Drug-Induced Cholestasis

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Drug-Induced Liver Injury (DILI) : A History

Toxins and Poisons of the Ancient World

• 1774 Bang: Arsenic hepatotoxicity
• 1849 Chloroform-induced hepatic necrosis
• 1888 Phosphorus and arsenic: liver/kidney necrosis
• 1923 1st Idiosyncratic drug reaction - cinchophen for gout
• 1940 Arsphenamine-induced cholestasis*
• 1940s Hepatitis-like drug reactions, e.g. aminothiazole
• 1940s-1970s isolated case reports and small series

* Yellow denotes cholestasis
Hy Zimmerman (1914-1999)

“Hepatoxicity - The Adverse Effects of Drugs and Other Chemicals on the Liver” 1st Edition 1978

- intrinsic vs idiosyncratic hepatoxicity
- prediction of fatal outcome of DILI, or “Hy’s Law”
  - ALT 3x + bili >3  ➔ 10% fatality
- hepatitic vs cholestatic reactions
- cholestasis: hepatocellular, hepatocanalicular, ductular

What Does Cholestasis Mean?

Like the blind men feeling the elephant
— it depends on your perspective
Cholestasis Literally is “Bile Stagnation”

• To physiologists
  – cholestasis means reduced secretion of bile by hepatocytes
  – abnormalities in the cellular and molecular mechanisms of bile formation that cause and/or result from cholestasis

• To Pathologists
  – cholestasis means some combination of: bilirubin retention in hepatocytes and/or canaliculi and/or bile ductules; canicular dilatation and loss of microvilli; bile duct injury (lymphocytic or neutrophilic) and proliferation; ductopenia; hepatocyte ballooning, and pseudoxanthomatous change (“cholate stasis”)

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- To Clinicians
  - cholestasis means reduced biliary excretion and retention of bile solutes

Clinical Manifestations of Cholestasis

- Reduced excretion of bile solutes into bile and the intestine
  - pale stools, diarrhea, steatorrhea
    → deficiency of Vitamin K due to fat malabsorption
Clinical Manifestations of Cholestasis

• Reduced excretion of bile solutes into bile and the intestine
  — pale stools, diarrhea, steatorrhea
  → deficiency of Vitamin K due to fat malabsorption

• Retention of bile solutes
  — jaundice, dark urine, itching and excoriations (prurigo nodularis), xanthomas and xanthelasmas
  — elevated serum bilirubin, elevated alkaline phosphatase and GGT, hypercholesterolemia, bilirubinuria (choluria), prolonged prothrombin time (↑INR) that responds to parenteral, not oral, vitamin K
  — Elevated alkaline phosphatase and cholesterol result from increased synthesis, leakage and “reflux”

Should We call it Jaundice or Icterus, or Just Plain Yellow?

lemon yellow
hemolysis

orange yellow
hepatitis

green yellow
Cholestasis – melanin deposition in skin
“Butterfly” Sign of Chronic Pruritus due to Cholestasis

...where the scratching fingers cannot reach.

Melanin deposition in traumatized areas

Prurigo Nodularis
Chronic Cholestasis - Xanthelasmas

Addison and Gull: Guys Hospital Reports 1851

Chronic Cholestasis - Xanthomas

Addison and Gull: Guys Hospital Reports 1851
Patterns of Drug-Induced Liver Injury - I

- Drug-induced injury mimics other liver diseases
  - acute hepatitis, cholestasis, cholangitis, ductopenia, chronic hepatitis, autoimmune hepatitis, fatty liver diseases, liver tumors
  - histology may be helpful if it shows a characteristic pattern or an unusual coincidence of features e.g. microvesicular steatosis and eosinophilia or steatohepatitis and cholestasis.
- Many drugs give similar patterns and some drugs may have several patterns. Histology is useful but not pathognomonic
- Predictable reactions are dose related and quick.
- Unpredictable reactions have latency (days to months) and occasionally a re-exposure history – idiosyncratic or immuno-allergic (hypersensitivity)
- Occasionally signature clinical syndromes
  - phenytoin: desquamating rash, eosinophilia
Patterns of Drug-Induced Liver Injury - II

