Drug-Induced Liver Injury
Common Offenders & Emerging Threats

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Disclosures

- I have no conflicts of interest related to this presentation
- Non-FDA approved herbal supplement products will be discussed
Objectives

- Describe types of drug induced liver injury (DILI)
- Review mechanisms of DILI
- Identify important causes and prognostic factors for DILI
- Discuss emerging causes of DILI
Drug Induced Liver Injury (DILI)

• Liver injury caused by:
  • Prescription medications
  • Non-prescription medications
  • Illicit ‘recreational’ drugs
  • Environmental toxins
  • Vitamins
  • Herbal supplements
  • Hormones

• DILI may be:
  • Predictable
  • Unpredictable (idiosyncratic)
DILI - Epidemiology

• More than 900 drugs, toxins & herbs have been reported to cause liver injury

• Occurs 1 in 10,000 to 100,000 persons

• Acute DILI reported in 5-10% of patients hospitalized for jaundice

• In U.S. ~2,000 cases of acute liver failure (ALF) per year
  • Acetaminophen ~39%
  • Other (idiosyncratic) ~13%

• ALF due to idiosyncratic DILI -- high mortality (60-80%) without liver transplantation

• DILI is a common reason for:
  • Failure of new drugs to obtain regulatory approval
  • Withdrawal of an approved drug
## DILI - Examples of Lessons Learned

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>FDA approval</th>
<th>FDA withdrawal</th>
<th>Reason for Withdrawal / Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemoline</td>
<td>ADHD</td>
<td>1975</td>
<td>October, 2010</td>
<td>13 cases liver failure requiring liver transplant or death</td>
</tr>
<tr>
<td>Tienilic acid Selacryn®</td>
<td>Diuretic Hypertension</td>
<td>May 2, 1979</td>
<td>1982</td>
<td>&gt; 500 cases severe liver/kidney damage 36 deaths</td>
</tr>
<tr>
<td>Troglitazone Rezulin®</td>
<td>Diabetes</td>
<td>Jan 29, 1997</td>
<td>March 21, 2000</td>
<td>&gt; 90 cases ALF (63 deaths)</td>
</tr>
<tr>
<td>Bromfenac Duract®</td>
<td>NSAID/Pain</td>
<td>July 15, 1997</td>
<td>June 22, 1998</td>
<td>12 severe liver damage, 4 deaths, 8 liver transplant</td>
</tr>
<tr>
<td>Trovafloxacin Trovan®</td>
<td>Antibiotic</td>
<td>December 18, 1997</td>
<td>June 16, 2006</td>
<td>&gt; 100 cases liver toxicity (14 cases ALF, 4 liver transplant)</td>
</tr>
<tr>
<td>Gemtuzumab Mylotarg®</td>
<td>AML</td>
<td>May, 2000</td>
<td>June 21, 2010</td>
<td>⚠️ risk death / veno-occlusive disease</td>
</tr>
</tbody>
</table>
Prevention of DILI - Lessons Applied

- Ximelagatran [Exanta®]
- Oral thrombin inhibitor
- Clinical trials
  - ALT > 3x ULN 6-13%
  - Majority reversible, but 3 deaths (2 hemorrhage, 1 HBV)
- **Not approved**

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Exanta (n=6948)</th>
<th>Comparator (n=6230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt; 3x ULN</td>
<td>7.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td>AST &gt; 3x ULN</td>
<td>5.1%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Tbili &gt; 3x ULN</td>
<td>1.2%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>
Pathogenesis of DILI

• **Idiosyncratic injury:**
  • Mechanisms not well understood for many drugs
  • Hypersensitivity reaction (?)

• **Predictable injury:**
  • Often involves formation of toxic, reactive intermediate
  • Liver, major organ for metabolism, is particularly susceptible

• **Metabolism:**
  • Phase I - mainly oxidation (CYP 450)
  • Phase II - mainly conjugation \(\Rightarrow\) more hydrophilic products
    - glutathione (GSH), sulfate, glucuronide
Drug Metabolism & Hepatic Injury

Phase I

Drug → CYP enzymes → Active metabolite

NADPH  NADP+

Phase II

Transферases → Conjugated drug

Glucuronide
Sulfate
Glutathione
Methyl

Hepatic injury
Predictable DILI – Acetaminophen (APAP)

- Most common cause of DILI in the U.S.
- Nearly half of APAP-associated overdose cases are unintentional
- Numerous OTC & Rx products contain APAP
- Short latency, dose-dependent toxicity

**Risk Factors:**
- Chronic alcohol use
- Malnutrition
- Concurrent use of drugs that induce CYP450 metabolism
- Polypharmacy (taking multiple APAP-containing products)

- Jan, 2011: FDA recommends drug manufacturers limit amount of APAP to 325mg/dosage unit by Jan, 2014
Predictable DILI: APAP Metabolism (Adults)

