CHAPTER 1

Drug-induced Liver Disease (DILD)

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Drug-induced Liver Disease (DILD)

- **Predictable**
  - Dose related
  - Intrinsically hepatotoxic drugs
  - Acute (hours)
  - Injury pattern is usually necrosis
  - Clinically → Fulminant (Acute Hepatitis)
  - Example: Acetaminophine

- **Unpredictable**
  - Not dose related
  - Rare 0.01-1.0 %
  - Weeks to months after ingestion of drug
  - **Idiosyncratic**
    - Immune mediated idiosyncrasy (Hypersensitivity)
      - Rash
      - Fever
      - Arthragia
      - Eosinophilia
      - Example: Phenytoin, Sulfonamides, Valproate
    - Metabolic idiosyncrasy (Production of toxic metabolites)
      - Example: INH, Ketoconazole, and Diclofenac
Overview of Drug induced Liver Injury

- Types of Drug Reactions
- Approach to the patient
- Natural History
Histological Classification

- Hepatocellular ------→ Hepatocytes
- Cholestatic ------→ Bile ducts or canaliculi
- Mixed
Categorization according to type of reaction

- Direct toxic reactions
- Idiosyncratic reactions
- Combined toxic/Allergic reactions
- Allergic hepatitis
- Cholestatic reactions
- Granulomatous reactions
- Chronic hepatitis and cirrhosis
- Fatty liver /NASH
- Veno-Occlusive disease
- Neoplastic
Diagnosis of (DILD)

- High index of suspicion
- Abnormalities in hepatic associated enzymes
- Hepatitis like symptoms
- Jaundice
- Drug history
  - Dose
  - Duration of therapy
  - Time between initiating therapy and the development of hepatic injury (latency)
- Exclusion of other causes of liver diseases
  - Hepatitis B
  - Hepatitis C
  - Alcoholic liver diseases
  - Non alcoholic fatty liver diseases
  - Hemochromatosis

2%-5% of general population
Diagnosis of (DILD)

Temporal relationship

- Most cases of acute DILD occurring within 1 week to 3 months of exposure

- Positive response to discontinuing the agent (Dechallenge)
  - In acute hepatocellular injury
    - 50% reduction in hepatic–associated enzymes after 2 weeks
    - Return to normal by 4 weeks
  - In cholestatic injury
    - May have prolonged recovery time
Diagnosis of (DILD)

Extrahepatic manifestations

- Hypersensitivity reactions
  - Fever
  - Rash
  - Arthralgias
  - Eosinophilia

- Unique clinical syndromes
Risk Factors For Susceptibility to DILD

- **Methotrexate**
  - Alcohol
  - Obesity
  - D.M
  - Chronic hepatitis

- **INH**
  - HBV, HCV, HIV
  - Alcohol
  - Older age
  - Female

- **Acetaminophen**
  - Alcohol
  - Fasting
  - INH

- **Valproate**
  - Young age
  - Anticonvulsants

- **Diclofenac**
  - Female
  - Osteoarthritis
Risk Factors For Susceptibility to DILD

- **Sulphonamide**
  - HIV
  - Slow acetylator
  - Genetic defect in defense

- **Anticonvulsats**
  - Genetic defect in detoxification

- **Rifampicin**
  - Slow acetylators
  - INH

- **Pyrazinamide**
  - Slow acetylators
  - INH
Clinical Presentations

Asymptomatic elevation in hepatic enzymes

- No progress despite Continued use of the Medication. (Drug tolerance)
  - INH
  - Phenytoin
  - Chlopromazine

- Progression to Hepatic injury with Continued use of the medication
- AST & ALT 3-5 times Upper limit of normal
- May progress to Hepatic failure
Acute Hepatocellular Injury
(Direct toxic reaction)

- Characterized by
  - Marked elevation in ALT and AST
  - Normal or minimally elevated alkaline phosphatase
  - Bilirubin variably increased---->worse prognosis.

- Comprise 1/3 of all cases of fulminant hepatic failure in the US.
  - 20% due to Acetominophen
  - 12%-15% due to other drugs
Acute Hepatocellular Injury
(Direct toxic reaction)

- Alcohol
  - AST is always 2-3 times higher than ALT
  - AST remains less than 300 IU.
  - ALT is almost always less than 100 IU.

