

Drug-Induced Liver Disease (2009)

- Can mimic any form or pattern of acute or chronic hepatobiliary disease
- Can be benign or clinically significant, acute or chronic, asymptomatic or clinically-evident
- DILD generally has low incidence of occurrence, but can have serious outcomes (10-52% of cases of FHF which is 75-90% fatal)

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
- Pts with previous history of severe hepatic injury
- Pts with chronic liver disease (specific pops. only)
- 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
Peds for valproate, salicylates, ceftriaxone
- Pregnancy for tetracyclines
- Rifampin+INH, macrolides+estrogens
- FHF - risk factors (female, hepatocell. damage, high baseline bili conc.)
- antibacterials, ecstasy and anti-TB are #1-3

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

Enzymes that detect hepatocellular necrosis

- **AST/(SGOT)** – aspartate aminotransferase; found in heart and liver.
- **ALT/(SGPT)** – alanine aminotransferase; mostly in liver.
- **LDH** – lactate dehydrogenase; found in same tissues as SGOT; generally poor LFT; also increased in heme malignancies, anemias, MI, rhabdomyolysis, pulmonary infarct, 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 source of incr. 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

Spectrum of Enzyme Activity

- Cytotoxic – overt damage to hepatocytes
Necrosis-zonal, diffuse or massive
Steatosis-fat infiltration
- Cholestatic – arrested bile flow
- Mixed – features of both

Non-specificity of LFTs

Enzyme	Cholestasis	Necrosis
Alk Phos	XX	X
GGT	XX	X
AST	X	XX
ALT	X	XX
LDH	X	XX

Patterns of LFT Abnormalities

1. Hepatitis/hepatocellular:
(ALT/ULN) ÷ (AP/ULN) \geq 5
2. Cholestasis:
equation result \leq 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

Bilirubin (pigment, byproduct of heme-protein breakdown)

- Generally, total serum bilirubin is not a sensitive indicator of hepatic dysfunction
- Cholestasis and hepatocellular injury
- Check skin, sclera (≥ 2 mg %)

Albumin

- Major plasma protein in blood
- Synthesized in liver
- ↓ albumin due to malnutrition (↓ amino acid availability), hepatic dysfunction (↓ synthesis), renal dysfunction (↑ excretion in urine)
- Role as LFT
- Anionic drugs carried by albumin (protein binding displacement interactions)

Prothrombin Time (INR)

- Increase in PT/INR secondary to dietary deficiency of K, destruction of intestinal bacteria->K, decreased K absorption due to decreased bile salts, malabsorption or decreased utilization of K secondary to liver cell destruction.
- Usually takes severe disease before PT/INR increased
- Lack of response of PT/INR to IV vit. K is of grave prognostic significance.

Types of DILD

- **Predictable** (intrinsic) – relatively high occurrence rate, often related to dose
 - Direct
 - Indirect--bioactivation
- **Unpredictable** (idiosyncratic) – generally no association with dos

Types of Hepatic Injury

- Centrilobular necrosis (commonest and worst outcome as death/transplant in 12% if jaundiced at diagnosis)

Drugs:

Predictable – Acetaminophen

Unpredictable – Methyl dopa, INH, Halothane, PTU

Cholestasis

- Drugs:
Predictable – Chlorpromazine, retinoids
Unpredictable – Sulfonamides, Macrolides, Amoxicillin-clavulanate, Penicillinase-Resistant Penicillins, TMP/SMX, Methimazole

Steatonecrosis

- Drugs:
Predictable – Ethanol, Valproic Acid, Amiodarone, Tetracyclines, Methotrexate

Toxic Hepatitis

- **Drugs:**
Unpredictable – Ketoconazole,
Nitrofurantoin, INH, Methyldopa,
TMP/SMX

Hepatic Vascular Disorders

- **Drugs:**
Predictable – Oral androgens/anabolic
steroids
Unpredictable – Azathioprine, combination
cancer chemotherapy
- **Types:**
Hepatic vein thrombosis (Budd-Chiari
syndrome), Peliosis hepatis, veno-occlusive
disease

Gallstones

- Fibrates-true (cholesterol)
- Ceftriaxone (pseudo)

Hepatotoxic Herbals

See appended table from Feb. 2002 issue of Seminars in Liver Disease

- Adulterated Chinese medicine (N-nitrosufenfluramine)

HAART

- Severe damage in up to 5-10%
- Mechanisms: mitochondrial toxicity → steatosis, hypersensitivity, ↑ hepatic lipid synthesis
- Risk ↑ with concurrent Hep B/C + ↑ drug conc.
- Protease inhibitors and nevirapine are big offenders
- Monitor LFT's at 2 & 4 weeks after start, then every 3 months (every month if concurrent Hep B/C)
- Avoid full-dose ritonavir, high-dose didanosine, and high-dose stavudine + didanosine combo

Diagnosis and Management of DILD

Presumptive Diagnosis

1. Complete drug exposure history and chronology
2. Exclude other causes of hepatic injury
3. Identify the "clinical signature":
 - a. pattern of LFT abnormalities
 - b. time to onset of symptoms
 - c. presence/absence of hypersensitivity signs/symptoms
 - d. course after drug withdrawal

Diagnosis and Management of DILD (cont'd)

Therapeutic rechallenge

1. Indications:

Cholestatic injury (not indicated if severe necrotic injury)

High potential need for the drug

Length of rechallenge < 1 day

2. Effectiveness: 40-60% will not manifest upon rechallenge

Diagnosis and Management of DILD (cont'd)

Treatment of DILD

- Prevention
- Withdrawal of offending agent
- Supportive
- Pharmacologic interventions:
 - Cholestyramine ("liver itch")
 - Corticosteroids-only if allergic source
 - Ursodeoxycholic acid-prolonged cholestasis only
 - Specific "antidotes" (eg. L-carnitine + VA, acetylcysteine + APAP)

Prevention of DILD

- LFT monitoring-Anti-TB, MTX