- 90% conjugated via glucuronidation (60%), sulfation (30%)
- 4% oxidized (CYP 2E1)

\[ \text{APAP} \rightarrow \downarrow \text{CYP 2E1} \rightarrow \text{NAPQI} \] (toxic intermediate)

\[ \text{NAPQI} \rightarrow \text{Glutathione} \rightarrow \text{Nontoxic cysteine & sulfate conjugates (excreted urine)} \]

\[ \text{Hepatocellular death} \]
\[ \text{Centrilobular necrosis} \]

APAP=acetaminophen, NAPQI=\(N\)-acetyl-p-benzoquinoneimine
Schilling A, Corey et al. CCJM 2010; 77(1): 19-27
Predictable Toxicity - Niacin Metabolism

NUA=nicotinuric acid, NAM=nicotinamide, 6HN=6-hydroxynicotinamide, MNA=N-methylnicotinamide, NNO=nicotinamide-N-oxide, NAD=nicotinamide adenine dinucleotide, 2PY, 4PY=pyridone metabolites AJHP 2003; 60: 995-1005. AJHP 2003; 60:Suppl 2: S9-S14.
Predictable Toxicity - Niacin Metabolism

Idiosyncratic DILI

- Unpredictable
- Longer, variable latency
- Less common cause of ALF vs Predictable DILI
- Higher risk of mortality
  - 60-80% mortality without transplantation in patients who develop ALF due to idiosyncratic DILI
- Possible risk factors:
  - Age (drug-specific)
  - Genetic
  - Environmental
  - Gender (female > male)
  - Drug dose
  - Other comorbidities
Idiosyncratic DILI - Clinical Manifestations

• Highly variable
  • Asymptomatic liver test abnormalities to fulminant hepatic failure

• Can mimic all forms of acute and chronic liver disease

• Typically occurs during 1st 6 months of treatment, but some drugs may have longer latency period

• Certain medications have ‘signature’ presentation, but clinical manifestation may still vary
Patterns of Liver Toxicity

Ratio (R) = \( \frac{\text{ALT level} \div \text{ULN}}{\text{ALP level} \div \text{ULN}} \)

- \( R \geq 5 \)  
  - Hepatocellular

- \( R > 2 \text{ but } < 5 \)  
  - Mixed

- \( R \leq 2 \)  
  - Cholestatic

**ALT** = alanine aminotransferase, **ULN** = upper limit of normal, **ALP** = alkaline phosphatase
### ‘Selected’ Drugs Associated with Acute Toxicity According to Pattern of Injury

<table>
<thead>
<tr>
<th>Hepatocellular</th>
<th>Cholestatic</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>Paroxetine</td>
<td>Amitryptilline</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Pyrazinamide</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Rifampin</td>
<td>Captopril</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Risperidone</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Clopidogrel</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Sertraline</td>
<td>Cyproheptadine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Statins</td>
<td>Enalapril</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Tetracycline</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Trazodone</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Amiodarone</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Losartan</td>
<td></td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Valproic acid</td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfonamides</td>
</tr>
</tbody>
</table>

Reference:
### ‘Selected’ Drugs Associated with Chronic Toxicity According to Pattern of Injury

<table>
<thead>
<tr>
<th>Type of Liver Injury</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>Amiodarone, tamoxifen, Valproate, NRTs</td>
</tr>
<tr>
<td>Microvesicular steatosis (pediatric)</td>
<td>Valproic acid, NRTIs, Tetracycline, ASA</td>
</tr>
<tr>
<td>Sinusoidal obstruction</td>
<td>Busulfan, cyclophosphamide</td>
</tr>
<tr>
<td>Granulomatous</td>
<td>Amiodarone, allopurinol, phenytoin</td>
</tr>
<tr>
<td>Hepatic fibrosis</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Hepatic adenoma</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>AIH</td>
<td>Minocycline, nitrofurantoin, anti-TNF</td>
</tr>
</tbody>
</table>

DILI - Diagnosis

- **Diagnosis of exclusion** - Rule out other possible causes of DILI
- Based primarily on:
  - Detailed history - accurate record of medication/supplement exposure & onset of symptoms
  - Laboratory tests
  - Hepatobiliary imaging and/or biopsy (if applicable)
- Scoring system (RUCAM) may be helpful as adjunct diagnostic tool
- Categorize type of liver injury pattern (R value)
- Estimate mortality risk (Hy’s law)
- Liver biopsy is not mandated, but may be helpful in selected cases
DILI Prognosis & ‘Hy’s Law’

Severe hepatocellular damage (ALT > 3x ULN) + Clinical jaundice (Total bilirubin > 2x ULN with normal alkaline phosphatase) \[ \downarrow \]

≥ 10% mortality (range 10-50%)