- Towering elevation of ALT & AST (5000-10000 IU)
  - Drugs (acetaminophen)
  - Differential:
    - Chemical toxins
    - Toxic Mushrooms
    - Shock liver
  - Unusual with other causes of liver diseases including Viral Hepatitis.
# Acute Hepatocellular Injury
(Direct toxic reaction)

## Examples

<table>
<thead>
<tr>
<th>Anesthetics</th>
<th>NSAIDS &amp; analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Halothane</td>
<td>• Acetaminophen</td>
</tr>
<tr>
<td>• Isoflurane</td>
<td>• Piroxicam, Diclofenac</td>
</tr>
<tr>
<td></td>
<td>• Sulindac</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>• INH</td>
<td>• Labetalol</td>
</tr>
<tr>
<td>• Rifampin</td>
<td>• Nicotinic acid</td>
</tr>
<tr>
<td>• Ketoconazole</td>
<td>• Propylthiouracil</td>
</tr>
<tr>
<td>• Sulfonamides</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Phenytoin</td>
<td></td>
</tr>
<tr>
<td>• Valproic acid</td>
<td></td>
</tr>
<tr>
<td>• Carbamazipine</td>
<td></td>
</tr>
</tbody>
</table>
Cholestatic Injury

Definition: Reduction in bile flow due to
- Reduced secretion
- Obstruction

Biochemically:
- Elevated Alk phosphatase
- Elevated GGT
- Elevated 5 NT

Acute illness that subsides when the offending drug is withdrawn.
Cholestatic Injury

Clinical presentation

- Jaundice
- Pruritis
### Types of cholestasis resulting from drugs

<table>
<thead>
<tr>
<th></th>
<th>Canaliculer (Bland Jaundice)</th>
<th>Hepato-canaliculer (Cholestatic Jaundice)</th>
<th>Ductuler (Cholangioler)</th>
<th>Cholangio-destructive (Vanishing bile duct synd)</th>
<th>Cholangio-sclerotic (Sclerosing cholangitis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bile casts</strong></td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Portal inflammation</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Hepatocellular necrosis</strong></td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Ductal lesion</strong></td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Cholangitis</strong></td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+to+++</td>
<td>+to+++</td>
</tr>
<tr>
<td><strong>Alk Phos</strong></td>
<td>&lt;3X</td>
<td>&gt;3X</td>
<td>&gt;3X</td>
<td>&gt;3X</td>
<td>&gt;3X</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td>+/-</td>
<td>++</td>
<td>+/-</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>AST/ALT</strong></td>
<td>&lt;5X</td>
<td>2-10X</td>
<td>&lt;5X</td>
<td>&lt;5X</td>
<td>&lt;5X</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>Contraceptive, Anabolic steroids</td>
<td>Chlorpromazine, Augmentin, Erythromycin</td>
<td>Benoxaprofen, Paraquat, Clorpromazine, Fluxuridine, Scoliocides</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- +: Present
- -: Absent
- +/-: Variable presence
- <3X: Less than 3 times normal
- >3X: Greater than 3 times normal
- 2-10X: 2 to 10 times normal
- <5X: Less than 5 times normal
- >5X: Greater than 5 times normal
Drugs causing chronic cholestasis and the vanishing bile duct syndrome

### Antibiotics
- Ampicillin
- Augmentin
- Clindamycin
- Erythromycin
- Organic arsenicals
- Septrin
- Tetracycline
- Thiabendazole
- Troleandomycin

### Psychotropic
- Amitriptyline
- Barbiturates
- Carbamazpine
- Chlorpromazine
- Haloperidol
- Imipramide
- Phenothiazines

### Miscellaneous
- Aprindine
- Azathioprine
- Carbutamide
- Ciproheptadine
- Chlorthiazide
- Cyamemazine
- Ibuprphen
- Cimetidine
- Prochlorperazine
- Terbinafine
- Terfenadine
- Tolbutamide
- Ticlodipine
- Xenalamine
- Ethenyl estradiol
## Comparison between PBC with DICC

<table>
<thead>
<tr>
<th></th>
<th>PBC</th>
<th>DICC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>women</td>
<td>both</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Middle-aged</td>
<td>All ages</td>
</tr>
<tr>
<td><strong>AMA</strong></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Insiduous</td>
<td>Acute</td>
</tr>
<tr>
<td><strong>Jaundice</strong></td>
<td>Late feature</td>
<td>Acute feature</td>
</tr>
<tr>
<td><strong>Pruritis</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Hypercholestremia</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Steatorrhea</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Xanthomas</strong></td>
<td>+</td>
<td>+(transient)</td>
</tr>
<tr>
<td><strong>VBDS</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Portal infiltrates</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Granulomas</strong></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Often progresses to biliary cirrhosis</td>
<td>Jaundice usually resolves after 6-76 m; rarely progresses to biliary cirrhosis</td>
</tr>
</tbody>
</table>

PBC : Primary billiary cirrhosis  
DICC : Drug induced chronic cholestasis
Granulamatous Hepatitis