Cell Types Affected

<table>
<thead>
<tr>
<th>Hepatocytes</th>
<th>Cholangiocytes</th>
<th>Endothelial Cells</th>
<th>Stellate Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute hepatitis</td>
<td>acute cholangitis</td>
<td>Sinusoid Obstruction</td>
<td>sinusoidal fibrosis</td>
</tr>
<tr>
<td>chronic hepatitis cholestasis</td>
<td>chronic cholangitis</td>
<td>Syndrome (SOS)</td>
<td>fibrosis</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>(sclerosing cholangitis) ductopenia</td>
<td>[Veno-Occlusive Disease (VOD)]</td>
<td>steatosis</td>
</tr>
<tr>
<td>phospholipidosis</td>
<td>cholangiocarcinoma</td>
<td></td>
<td>cirrhosis</td>
</tr>
<tr>
<td>granulomatous hepatitis cirrhosis</td>
<td></td>
<td></td>
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<tr>
<td>adenoma and hepatocellular carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Also can undergo benign and malignant tumor transformation

Several Forms of Cholestatic Injury

1. ACUTE: Anabolic Steroid
2. CHRONIC: Amoxicillin-Clavulinate
3. MIXED HEPATOCELLULAR-CHOLESTATIC: Duloxetine (Cymbalta™)

From Kleiner DE et al. Hepatology 2013 (in press)

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Other Forms of Drug-Induced Liver Injury

1. COAGULATIVE NECROSIS:
   Duloxetine (Cymbalta™)

2. MICROVESICULAR STEATOSIS:
   Erythromycin

3. DUCTULAR REACTION, CHOLANGIOLAR CHOLESTASIS & NEUTROPHILIC INFILTRATE:
   Duloxetine (Cymbalta™)

4. GRANULOMATOUS AND EOSINOPHILIC INFLAMMATION:
   Atenolol

From Kleiner DE et al. Hepatology 2013 (in press)

Patterns of Drug-Induced Liver Injury - III

Biochemical Classification

Defined by Serum ALT and Alkaline Phosphatase (ALKP)

- not by bilirubin

\[ R = \frac{\text{Ratio of } [\text{ALT}/\text{ULN}^*]}{\text{divided by } [\text{ALKP}/\text{ULN}]} \]

- **Hepatocellular**
  - \( R > 5 \)
  - or ALT \( \geq 3 \times \text{ULN} \)

- **Cholestatic**
  - \( R < 2 \)
  - or ALKP \( \geq 2 \times \text{ULN} \)

- **Mixed**
  - \( R \) is 2-5
  - or ALT \( \geq 3 \times \text{ULN} \) and ALKP \( \geq 2 \times \text{ULN} \)

*ULN = Upper Limit of Normal
Liver Biopsy Diagnoses vs Biochemical Categories (R) in DILI

Biochemical Diagnoses:
- Hepatocellular
- Mixed
- Cholestatic

Patterns of Liver Injury III: Examples
- Hepatocellular (ALT) acute INH; chronic trazodone estrogens, anabolic steroids
- Bland cholestasis clodipogrel, amox-clavulenic acid
- Cholestatic (ALP + bili) trimeth-sulphamethoxazole
- Mixed (ALT + ALP) halothane, phenytoin
- Immunoallergic quinidine, sulphas, diltiazem
- Granulomatous DDI, valproic acid
- Microvesicular fat amiodarone, tamoxifen
- Fatty hepatitis nitrofurantoin, minocycline
- Autoimmune hepatitis methotrexate
- Fibrosis cytoreductive therapy
- Endothelial injury (SOS/VOD) nicotinic acid, cocaine
- Ischemia oral contraceptive steroids
- Tumor, e.g. adenoma
Patterns of Liver Injury III: 
Biochemical Classification

