DRUG INDUCED LIVER INJURY

Alaska Liver Disease ECHO
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I have no conflict of interest to disclose
OBJECTIVES

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

- Diagnosis
- Management
- Prognosis
- Prevention
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.
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
**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
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
Acetaminophen most common medication cause
Antibiotics and antiepileptic drugs >60% DILI in US
Illicit drugs can cause acute liver failure (methyleneoxymethamphetamine)
Most drugs cause DILI within 6 months of onset
<table>
<thead>
<tr>
<th>Intrinsic</th>
<th>Idiosyncratic</th>
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</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Amiodarone§</td>
<td>Amiodarone§</td>
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<tr>
<td>Anabolic steroids</td>
<td>Amoxicillin-clavulanate</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Bosentan</td>
</tr>
<tr>
<td>Cholesyramine**</td>
<td>Dantrolene</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Diclofenac</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Disulfiram</td>
</tr>
<tr>
<td>HAART drugs</td>
<td>Felbamate</td>
</tr>
<tr>
<td>Heparins**</td>
<td>Fenofibrate</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Flucloxacillin</td>
</tr>
<tr>
<td>Statins§</td>
<td>Flutamide</td>
</tr>
<tr>
<td>Tacrine**</td>
<td>Halothane</td>
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<tr>
<td>Isoniazid</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Ketocapazole</td>
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<tr>
<td>Leflunomide</td>
<td>Leflunomide</td>
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<tr>
<td>Lisinopril</td>
<td>Lisinopril</td>
</tr>
<tr>
<td></td>
<td>**Mild ALT elevations without jaundice</td>
</tr>
<tr>
<td></td>
<td>§Both intrinsic and idiosyncratic</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Antimicrobials: Short-moderate onset</strong></th>
<th><strong>Antimicrobials: Moderate-long onset</strong></th>
<th><strong>Antiepileptics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>Isoniazid</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Minocycline</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Nitrofurantoin (rarely)</td>
<td>Nitrofurantoin</td>
<td>Phenytoin (short onset)</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td></td>
<td>Valproate</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Miscellaneous: Short-moderate onset</strong></th>
<th><strong>Miscellaneous: Moderate – long</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>Amiodarone (oral)</td>
</tr>
<tr>
<td>Immune-checkpoint inhibitors (&lt;12 weeks)</td>
<td>Analgesics (NSAIDs and diclofenac)</td>
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<tr>
<td>Inhaled anesthetics</td>
<td>Androgen-containing steroids</td>
</tr>
<tr>
<td>Proton Pump Inhibitors (rare)</td>
<td>Methotrexate</td>
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<td>Sulfasalazine</td>
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**DRUGS BY ONSET TIME**
MECHANISM

- Parent drug
- Metabolites
- Host immune system

MECHANISM

- 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
### Clinical presentation
- Hepatocellular (cytotoxic) injury
- Cholestatic injury
- Mixed injury

### Hepatotoxicity Mechanism
- Predictable
- Idiosyncratic

### Histological Findings
- Hepatitis
- Cholestasis
- Steatostasis

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
CLINICAL PRESENTATION

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


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)
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
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
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
PROGNOSIS FOR ACUTE HEPATOCellular LIVER INJURY

- 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

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)
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
True or False:

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CONCLUSIONS

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