORTANT FORM OF LIVER DISEASE
3. CATEGORY X IS EQUIVALENT TO LIKELIHOOD OF FATALITY

Questions?

ADDITIONAL LEARNING OPPORTUNITIES

- HCV Simplified Treatment Training – Available Online until December 2nd https://www.anthc.org/provider-resources/new-provider-webinars/
  - Scroll down to topic titled: **HCV Treatment Training**
- AK ID ECHO: HCV, HIV, PrEP, STIs
  - The 2nd Tuesday of every month from 12:00-1:00PM Alaska Standard Time
    - 1CE/CME offered per session
  - anthc.org/project-echo/hcv-hiv-prep-stis-echo
- LiverConnect Webinar Program
  - Second Tuesday of every month 8:00-9:00AM Alaska Standard Time
    - Full Hour didactic topics on Liver Disease and related topics 1CE/CME offered
  - anthc.org/what-we-do/clinical-and-research-services/hep/liverconnect/

AK LIVER DISEASE ECHO -TEAM CONTACTS

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Thank you

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