Approach to Identification and Treatment of Alcoholic & Non-Alcoholic Fatty Liver Disease

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September 27, 2012
Alcoholic Liver Disease (ALD)

- Epidemiology
- Risk Factors
- Pathogenesis
- Diagnosis

- Prognosis
- Alcoholic Hepatitis
- Chronic ALD

- Treatment
- Alcoholic Hepatitis
- Chronic ALD
ALD: Epidemiology

Alcoholism

- 3rd leading cause of preventable death in the US\(^1\)
  - 79,000 deaths annually (2001-2005)\(^2\)
- 223 billion dollars sent on sequelae of alcoholism in 2006\(^3\)
  - 72.2% in lost productivity
  - 11.4% in healthcare costs
- 67.3% of adult population consume alcohol\(^4\)
  - 4.7% meet DSM IV criteria for alcohol abuse\(^5\)
  - 3.8% meet DSM IV criteria for alcohol dependence\(^5\)

1. Mokdad et al. JAMA 2004;291(10):1238-45
2. [http://www.cdc.gov/alcohol/ardi.htm](http://www.cdc.gov/alcohol/ardi.htm)
5. Hasin et al. Arch Gen Psychiatry 2007;(64)7:830-42
**ALD: Epidemiology**

- **Alcoholic Liver Disease (ALD)**
  - Spectrum of disease from steatosis to cirrhosis
  - Risk of cirrhosis increases with \( \geq 30 \) g/d alcohol
  - Highest risk of cirrhosis with consumption \( \geq 120 \) g/d
    - ALD does not occur universally in all who use heavy alcohol
    - Of those consuming \( \geq 120 \) g/d, 13.5% developed ALD
  - Second most frequent indication for liver transplantation

ALD: Risk Factors

- Dose, duration and type of alcohol consumption
- Drinking patterns
- Sex
- Ethnicity
- Genetic factors
- Other potential causes of liver injury
ALD: Risk Factors

- Dose, duration and type of alcohol consumption
  - Single most important risk factor for ALD!
- Drinking patterns
- Sex
- Ethnicity
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- Other potential causes of liver injury
ALD: Risk Factors

One mixed drink with
• 1.5 fl oz (44 mL) of 80-proof liquor (such as vodka, gin, scotch, bourbon, brandy, or rum)

5 fl oz (148 mL) of wine

12 fl oz (355 mL) of beer or wine cooler

Grams of alcohol per day = (% volume / volume mL) x (0.79 grams)
ALD: Risk Factors

**ALD: Risk Factors**

**TABLE 1** Classes of daily alcohol consumption of the screened population (n=6534), expressed as absolute number (n) and percentage of lines (%), according to the presence of either non-cirrhotic alcohol-induced liver damage (NCLD) or cirrhosis or hepatocellular carcinoma (=cirrhosis)

<table>
<thead>
<tr>
<th>Alcohol intake (g/day)</th>
<th>No (n=6442)</th>
<th>NCLD (n=57)</th>
<th>Cirrhosis (n=35)</th>
<th>Multivariate analysis (odds ratio) (95% CI)</th>
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<tr>
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ALD: Risk Factors

- Dose, duration and type of alcohol consumption
- Drinking patterns
- Sex
- Ethnicity
- Genetic factors
- Other potential causes of liver injury
ALD: Risk Factors

- Drinking patterns
  - Drinking outside of meal times
    - 2.7 fold increased risk of ALD
  - Binge drinking
    - Increased risk of ALD

Table 4. Multivariate Analysis of Factors Associated With Alcoholic Hepatitis and With Liver Cirrhosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Alcoholic hepatitis (^1)</th>
<th>Liver cirrhosis (^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>4.92 (2.40–10.08)(^c)</td>
<td>2.19 (1.04–4.59)(^a)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
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<tr>
<td>Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–15 years</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>16–20 years</td>
<td>1.91 (0.93–3.90)</td>
<td>2.97 (1.19–7.39)(^a)</td>
</tr>
<tr>
<td>&gt;20 years</td>
<td>1.14 (0.56–2.34)</td>
<td>3.72 (1.51–9.16)(^b)</td>
</tr>
<tr>
<td>Habitual quantity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80–150 g/day</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>151–200 g/day</td>
<td>1.37 (0.61–3.04)</td>
<td>1.32 (0.51–3.45)</td>
</tr>
<tr>
<td>&gt;200 g/day</td>
<td>0.91 (0.42–1.96)</td>
<td>3.44 (1.45–8.14)(^b)</td>
</tr>
<tr>
<td>Drinking pattern (irregular)</td>
<td>5.49 (2.83–10.66)(^c)</td>
<td>1.10 (0.52–2.31)</td>
</tr>
<tr>
<td>Spirits drinking habit</td>
<td>1.48 (0.75–2.91)</td>
<td>0.71 (0.33–1.50)</td>
</tr>
<tr>
<td>Presence of SAWS</td>
<td>1.79 (0.92–3.48)</td>
<td>0.35 (0.17–0.75)(^b)</td>
</tr>
</tbody>
</table>

