Alcohol and the liver: epidemiology

- most common drug of abuse
  - 15 million Americans are alcoholics
  - contributes to 250,000 deaths annually, $2.5B / yr

- liver disease a threshold effect
  - men: 7 beers / d (80 g)
  - women: 5 beers / d (60 g)

- not all abusers of alcohol will develop liver disease
  - (autopsy incidence of cirrhosis 10-15% among alcoholics)

- basis for predisposition to cirrhosis remains unknown
Metabolism of alcohol

- unlike its *direct* toxic effects on other organs, the *metabolites* of alcohol most responsible for liver disease

- first-pass metabolism by gastric alcohol dehydrogenase (ADH)
  - significantly reduces circulating EtOH levels
  - gastric ADH less active in women and may account for their greater susceptibility to effects of EtOH
  - chronic ingestion lowers gastric ADH and augments availability of EtOH in both sexes
Hepatic metabolism of alcohol

- > 90% of absorbed alcohol metabolized in liver by 2 pathways:

1. **hepatic alcohol dehydrogenase (ADH)**
   - alters redox state of hepatocytes, leading to multiple metabolic derangements

2. **microsomal ethanol oxidizing system (MEOS)**
   - oxidizes small fraction of EtOH in normals but induced by chronic use
   - key component is P450 IIE1
   - generates ROIs that cause lipid peroxidation
   - enhances conversion of drugs (acetaminophen) and xenobiotics into highly toxic metabolites
Alcohol oxidation (inc. NADH) leads to multiple metabolic derangements

- inc. FA synthesis, dec. FA oxidation (steatosis, hyperlipidemia)
- impaired gluconeogenesis (hypoglycemia)
- inhibition of Krebs cycle (inc. lactic acid, ketones)
- inc. lactic acid impairs renal uric acid excretion (hyperuricemia)
Hepatotoxicity of alcohol: mechanisms

1. **Redox alteration**
   - a consequence of increased NADH/NAD

2. **Oxidant stress**
   - MEOS metabolites cause lipid peroxidation and membrane alterations
   - aggravated by depletion of antioxidants (Vit A, C, glutathione)
3. **Acetaldehyde effects**

- high chemical reactivity causes covalent modification of cell proteins
- aggregation of intermediate filaments (Mallory's hyaline)
- inhibition of protein secretion with resultant ballooning of cells
- directly stimulates collagen synthesis by stellate cells
4. **Perivenular fibrosis**

- Activation and transformation of the stellate cell by acetaldehyde and other by-products leads to collagen deposition in perivenular regions.

- Propensity for venular locations may be enhanced by hypermetabolic state induced by alcohol.

- Activated stellate cell is prime mover in fibrosis.
Image removed due to copyright reasons.

Features of chronic liver injury leading to stellate cell (lipocyte) activation and induction of fibrosis (from Friedman)
Hepatotoxicity of alcohol: mechanisms

5. Cytokine production and Kupffer cell activation

» proinflammatory cytokines (IL-1, IL-6, IL-8, TGF-β, TNF-α) overproduced by Kupffer cells in majority of patients with alcoholic hepatitis

» IL-8 important in neutrophil recruitment

» TNF-α can cause direct liver injury or promote leukocyte activation

» together with IL-6 and TGF-β, TNF-α promotes stellate cell proliferation and collagen synthesis
Hepatotoxicity of alcohol: mechanisms

6. **Autoimmunity to altered cellular proteins**
   - high frequency of antibodies to HCV (up to one third) in alcoholic liver disease suggest that other antigens may trigger immune-mediated liver injury
   - enhanced humoral or cellular immune responses activated by acetaldehyde- and free radical-modified proteins (neoantigens) may aggravate or perpetuate liver injury
Clinical spectrum of alcoholic liver disease

- Alcoholic fatty liver (steatosis)
- Alcoholic hepatitis
- Cirrhosis
Alcoholic fatty liver (steatosis)

- direct effect of EtOH, seen in up to 90% of heavy drinkers
- earliest precirrhotic lesion, but only 20-30% will develop cirrhosis
- results from accumulation and formation of triglycerides and VLDL from fatty acids faster than their export from hepatocytes
- fatty acids accumulate as result of:
  - inhibition of FA oxidation by inc. NADH
  - inc. FA synthesis using acetate as substrate
  - inc. lipolysis in adipocytes with elevated circulating corticosteroid levels caused by adrenal toxic effects
Alcoholic steatosis

