DRUG INDUCED LIVER INJURY

Alaska Liver Disease ECHO

August 19, 2021

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- I have no conflict of interest to disclose

OBJECTIVES

- Epidemiology
- Associated Drugs
- Mechanism
- Classification
- Clinical Manifestations
- Diagnosis
- Management
- Prognosis
- Prevention

PRE-TEST

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.

BACKGROUND

- Occurrence of Drug-induced Liver Injury (DILI)
  - 10 to15 out of 10,000 to100,000 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

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- 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

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ADDITIONAL EPIDEMIOLOGY

- 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

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ASSOCIATED DRUGS

- 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

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Lisi DM. Drug Induced Liver Injury: An Overview. *Gastroenterology*. 2016; 41(12): 30-34.

ASSOCIATED DRUGS

Intrinsic	Idiosyncratic	
Acetaminophen	Allopurinol	Lapatinib
Amiodarone§	Amiodarone§	Methyldopa
Anabolic steroids	Amoxicillin-clavulanate	Minocycline
Antimetabolites	Bosentan	Nitrofurantoin
Cholesyramine**	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	

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

Raúl J. Andrade, Guruprasad P. Aithal, Einar S. Björnsson, Neil Kaplowitz, Gerd A. Kullak-Ublick, Dominique Larrey, Tom H. Karlsen, EASL Clinical Practice Guidelines: Drug-induced liver injury. Journal of Hepatology. 70(6) 222-1261. https://doi.org/10.1016/j.jhep.2019.02.014.

DRUGS BY ONSET TIME

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

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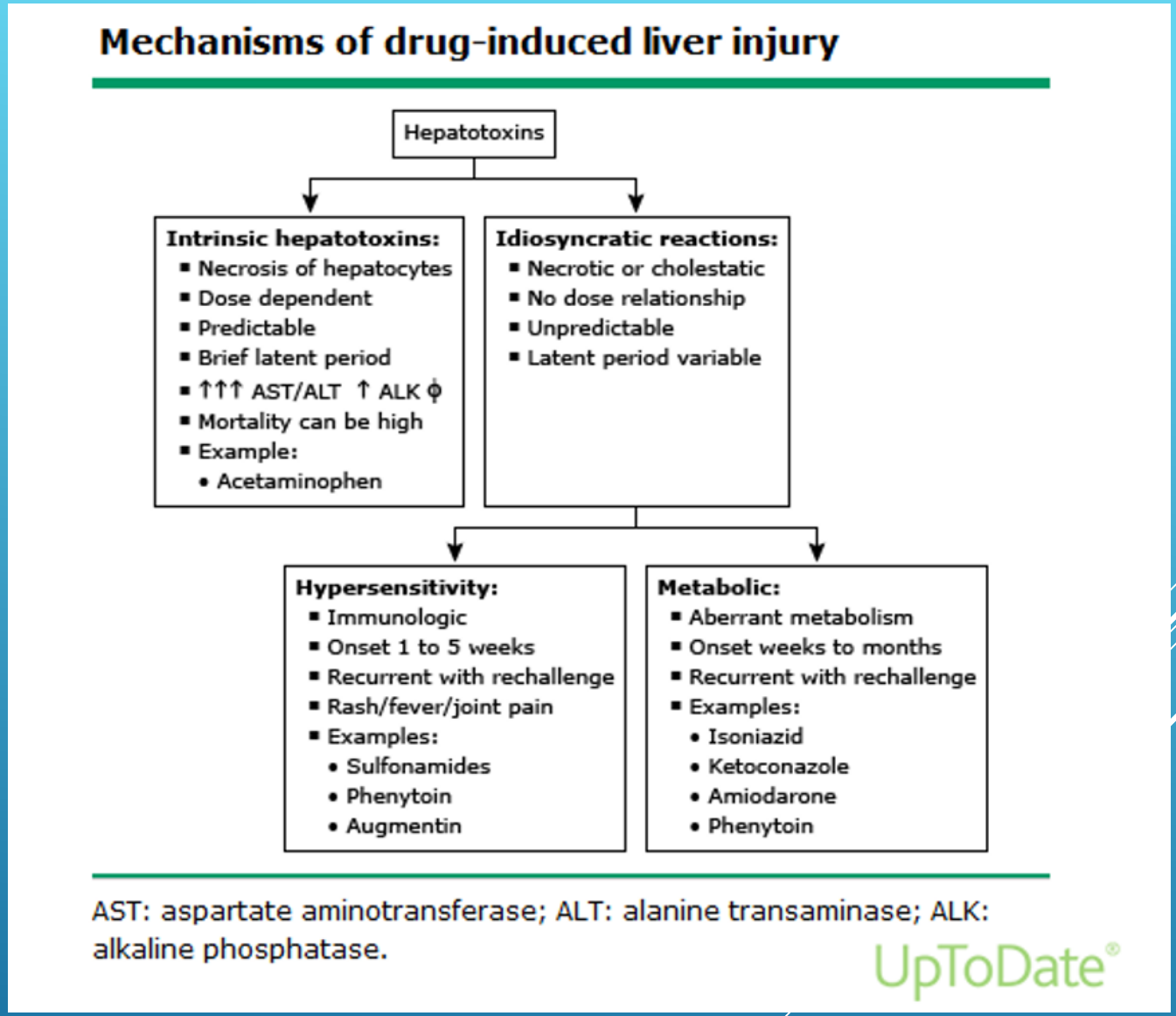
MECHANISM