<table>
<thead>
<tr>
<th>Hepatocellular (Elevated ALT)</th>
<th>Mixed (Elevated ALP + Elevated ALT)</th>
<th>Cholestatic (Elevated ALP + TBL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>Amisulpride</td>
<td>Amoxicillin–disulfiram acid</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Azathioprine</td>
<td>Anabolic steroids</td>
</tr>
<tr>
<td>Algoparin</td>
<td>Cyclosporine</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Carbamazepine</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Cinnarizine</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Ciprofloxacin</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Enalapril</td>
<td>Estrogens</td>
</tr>
<tr>
<td>HAART drugs</td>
<td>Flutamide</td>
<td>Imuran</td>
</tr>
<tr>
<td>Herbal: kava kava</td>
<td>Nifedipine</td>
<td>Mirtazapine</td>
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<tr>
<td>and germander</td>
<td>Phenoxybarbital</td>
<td>Phenoctizason</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Phenytin</td>
<td>Telithromycin</td>
</tr>
<tr>
<td>Ketonecorazole</td>
<td>Sulfamethoxazole</td>
<td>Ticarcillin</td>
</tr>
<tr>
<td>Lidiopril</td>
<td>Trazodone</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Lorcarnon</td>
<td>Tizanidine</td>
<td>Tremoridine</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Valproic acid</td>
<td>Tylosin</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
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<tr>
<td>Omeprazole</td>
<td></td>
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<tr>
<td>Paroxetine</td>
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<tr>
<td>Pyrazinamide</td>
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<tr>
<td>Rifampin</td>
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<tr>
<td>Rivaroxibine</td>
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<tr>
<td>Sertraline</td>
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<tr>
<td>Statins</td>
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<tr>
<td>Tetracyclines</td>
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<tr>
<td>Ticlopidine</td>
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<tr>
<td>Truvada</td>
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<tr>
<td>Valproic acid</td>
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</tr>
</tbody>
</table>


In Some Examples, DILI is Due to Cumulative Doses of Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Increased dose: hepatocyte necrosis, apoptosis</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Cumulative dose: steatohepatitis</td>
</tr>
<tr>
<td>Bromfenac</td>
<td>Cumulative dose: hepatocyte necrosis</td>
</tr>
<tr>
<td>Cocaine, phencyclidine</td>
<td>Increased dose: ischemic necrosis</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Increased dose: hepatocyte necrosis (worse with increased aminotransferase levels)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Increased dose: cholestatic injury</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Increased or cumulative dose: hepatocyte necrosis, fibrogenesis</td>
</tr>
<tr>
<td>Niacin</td>
<td>Increased dose: ischemic necrosis</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Cumulative dose: associated with hepatic adenomas</td>
</tr>
</tbody>
</table>

* Although many of these reactions may be considered idiosyncratic, the individual or total dose has a role with these agents.

But, Most Cases are Idiosyncratic


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Features of Idiosyncratic Drug Reactions

- Occurs rarely, *not really* dose related
- Often similar consistent pattern for each drug
- Similar drugs exhibit similar features, “class effects”
- Individual drugs in a class still vary considerably
- Reactions occur at varying time intervals after ingestion (3 days to one year)
- Reactions vary in severity, but typically severe and fatal if drug continued
- Mild injury often disappears with continued use (adaptation)
- Rarity of most reactions suggests many “hits” in pathogenesis
- Re-challenge is virtually always met with greater severity, shorter latency
- Most drugs causing idiosyncrasy are at doses >100 mg/day
Diagnosis of Drug-Related Hepatotoxicity

NO SPECIFIC MARKERS AND NO DIAGNOSTIC TESTS

Suspect DILI if:
- Other causes of hepatobiliary disease excluded
- Age > 50 years
- Patient taking many drugs
- Patient has taken a known hepatotoxin
- Liver biopsy has unusual appearance

