Drug induced liver disease (DILD)

Selected Groups Exhibit Higher or Lower Incidences of DILD

- Drugs implicated in 43% of admissions for “acute hepatitis” in patients over 50 years of age
- Less common in children vs. adults
- patients with previous history of severe hepatic injury
- patients with chronic liver disease
- Type of disorder being treated (e.g. methotrexate in psoriasis vs. rheumatoid arthritis)

Selected Risk Factors for Drug-Induced Hepatic Disease

- Age > 60 for INH, nitrofurantoin
- Pediatrecs for valproate, salicylates, ceftriaxone
- Pregnancy for tetracyclines
- Rifampin+INH, macrolides+estrogens
- antibacterials, ecstacy and anti-TB
- old + male = cholestasis
- young + female = hepatocellular

Clinical Monitoring-LFTs

- The liver contains thousands of enzymes, some of which are present in the serum.
- The elevation of a given enzyme activity in serum is thought to primarily reflect its increased rate of entrance into serum from damaged liver cells.
- Serum enzymes can be grouped into two categories: those reflective of damage/necrosis or those reflective of cholestasis.
- LFT is often a misnomer – most do NOT quantitate liver FUNCTION

Types of DILD

- **Predictable (intrinsic)** :

- Dose related
- Intrinsically hepatotoxic drugs
- Acute (hours)
- Injury pattern is usually necrosis
- Clinically → 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
    - Eosinophilia
    - Example: Phenytoin, Sulfonamides, Valproate
  - Metabolic idiosyncrasy (Production of toxic metabolites)
    - Example: INH, Ketoconazole, and Diclofenac

Histological Classification

- Hepatocellular injury ------› Hepatocytes
- Cholestatic -------› Bile ducts or canaliculi
- Mixed

Hepatitis pattern

- Hepatocellular injury
- Patient may be asymptomatic or present with fatigue, right upper quadrant pain, jaundice or acute liver failure
- usually poor correlation between degree of ALT elevation and the severity of the liver disease
- clinical and biochemical parameters often underestimate the degree of liver injury, histology being a more accurate indicator
- a good predictor of mortality in drug-induced hepatitis is jaundice

Cholestatic pattern

- Definition: Reduction in bile flow due to
  - Reduced secretion
  - Obstruction
- Biochemically:
  - Elevated Alk phosphatase
  - Elevated GGT
  - Elevated 5 NT
- . Mortality appears to be less than with the hepatitis

pattern (1-7.8%) and death is usually not liver-related.

Mixed pattern:

- combination of acute hepatitis and cholestasis.
- This pattern of liver injury probably has the lowest mortality

Enzymes that detect hepatocellular necrosis

- **AST – aspartate aminotransferase;**
  found in heart and liver.
- **ALT– alanine aminotrasferase;**
  mostly in liver.
- **LDH – lactate dehydrogenase;** found in same tissues as AST; generally poor LFT; also increased in heme malignancies, anemias, MI, shock

Enzymes that detect Cholestasis

- **Alk Phos (AP) – alkaline phosphatase**

Liver and bone mainly, also kidney, placenta, leukocytes

Bone-> Paget's, hyperparathyroidism, rickets, osteomalacia

- **GGT – gamma-glutamyl transpeptidase**

Found in liver, seminal vesicles, pancreas, spleen, heart, brain.

Confirms liver as source of ↑ alk phos. (e.g. bone disease, childhood, pregnancy where alk. phos. is normally increased)

Enzymes that detect Cholestasis (cont'd)

- **5'-Nucleotidase (5-NT)**

Found in liver, intestine, brain, heart, blood vessels, pancreas

Confirms liver source of increased alk phos

- **Leucine Aminopeptidase (LAP)**

Exclusively produced by liver

Confirms liver source of increased alk phos

Patterns of LFT Abnormalities

1. Hepatitis/hepatocellular:

(ALT/ULN) ÷ (AP/ULN) > 5

2. Cholestasis:

equation result < 2

3. Mixed:

equation result > 2 to < 5

(ULN = upper limit of normal)

Patterns of LFT Abnormalities (cont'd)

AST/ALT Ratio:

> 1 in alcoholic hepatitis or cirrhosis, chronic hepatic disease, hepatic cancer

< 1 in acute hepatitis

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

Management

- take a good drug and exposure history
- lab monitoring
- discontinuation of the possible offending drugs
- specific therapy may not be available, and most of the time, management is supportive
- liver biopsy may be helpful in excluding other causes of liver injury
- if there's evidence of acute liver failure/fulminant liver failure, then refer patient to a liver transplant center