- Parent drug
- Metabolites
- Host immune system



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MECHANISM

- Direct hepatotoxicity
- Acute hepatitis
- Nodular regenerative hyperplasia
- Sinusoidal obstructive syndrome (SOS)
- Idiosyncratic hepatotoxicity

- Nonimmune
- Immune-mediated
- Drug-inducted autoimmune-like hepatitis (DI-AIH)
- Indirect hepatotoxicity

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CLASSIFICATION

Clinical presentation	Hepatotoxicity Mechanism	Histological Findings

• Hepatocellular (cytotoxic) injury
  • Cholestatic injury
  • Mixed injury
	• Predictable
	• Idiosyncratic
		• Hepatitis
		• Cholestasis
		• Steatostasis

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R-VALUES

- 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

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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

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CLINICAL CONFOUNDERS

- 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)

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CLINICAL MANIFESTATIONS

- 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.)

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DIAGNOSIS

- 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

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MANAGEMENT

- 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

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- 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

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PROGNOSIS FOR ACUTE CHOLESTATIC INJURY

- 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

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PROGNOSIS FOR CHRONIC 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

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PREVENTION

- 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)

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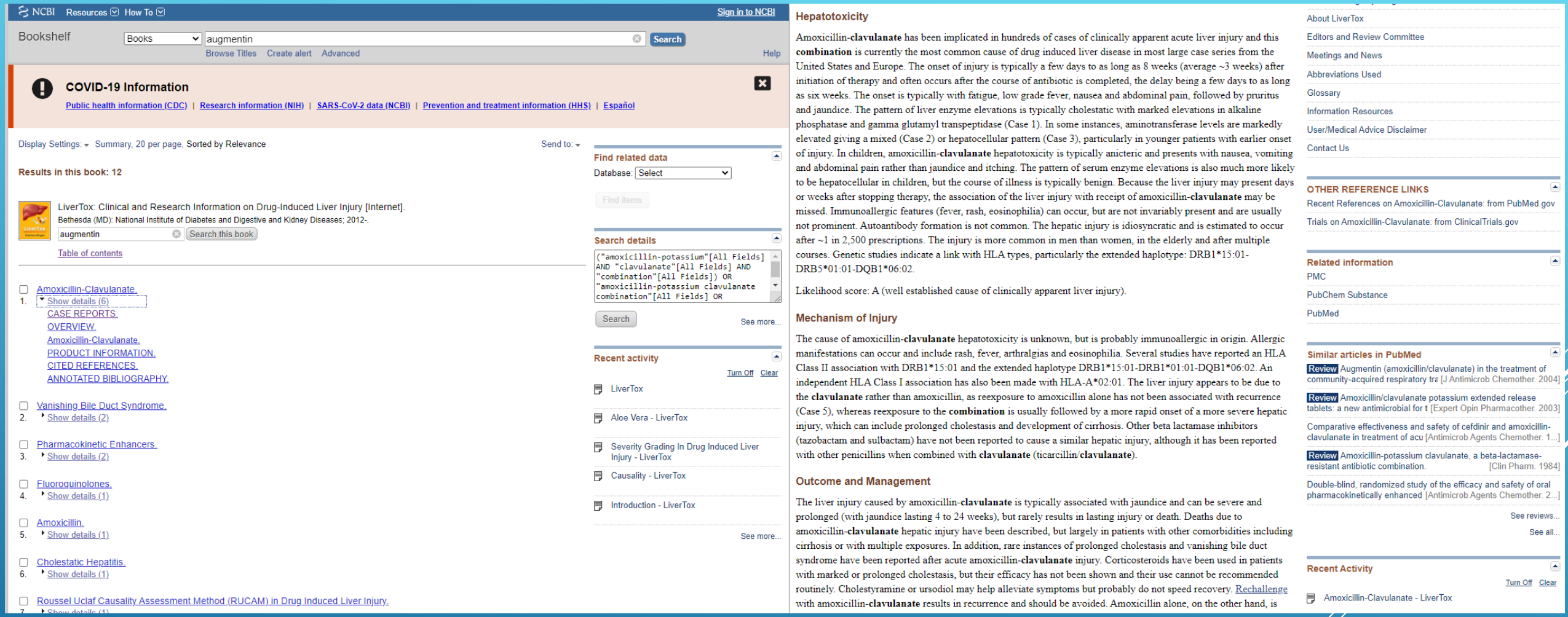
CLINICAL RESOURCES

- 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

Lisi DM. Drug Induced Liver Injury: An Overview. *Gastroenterology*. 2016; 41(12): 30-34.



CLINICAL RESOURCES

LiverTox. https://www.ncbi.nlm.nih.gov/books/NBK547852/. Updated July 29, 2021. Accessed July 30, 2021.

POST-TEST

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.

CONCLUSIONS

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