ALD: Risk Factors

- Dose, duration and type of alcohol consumption
- Drinking patterns
- Sex
- Ethnicity
- Genetic factors
- Other potential causes of liver injury
ALD: Risk Factors

- **Sex**
  - Incidence of ALD modified by sex
    - ALD: 0.3% vs 0.1% per year in men vs women
    - Cirrhosis/ ALD: 0.2% vs 0.03% per year in men vs women
    - Risk of development of cirrhosis
      - > 60-80 g/d for 10 or more years in men
      - > 20 g/d for 10 or more years in women
  - Women have a higher relative risk of developing ALD than men for every given level of reported alcohol consumption
  - Difference may be on the basis of decreased levels of alcohol dehydrogenase, increased body fat, and changes in metabolism with menstruation.

ALD: Risk Factors

- Dose, duration and type of alcohol consumption
- Drinking patterns
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ALD: Risk Factors

- **Ethnicity**
  - Increase in ALD mortality in Hispanics

- **Genetics**
  - Polymorphisms of alcohol metabolism pathway
    - Alcohol dehydrogenase ADH
    - Aldehyde dehydrogenase ALDH
  - ADH and ALDH polymorphisms recently identified

- **Other potential causes of liver injury**
  - Viral Hepatitis
  - Obesity
  - Iron overload
ALD: Pathogenesis

- **Acute Alcoholic Hepatitis**
  - Nutrition
  - Genetics
  - Direct Toxic Effect
  - Immunologic

ALD: Pathogenesis

- Morphology of Chronic ALD
  - Macrøvesicular Steatosis
  - Steatohepatitis
  - Hepatocyte ballooning
  - Mallory bodies
  - Perivenular/ pericellular fibrosis

ALD: Diagnosis

- **Acute Alcoholic Hepatitis**
  - Screening for alcohol dependence
  - Laboratory assessment
    - AST > ALT:
      - Ratio > 2.0
    - ↑Total Bilirubin
    - ↑International normalized ratio (INR)
    - ↑White blood cell count (WBC)
    - ↑Mean corpuscular volume (MCV)
  - Physical examination
    - Fever
    - Right upper quadrant tenderness
    - Ascites
ALD: Diagnosis

**Chronic ALD**

- Screening for alcohol dependence
- Laboratory assessment
  - AST > ALT:
    - Ratio > 2.0
    - Respective values < 300 IU/L and almost never > 500 IU/L
  - ↑Gamma-glutamyl transferase (GGT)
  - ↑Mean corpuscular volume (MCV)
  - ↑Carbohydrate-deficient transferrin (CDT)
- Physical examination
  - Signs of chronic liver disease

ALD: Prognosis-Alcoholic Hepatitis

- Maddrey’s discriminant function (MDF)
  - \(4.6 \times [\text{PT} - \text{control PT}] + (\text{serum bilirubin})\)
  - \(\text{MDF} \geq 32:\)
    - 35 - 45% 28 day mortality
  - \(\text{MDF} \geq 32 \text{ with encephalopathy}\)
    - > 50% 28 day mortality
  - \(\text{MDF} \geq 32\)
    - Threshold for initiating therapy

ALD: Prognosis-Alcoholic Hepatitis

- **Model for End Stage Liver Disease Score (MELD)**
  - \[3.8[\text{Ln serum bilirubin (mg/dL)}] + 11.2[\text{Ln INR}] + 9.6[\text{Ln serum creatinine (mg/dL)}] + 6.4\]
  - Comparable to MDF at predicting 30/90 day mortality
    - MELD of 21 equivalent to MDF > 32
  - Better predictor of in-hospital mortality

<table>
<thead>
<tr>
<th>Score</th>
<th>Cut-off</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>+LR</th>
<th>−LR</th>
<th>OR</th>
</tr>
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<tbody>
<tr>
<td>Admission MELD</td>
<td>18</td>
<td>85</td>
<td>84</td>
<td>47</td>
<td>97</td>
<td>5.3</td>
<td>0.2</td>
<td>28.8</td>
</tr>
<tr>
<td>Week 1 MELD</td>
<td>20</td>
<td>91</td>
<td>85</td>
<td>51</td>
<td>98</td>
<td>6.09</td>
<td>0.11</td>
<td>55.7</td>
</tr>
<tr>
<td>ΔWeek 1 MELD</td>
<td>2</td>
<td>80</td>
<td>75</td>
<td>35</td>
<td>96</td>
<td>3.2</td>
<td>0.3</td>
<td>12.0</td>
</tr>
</tbody>
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Srikureja et al. J Hepatol 2005;42:700-6
ALD: Prognosis-Alcoholic Hepatitis