But, also attempt causality assessment

Causality Assessment Methods (CAMs)

- RUCAM or CIOMS
  - Roussel Uclaf Causality Assessment Method (RUCAM) developed by the Council for International Organizations of Medical Sciences (CIOMS)
    - [Danan C and Benichou J. Clin Epidemiol 1993]
- CDS
  - Clinical Diagnostic Scale
  - developed by Maria and Victorino
    - [Maria VA and Victorino RM. Hepatology 1997]
Features “Scored” in Causality Assessment Methods

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>CIOMS (&gt;5)</th>
<th>CDS (&gt;9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from drug intake to onset</td>
<td>+1 to +2</td>
<td>+1 to +3</td>
</tr>
<tr>
<td>Time from withdrawal to onset</td>
<td>0 to +1</td>
<td>-3 to +3</td>
</tr>
<tr>
<td>(Hepatitis shorter than Cholestatic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time course (Hepatitis shorter than Cholestatic)</td>
<td>-2 to +3</td>
<td>0 to +3</td>
</tr>
<tr>
<td>Risk factors (Age, alcohol)</td>
<td>0 to +2</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td>-3 to 0</td>
<td>X</td>
</tr>
<tr>
<td>Exclusion of other causes</td>
<td>-3 to +2</td>
<td>-3 to +3</td>
</tr>
<tr>
<td>Literature</td>
<td>0 to +2</td>
<td>-3 to +2</td>
</tr>
<tr>
<td>Extrahepatic manifestations</td>
<td>X</td>
<td>0 to +3</td>
</tr>
<tr>
<td>Rechallenge</td>
<td>-2 to +3</td>
<td>0 to +3</td>
</tr>
</tbody>
</table>

CDS versus CIOMS

- **CDS simpler**, score > 9 (in 135 cases)
  - Identified 88% of cases classified as drug-related
  - Excluded 98% of those classified as drug-unrelated
    
    \[\text{Aithal et al 2000}\]
  - BUT

- **CIOMS more reliable** for
  - Long latency eg. Amoxicillin-clavulinic acid (3-4 weeks)
  - Chronicity eg. Flucloxacillin
  - Fulminant cases (no time to recover!)

\[\text{Lucena et al 2001, Kaplowitz 2001}\]
Role of Liver Biopsy in DILI

1. When information for CAMs is unavailable
2. DILI “unlikely” from rest of diagnostic work-up
3. DILI possible/probable but drug useful and there are no alternatives
   • To confirm diagnosis (typical histology)
   • To assess severity (risk benefit ratio)
4. DILI is probable and drug has been stopped but recovery is slow
   • To confirm diagnosis
   • To assess degree of/potential for recovery
5. New drugs (for society rather than patient)

Therapy of Drug Hepatotoxicity

• STOP drug if enzymes > 5-fold elevated above baseline, or 3x elevated and bilirubin elevated too [Hy’s Law]
• supportive measures
  – low fat diet with medium chain triglycerides
  – Intravenous vitamin K for severe coagulopathy (1 mg/100 mL saline over 30 minutes)
  – replace other fat-soluble vitamins
• no role for steroids except, possibly, in Idiosyncratic Drug-Induced Autoimmune Hepatitis
• pruritus: ursodeoxycholic acid, cholestyramine, rifampin, naltrexone, serotonin uptake-inhibitor antidepressants
• questionable role for ursodeoxycholic acid in alleviating cholestasis
• liver transplantation
Natural History of Drug-Induced Cholestasis

• Prolonged resolution
  – Usually takes weeks or months for recovery
  – Can take a year for alkaline phosphatase elevation to resolve

• Propensity for progression to secondary cirrhosis, exaggerated by continuation of drug

• Mortality (16.4%) similar to or greater than hepatitic DILI (7.5%) – Chalasani et al Gastroenterology 2008: 135: 1924-1934