*Note: after excluding other potential causes of liver injury

Drug Induced Liver Injury

**Emerging Threats.....**
A case of severe liver injury…

• 52 yr female referred to Hepatology Clinic for evaluation of jaundice & elevated liver enzymes

• 2-3 wks prior to visit - routine labs revealed abnormal liver tests

• PMH: unremarkable, no history of alcohol abuse

• Tbili 10.1, AST 723, ALT 568, INR 2.03 (MELD 23)

• Medication/supplements:
  • \textit{Garcinia cambogia} (1 month - recently discontinued)
  • Topical cream (Bi estrogen/progesterone/DHEA) (1+ yrs)
  • Melatonin (1+ yrs)
  • Dicyclomine as needed (1+ yrs)
  • Topical antifungal nail oil (\textit{Dancing willow herbs})(1+ yrs)
A case of severe liver injury...

- Admitted to hospital due to worsening liver tests, coagulopathy
- Extensive testing performed for other possible causes of liver disease - all negative
- Liver biopsy: (prior to referral)
  - “Severe acute hepatitis with confluent necrosis and massive parenchymal collapse, very few viable hepatocytes remain”
- Despite supportive management, patient continued to deteriorate w/ worsening coagulopathy (INR 7.1), hepatic encephalopathy, rising Tbili (19.7), labile BP, and hypoglycemia despite supplemental dextrose
- Transferred to ICU ⇒ listed for liver transplantation (status I)
- Received OLT ⇒ unremarkable postop course, d/c on POD 7
Herbal Supplements

- Used by millions Americans (~$15-30 billion annually)
- Majority (60-70%) do not disclose supplement use to healthcare providers
- False assumption that ‘natural’ means ‘safe’
- Herbal supplements can interact with prescription drugs & may also cause renal, cardiac, or hepatic toxicity
- Misleading advertising & false claims by some manufacturers
- Many consumers are unaware of hidden dangers that may be associated with herbal supplement use
<table>
<thead>
<tr>
<th></th>
<th>Rx Drugs</th>
<th>Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proof of Safety</strong></td>
<td>Required</td>
<td>Not Required*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Unless it contains a “new dietary ingredient”</td>
</tr>
<tr>
<td><strong>Proof of Effectiveness</strong></td>
<td>Required</td>
<td>Not Required</td>
</tr>
<tr>
<td><strong>Post-marketing surveillance</strong></td>
<td>Required</td>
<td>Not Required*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*As of 2007 - must report serious adverse effects to FDA</td>
</tr>
<tr>
<td><strong>Good Manufacturing Practices</strong></td>
<td>Required</td>
<td>Not Required until Recently*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*GMPs implemented 2007-2010</td>
</tr>
<tr>
<td><strong>Disease Treatment Claims</strong></td>
<td>Allowed (FDA approved indications)</td>
<td>Not Allowed</td>
</tr>
</tbody>
</table>

*new dietary ingredient* = ingredient that did not exist prior to 1994; this is difficult to prove because there is no authoritative list of dietary ingredients that were available before 1994. GMP = Good manufacturing practices
Liverite Liver Aid with Milk thistle contains all the ingredients of Liverite Liver Aid as well as 175mg Milk Thistle Extract standardized to 80% Silymarin 140 mg per dose (2 capsules).
Liverite Liver Aid with Milk thistle contains all the ingredients of Liverite Liver Aid as well as 175mg Milk Thistle Extract standardized to 80% Silymarin 140 mg per dose (2 capsules).

**You may not experience this result. There is no evidence that this product reduces hepatitis viral levels or prevents you from transmitting this disease to others.**
Acute Liver Failure Induced by Green Tea Extracts: Case Report and Review of the Literature

- Green tea extract supplements
- Marketed for weight loss & some types of cancer

**Case report:**
- 44 yr previously healthy female
- Working as community pharmacist
- Using green tea extract for weight loss
- Developed acute liver failure requiring transplantation
- No other causes for liver failure were identified

Liver Transpl 2006; 12: 1892-95
Fulminant Hepatic Failure Due to Herbal Supplements

Jan 2001 - Oct 2002
20 cases; 50% were taking potentially hepatotoxic herbs or supplements

