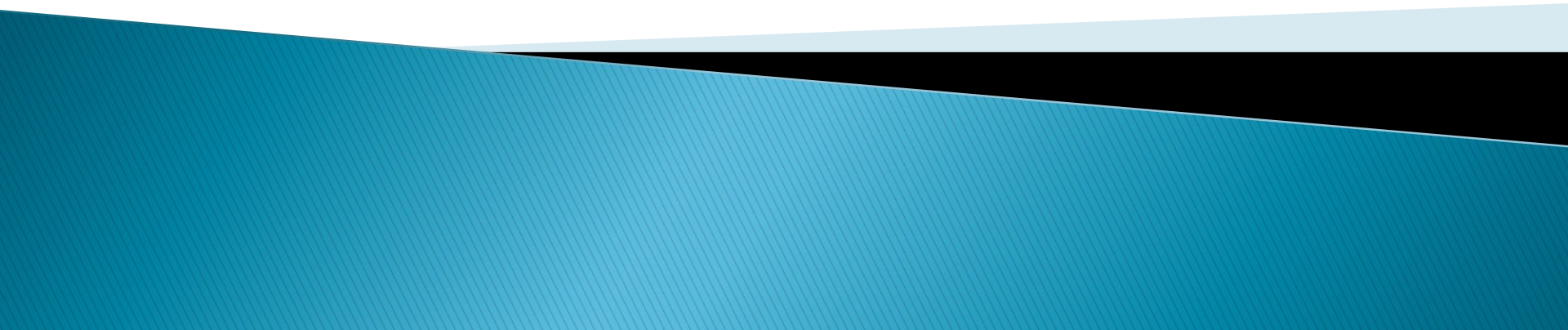
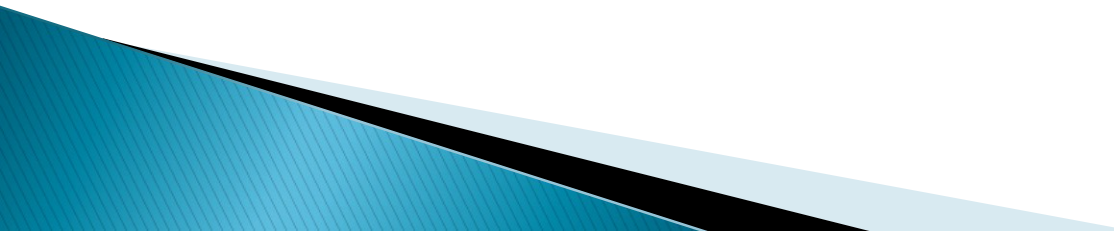


Drug induced liver disease (DILD)

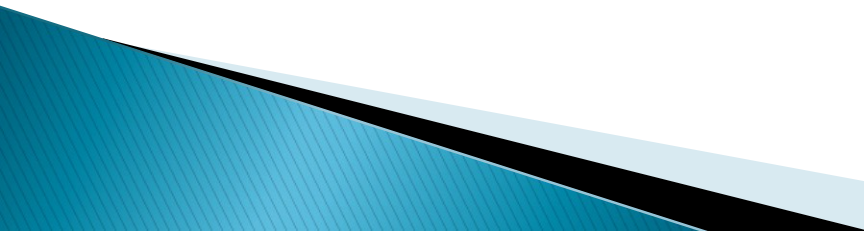
Selected Groups Exhibit Higher or Lower Incidences of DILD

- 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
 - ▶ Pediatrics for valproate, salicylates, ceftriaxone
 - ▶ Pregnancy for tetracyclines
 - ▶ Rifampin+INH, macrolides+estrogens
 - ▶ antibacterials, ecstasy 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
- 

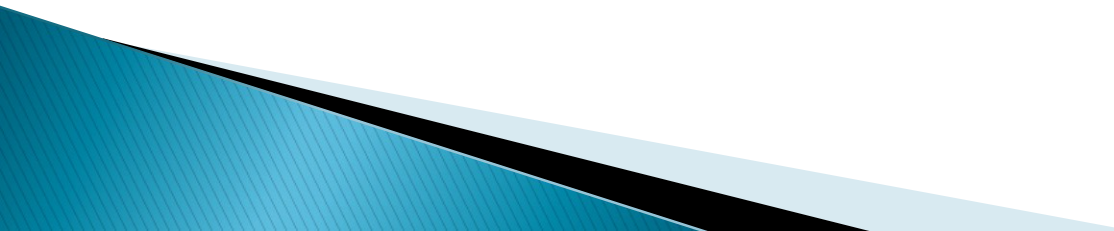
Cholestatic pattern

- ▶ 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:

$$(\text{ALT/ULN}) \div (\text{AP/ULN}) > 5$$

2. Cholestasis:

$$\text{equation result} < 2$$

3. Mixed:

$$\text{equation result} > 2 \text{ to } < 5$$

(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
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