- **Pathological changes**
  - macro- and microvesicular fat (mitochondrial toxicity)
  - proliferation of ER (and inc. MEOS activity)
  - cell necrosis rare
  - occ. lymphocytic inflammation

- **Clinical features**
  - asymptomatic hepatomegaly, occ. tender
  - mild elevation in ALT
  - cholestasis most prominent, may be severe (GGTP disproportionately elevated)
  - severe dysfunction rare
  - with cessation, steatosis regresses in 1-6 wks
Alcoholic hepatitis: laboratory picture

- Mild elevation of enzymes, bilirubin characteristic but nondiagnostic
- Transaminases rarely more than 5 x ULN
- Elevated AST:ALT > 2 characteristic (68% sensitive, 91% specific) - pyridoxal phosphate deficiency
- Leukocytosis frequent
Alcoholic hepatitis: predictors of outcome

- Most important negative prognostic factor is continued ingestion: abstinent 80% 7YS, not abstinent 50%
- Poor outcome portended by: PSE, coagulopathy, jaundice, ascites, renal dysfunction, inflammation on biopsy, poor nutritional status
- Maddrey discriminant function predicts 50% 4-wk mortality:
  \[ 4.6 \times (\text{PT- control}) + \text{bili (mg/dL)} > 32 \]
- Abstinence leads to recovery in 50-60% but may take years
- Persistent hepatitis without cirrhosis seen in one third; 20% may proceed to cirrhosis despite abstinence
Alcoholic hepatitis: pathology/pathophysiology

- severity of pathological changes correlates with symptoms but **not** mortality
- pathological changes most prominent in pericentral regions and extend to portal tracts in more severe cases

Findings include:

- hepatocellular necrosis with ballooning degeneration
- steatosis, PMN infiltration, megamitochondria
- Mallory’s hyaline - eosinophilic cytoplasmic microfilaments (not pathognomonic - also seen in PBC, ICC, WD, NASH)
- perivenular sclerosing hyaline fibrosis - can be accompanied by reversible portal HTN
Alcoholic hepatitis: treatment

1. Abstinence - the mainstay of therapy
   - the only means of reversing the underlying process
   - reversal of steatosis seen in weeks to months
   - however, active inflammation and fibrosis may persist for several mos
2. **Corticosteroids**

» use based on evidence for immunologic factors in perpetuation of liver injury

» many studies, variable results

» better designed, RCTs tend to show benefit

» *no* demonstration of effect on long-term survival
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Corticosteroids in alcoholic hepatitis

- Imperiale (1992)
  - meta-analysis of 11 RCTs
  - steroids reduced short-term mortality by 35%
  - benefit was confined to those with PSE and without GI bleeding
  - no predictors of response identified

- In severe alcoholic hepatitis with encephalopathy and without bleeding, there is a short-term benefit for steroids
Pentoxifylline and alcoholic hepatitis

- Pentoxifylline (PTX) a phosphodiesterase inhibitor with TNF suppressive effects
- early pilot data suggested suppression of TNF levels in pts with AH
- Akraviadis (2000): RCT of PTX v placebo:
  - 1992-97 (begun pre-establishment of steroids)
  - 101 pts
  - 4 wk tx PTX 400 po tid
  - 1 endpoint short-term survival, progression to HRS
Pentoxifylline improves short-term survival in severe AH
Pentoxifylline in severe AH

- Mortality: PTX v placebo, 24% v 46%
- HRS: 6 v 22 pts, p = 0.009
- Inc in TNF levels correlated with inc mortality
- No significant AEs associated with PTX
- PTX is associated with significant reduction in mortality, HRS
- Confirmation required, steroid control arm desirable

Akraviadis, Gastroenterology, 2000
Alcoholic cirrhosis

- commonly found to coexist in pts presenting with alcoholic hepatitis (up to 15%)

- progression from alcoholic hepatitis to cirrhosis cannot be predicted, and can occur despite abstinence
Alcoholic cirrhosis: clinical features