- Lille Model
  - 6 variables (age, renal function, albumin, prothrombin time, bilirubin, and evolution of bilirubin at day 7)
  - Accurate prognostic marker of 6-month survival
  - Score of > 0.45 associated with a 6 month survival of 25%
  - Score utilized to identify patients in whom steroids should be discontinued after 7 days

Louvet et al. Hepatology 2007;45:1348-1354
ALD: Treatment-Alcoholic Hepatitis

- Abstinence
- Nutritional support
  - Degree of malnutrition associated with outcome in acute alcoholic hepatitis
  - In a study of patients treated with steroids or enteral nutrition, mortality was not significantly different between the groups
- Pharmacologic therapy

Cabre et al. Hepatology 2000; 32:36-42
ALD: Treatment-Alcoholic Hepatitis

- **Corticosteroids**
  - Inhibits the action of transcription factors such as activator protein 1 (AP-1) and NF-κB
  - Indicated when discriminant function > 32 or hepatic encephalopathy
  - Course of prednisolone 40 mg daily administered 4 weeks

- **Contraindications**
  - Infection/ sepsis
  - Hepatorenal syndrome
  - Gastrointestinal bleeding
28-DAY SURVIVAL OF PATIENTS WITH DF ≥ 32:
Individual Data Analysis of the Three RCTs

- Prednisolone-randomized patients, n=113
- Placebo-randomized patients, n=102

Mathurin et al. J Hepatol 2002; 36:480-487
ALD: Treatment-Alcoholic Hepatitis

- Pentoxifylline
  - Non-selective phosphodiesterase inhibitor
  - Modulation of transcription of TNF-α gene is thought to be putative mechanism
  - Used as an alternative to steroids when discriminant function > 32
  - 41% reduction in mortality at 28 days
    - Survival 46.1% vs 24.5% in placebo
    - Relative Risk 0.59; 95% CI 0.35 - 0.97
    - Improvement in survival based upon prevention of HRS

Akriviadis et al. Gastro 2000; 119:1637-1648
ALD: Treatment-Alcoholic Hepatitis

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ALD: Treatment-Alcoholic Hepatitis

- **Pentoxifylline vs. Steroids**
  - Three month mortality 35% in pentoxifylline group vs 14.7% in steroid group
  - Increase in HRS incidence in steroid group

- **Pentoxifylline after Steroids**
  - No survival benefit to steroid non-responsive patients

De et al. Word J Gastroenterol 2009;15:11613-1619
ALD: Treatment-Alcoholic Hepatitis

Therapeutic Algorithm for the Management of Alcoholic Hepatitis

1. Establish Disease Severity

   - **Low Risk:**
     - MDF < 32 and 1st week decrease in bilirubin, or MELD < 18 and 1st week decrease in MELD by 2 points
     - Nutritional Assessment / Intervention
     - Supportive Care & Close follow-up

   - **High Risk:**
     - MDF ≥ 32, presence of HE, or MELD ≥ 18
     - Nutritional Assessment / Intervention
     - Consider Liver Biopsy if Diagnosis is uncertain
     - If steroid contraindications or early renal failure
       - Prednisolone
       - Pentoxifylline
ALD: Treatment – Chronic ALD

- Abstinence

- Liver transplantation
  - Contraindicated in acute alcoholic hepatitis
  - 6 months of sobriety

- Baclofen
**ALD: Treatment-Chronic ALD**

**Therapeutic Algorithm for the Long-term Management of ALD**

- Emphasize Abstinence
- Evaluate and treat Co-morbidities

- Need for Rehabilitation +/- drug treatment?

- Determine Stage of Disease

- Fatty Liver
- Alcoholic Hepatitis
- Fibrosis / Cirrhosis

- Nutritional Assessment / Intervention

- Frequent feeding / night-time snacks micronutrient & vitamin replacement

- Consider Clinical Trials

- Manage Complications of Liver Disease
ALD: Take Home Points

- ALD is a spectrum of disease
- Risk of developing ALD is proportion to the amount of alcohol ingested
- Co-factors such as obesity, viral hepatitis and iron overload increase disease progression
- Acute alcoholic hepatitis is associated morbidity and mortality
  - Evaluate prognosis quickly
  - Institute pharmacologic therapy if indicated
- Alcohol cessation is essential to the management of ALD
ALD: Broad Question 1

- 47 year old woman presents with severe alcoholic hepatitis presents to the hospital for management. In which of the following situations is pentyoxifylline more appropriate than glucocorticoids?

- A. Ascites and gastrointestinal bleeding
- B. Mild jaundice and encephalopathy
- C. Severe jaundice, coagulopathy and encephalopathy
- D. Severe jaundice, encephalopathy and HRS
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- A. Tighter blood glucose control
- B. Marijuana smoking cessation
- C. Nutritional and protein supplementation
- D. Weight loss
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- A. Sex
- B. Chronic hepatitis C infection
- C. Diabetes mellitus/insulin resistance
- D. Obesity
- E. Smoking
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