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y/Sex</th>
<th>Agent</th>
<th>Duration of Use</th>
<th>Cofactor</th>
<th>Hepatic Histological Analysis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>25/F</td>
<td>1 year</td>
<td>None</td>
<td>Massive necrosis</td>
<td></td>
<td>Death (herniation)</td>
<td></td>
</tr>
<tr>
<td>42/M</td>
<td>Several months</td>
<td>None</td>
<td>Submassive necrosis, inflammatory infiltrate</td>
<td></td>
<td>Recovery</td>
<td></td>
</tr>
<tr>
<td>54/F</td>
<td>3 weeks</td>
<td>None</td>
<td>Bridging necrosis, lymphocyte mediated</td>
<td></td>
<td>OLT; survival</td>
<td></td>
</tr>
<tr>
<td>23/F</td>
<td>Several days</td>
<td>None</td>
<td>Subtotal necrosis, noninflammatory, c/w toxin</td>
<td></td>
<td>Death (subarachnoid hemorrhage)</td>
<td></td>
</tr>
<tr>
<td>30/F</td>
<td>Unknown</td>
<td>None</td>
<td>Massive necrosis</td>
<td></td>
<td>OLT; survival</td>
<td></td>
</tr>
<tr>
<td>56/M</td>
<td>15 years</td>
<td>None</td>
<td>Patchy necrosis, mild lymphoid infiltrate</td>
<td></td>
<td>Death (multiorgan failure)</td>
<td></td>
</tr>
<tr>
<td>40/F</td>
<td>Weeks</td>
<td>None</td>
<td>Massive necrosis, lymphocytic infiltrate</td>
<td></td>
<td>OLT; death (herniation)</td>
<td></td>
</tr>
<tr>
<td>51/M</td>
<td>Unknown</td>
<td>Chronic HBV</td>
<td>Marked necrosis, chronic HBV</td>
<td></td>
<td>OLT; survival</td>
<td></td>
</tr>
<tr>
<td>21/M</td>
<td>Several months</td>
<td>Disulfiram</td>
<td>Massive necrosis, c/w toxic or metabolic injury</td>
<td></td>
<td>OLT; death (herniation)</td>
<td></td>
</tr>
<tr>
<td>54/M</td>
<td>Unknown</td>
<td>Acute HBV</td>
<td>Subtotal necrosis</td>
<td></td>
<td>OLT; survival</td>
<td></td>
</tr>
</tbody>
</table>

Arch Surg 2003; 138: 852-58
DILI - OxyElite Pro®

- Dietary/Herbal supplement promoted for weight loss and body-building
- Contained unapproved ‘new dietary ingredient’ (aegeline)
- April to October 2013
- 97 identified cases of liver toxicity
- 47 hospitalized, 3 liver transplant, 1 death
- Oct 11, 2013: FDA/CDC issued warning to USP Labs, LLC
- November 9, 2013: USP Labs, LLC recalled OxyElite products
**‘Selected’ Hepatotoxic Herbal Supplements**

- Astractylis gummifera
- Bajiaolian
- Chaparral leaf
- Chinese herbal medicine
- Comfrey
- Dai-saiko-to (or Sho-saiko-to)
- Germander
- Glycyrrhizin
- Greater celandine
- Jin Buh Huan
- Saw palmetto
- Kombucha ‘mushroom’
- Ma-huang (ephedrine)
- Noni juice
- Tu-San-chi’
- Yerbe maté
- Margosa oil
- Mistletoe
- Valerian
- Skullcap
- Senna
- Oil of cloves
- Pennyroyal oil
- Kava
- Sassafras
- Venencapsan
- callilepsis laureola
- Green tea extract
- Crotolaria
- Gordolobotea
- Heliotropium
- Paenoia spp.
- Camphor
- Carp capsules
- Cascara sagrada
- Garcinia Cambogia
- Shoi-win-pian
- Lipokinetix (usnic acid)
- Hydroxycut
- Aloe vera
- Black Cohosh
- Artemisinin

Management of DILI

• **Discontinue offending agent**

• If etiologic agent is not clear, discontinue all ‘non-essential’ medications & supplements

• Supportive Care, close laboratory monitoring

• Early referral to Transplant Center for patients with severe ALF

• Ursodeoxycholic acid: efficacy not established

• N-acetylcysteine:
  • Proven efficacy for APAP overdose
  • May also be beneficial (↓ mortality) in patients with non-APAP ALF

• Corticosteroid- may be helpful if drug-induced AIH
Summary

• DILI is an important cause of morbidity and mortality in the U.S.

• Healthcare providers must be vigilant in identifying drug-related liver injury

• A detailed medical history including all medications and all herbal/dietary supplements is essential

• Early detection can decrease the severity of hepatotoxicity if the offending agent is discontinued
Key principle: Risk - Benefit Assessment

“Judgement regarding the usefulness of a drug that is known to lead to hepatic injury requires comparison of the magnitude of the hepatotoxic risk with that of the therapeutic benefit.”

-- Hyman Zimmerman (1917-1999)

DILI Resources

- FDA: [http://www.FDA.gov](http://www.FDA.gov)
- Acute Liver Failure Study Group (ALFSG)
- American College of Gastroenterology Clinical Guideline: The Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury - 2014
- *Natural Medicines* (requires subscription)
- National Center for Complementary and Alternative Medicine (NCCAM)
- Medwatch: [http://www.fda.gov/safety/medwatch](http://www.fda.gov/safety/medwatch)