- silent in up to 40%
- frequently manifests as portal HTN, liver failure
- most commonly presents with anorexia, weight loss, weakness
- fulminant hepatic failure rare, usually a result of superimposed acute insult
- prognosis improved by cessation
  - compensated cirrhosis: 85% v. 60% 5YS with drinking
  - decompensated: 50% v. 30% 5YS with drinking
Alcoholic cirrhosis: pathology/pathophysiology

- Transformation of hepatic stellate cells to collagen-producing myofibroblasts a key underlying step
- Distorted architecture interferes with secretory function of regenerated hepatocytes
- Hypoxic injury due to collagen deposition and decreased hepatic blood flow with formation of portasystemic collaterals further limits synthetic function of regenerated hepatocytes
Alcoholic cirrhosis: treatment

• no effective treatments identified
  – Corticosteroids
  – Colchicine
Orthotopic liver transplantation for alcoholic cirrhosis

- definitive treatment for those with decompensated disease, excellent graft outcomes
- most centers require a minimum 6 month period of abstinence
- nonetheless, recidivism rates as high as 25-33% indicate selection procedure still suboptimal
- interventions aimed at optimizing selection and preventing relapse of drinking will be critical as allocation of organs tightens
Drug-induced liver injury

1. Electrophilic radical production

Phase I (toxification)

**DRUG** \[\rightarrow\] **ACTIVE METABOLITE**

cytochrome P450

Phase II (detoxification)

**ACTIVE METABOLITE** \[\rightarrow\] **CONJUGATE**

GSH-transferase

GSH-glucuronyltransferase

(sulfate)

(glutathione)

(glucuronide)

**HEPATIC INJURY**
Acetaminophen hepatotoxicity

- toxicity increased by chronic EtOH (dec. GSH, inc. P450)
- N-acetylcysteine repletes GSH
2. Free radical mediated injury

- free radicals lead to lipid peroxidation, cell death ($\text{CCl}_4$)
- Phase I leads to $\text{CCl}_3 \rightarrow$ cell death, esp. in zone III
- $\text{N}$-acetylcysteine may enhance Phase II detoxification
- hyperbaric $\text{O}_2$ may promote linkage of $\text{CCl}_3$ to P450, shutting off free radical production
3. Immunologic liver injury

- prototype = halothane
- halothane hepatitis 1:35,000 exposures
- marked by fever, rash, eosinophilia
- incidence increases with repeated exposures
- TFA P450 metabolite reacts with cellular proteins, leading to neoantigens --> autoantibodies
- picture resembles viral hepatitis -- mortality 15-50%
Histopathologic patterns of injury

- Zonal necrosis
  - predictable, dose related direct toxins (CCl₄, acetaminophen --> centrizonal necrosis)

- Viral hepatitis-like reactions
  - sporadic, ? host idiosyncrasy (INH, halothane, methyldopa, phenytoin)

- Cholestatic
  - noninflammatory - direct effect on canaliculi (estrogens)
  - inflammatory - multiple sites (e`mycin, CPZ)
- Chronic hepatitis
  - usually depends on continued use of agent but can be irreversible if advanced (INH, nitrofurantoin, methylodopa)

- Fatty liver
  - macrovesicular: usually benign, (EtOH, MTX)
  - microvesicular: severe metabolic derangement of mitochondrial FA oxidation (TCN, valproate)

- Granulomas
  - mechanism unknown (allopurinol, quinidine, DPH)
• Tumors
  – adenoma, FNH, HCC (OCPs, anabolic steroids)
• Vascular reactions
  – Budd Chiari syndrome (OCPs)
  – veno-occlusive disease (alkaloids, high dose antimetabolites)
  – peliosis hepatis (androgens)
  – angiosarcoma (vinyl chloride, arsenic)
Isoniazid (INH) hepatotoxicity

- subclinical increase ALT 10-20%
  - focal necrosis on biopsy
  - self limited despite continued Rx
  - no correlation with levels

- clinical hepatitis 1%
  - rare in age < 20, 2% in age > 50, usu within 12 months of starting Rx
  - acute viral hepatitis-like lesions
  - 10-20% mortality (highest in A-A women)
  - surveillance in those > 35