- A form of hepatic injury characterized by:
  - Fever
  - Diaphoresis
  - Malaise
  - Anorexia
  - Jaundice
  - Rt upper quadrant discomfort
  - Granuloma on liver biopsy
  - Illness usually occurs within the first 2 months of therapy

- Examples:
  - Quinidine
  - Carbamazipine
  - Allopurinol
  - Hydralazine
  - Phenytoin
  - Gold
  - Mineral oil ingestion
  - Phenylbutazone
Drug induced chronic hepatitis

- Can resemble chronic active hepatitis including cirrhosis as well as a form of chronic autoimmune hepatitis

- **Characteristics of drug-induced autoimmune hepatitis**

<table>
<thead>
<tr>
<th>Duration of drug intake</th>
<th>≥ 2-24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female predominance</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>Onset</td>
<td>Insidious, gradual</td>
</tr>
<tr>
<td>Clinical</td>
<td>Fatigue, anorexia, wt loss, jaundice, ascites, hepatosplenomegaly, and portal hypertension</td>
</tr>
<tr>
<td>Biochemical</td>
<td>AST, ALT= 5-50 × ULN</td>
</tr>
<tr>
<td></td>
<td>Increased gamma globulin level</td>
</tr>
<tr>
<td>Serology</td>
<td>ANA, ASMA, LE factor</td>
</tr>
<tr>
<td></td>
<td>Anti-P4501A2, AntiP4502C9</td>
</tr>
<tr>
<td>Histology</td>
<td>Very active necro-inflammatory lesion</td>
</tr>
<tr>
<td></td>
<td>Prominent plasma cells</td>
</tr>
<tr>
<td>Usual course</td>
<td>Resolution on withdrawal of drug</td>
</tr>
</tbody>
</table>
Drugs leading to a syndrome resembling type I autoimmune chronic hepatitis

Multiple cases

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Serologic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clometacin</td>
<td>ASMA, Anti-DNA</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>ANA(16%), ASMA(35%)</td>
</tr>
<tr>
<td>Minocycline</td>
<td>ANA, Anti-DNA</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>ANA(80%), ASMA(72%)</td>
</tr>
<tr>
<td>Oxyphenisatin</td>
<td>ANA(67%), ASMA(67%), LE(33%)</td>
</tr>
</tbody>
</table>

Few cases

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Serologic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzarone</td>
<td>ASMA</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>ANA</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>ANA</td>
</tr>
<tr>
<td>Papverine</td>
<td>ANA, ASMA</td>
</tr>
<tr>
<td>Pemoline</td>
<td>ANA, Automicrosomal antibody</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>ANA</td>
</tr>
<tr>
<td>Captopril</td>
<td>ANA, Antilaminin</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>AMA,(Anti-M2)</td>
</tr>
<tr>
<td>Procainamide</td>
<td>ANA, LE factor(50-70%)</td>
</tr>
</tbody>
</table>
Vascular injury

- May involve all of the vascular components of the liver, including the sinusoids, hepatic veins, and hepatic arteries.

- Veno-occlusive disease (VOD):
  - May be caused by:
    - Toxic plant alkaloids (certain herbal tea)
    - A serious complication complication of bone marrow transplant
  - Azathioprine is probably the culprit
  - Clinically presents as
    - Mild viral-like illness → Fulminent hepatic failure
    - Rapid weight gain
    - Ascites
    - Jaundice
    - Evidence of portal hypertension

- Chronic form of VOD may also exist.
<table>
<thead>
<tr>
<th>Neoplastic lesions</th>
<th>Clinical findings</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal nodular hyperplasia</td>
<td>- Hepatic mass</td>
<td>Contraceptive steroids</td>
</tr>
<tr>
<td>Adenoma</td>
<td>- Hepatic mass</td>
<td>- Contraceptive steroids</td>
</tr>
<tr>
<td></td>
<td>- Hemoperitoneum</td>
<td>- Anabolic steroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Danazole</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>- Malignant mass</td>
<td>- Anabolic steroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Contraceptive steroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Venyl chloride</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Thorium dioxide (Thorotrast)</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>- Malignant mass</td>
<td>- Anabolic steroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Inorganic arsenicals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Thorium dioxide (Thorotrast)</td>
</tr>
</tbody>
</table>
Natural History and Prognosis

- When recognized promptly and the offending agent is discontinued most cases resolve without chronic sequelae.

- Mortality principally depend on the degree of hepatocellular injury.

- 10% mortality for agents causing fulminant hepatitis or toxic steatosis.

- Agents that cause cholestatic injury rarely, if ever, produce acute fatalities.

- The prognosis is worse whenever jaundice accompanies hepatocellular injury.
Hepatic injury resulting from individual agents
Anesthetics