ALCOHOLIC LIVER DISEASE (ALD)

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Objectives

• Spectrum of alcoholic liver disease
  • Focus on Alcoholic Hepatitis (AH)
• Pathophysiology and role of inflammation in AH
• Scoring systems to assess severity
• Treatment algorithm
• Role of corticosteroids and pentoxifylline (PTX)
Epidemiology

- In the U.S., approximately 67% of people drink alcohol
- Majority drink small or moderate amounts
  - No evidence of clinical disease
- Alcohol dependence - drink excessively, develop physical tolerance and withdrawal (3.8%)
- Alcohol abusers and problem drinkers (4.5%)
  - those who engage in harmful use of alcohol, defined by the development of negative social and health consequences of drinking (e.g., repeated absences or poor work performance, recurrent legal problems, neglect of family or children, organ damage, accidental injury, or death)
Epidemiology

- Alcoholic cirrhosis – 8th leading cause of death in US
- 40% of deaths from cirrhosis
- 30% of deaths from HCC
Spectrum of Disease

Risk Factors:
- Female
- Obesity
- Dietary factors
- Polymorphisms
- Drinking pattern
- Smoking
- Etc.

Comorbidity:
- Viral hepatitis
- Hemochromatosis
- HIV

Chronic alcohol abuse 90–95% → Normal liver

Steaosis 20–40% → Fibrosis 8–20% → Cirrhosis 3–10% → HCC

Alcoholic hepatitis
ALD

- Development of liver injury
  - the dose, duration, drinking patterns, sex, ethnicity;
  - associated risk factors including obesity, iron overload, concomitant infection with viral hepatitis, and genetic factors

- The amount of alcohol ingested (independent of the form in which it is ingested) is the most important risk factor for the development of ALD

- Risk of cirrhosis
  - Men >60-80 grams/day
  - Women >20 grams/day

- One drink (12 oz beer, 4 oz wine, 1-1.5 oz spirit) = 10-12 grams
# ALD

<table>
<thead>
<tr>
<th>BEVERAGE</th>
<th>ALCOHOL CONTENT</th>
<th>SERVING SIZE</th>
<th>AMOUNT OF ALCOHOL</th>
<th>Daily Intake Needed to Exceed Threshold for Alcoholic Liver Disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MEN</td>
</tr>
<tr>
<td>Beer</td>
<td>5%</td>
<td>12 oz</td>
<td>13.85 g</td>
<td>3-6 cans</td>
</tr>
<tr>
<td>Wine</td>
<td>12%</td>
<td>4 oz</td>
<td>10.7 g</td>
<td>4-8 glasses</td>
</tr>
<tr>
<td>Fortified wine</td>
<td>20%</td>
<td>4 oz</td>
<td>17.8 g</td>
<td>2-4 glasses</td>
</tr>
<tr>
<td>Hard liquor</td>
<td>40%</td>
<td>1.5 oz</td>
<td>13.4 g</td>
<td>3-6 drinks</td>
</tr>
</tbody>
</table>
Alcohol

- Gut permeability
- Endotoxemia
  - CD14, TLR4
  - Kupffer cell activation
    - TNF-α
  - Adducts
- Acetaldehyde
- CYP2E1
- Oxidant stress
  - PDGF, TGF-β
  - Stellate cell activation
- Malnutrition

- Inflammation
- Hepatocyte injury
- Fibrosis
- Impaired regeneration

Alcoholic hepatitis
Ethanol Metabolism

- Alcohol dehydrogenase (ADH),
- Cytochrome P450 2E1 (CYP2E1),
- Catalase (less important)

- ADH is the primary enzyme system responsible for metabolism of ethanol at low concentrations,
- CYP2E1 contributes at higher concentrations of ethanol and is induced by exposure to ethanol
  - Influences drug metabolism (acetaminophen/isoniazid toxicity)
Liver Injury

- **Acetaldehyde**: highly reactive and potentially toxic compound that is responsible for many of the systemic toxic effects of alcohol, such as nausea, headaches, and flushing
- Increased levels in blood and liver tissue in alcoholic liver disease
Effect of increased acetaldehyde (triggered by heavy drinking): production of protein adducts and immune response leading to liver damage. Activation of stellate cells and fibroblasts, leading to liver fibrosis.
Liver Injury – Oxidant Stress

• Induction of CYP2E1 by alcohol intake stimulates the formation of reactive oxygen species (ROS) during ethanol oxidation
• Overproduction of ROS, or inadequate antioxidant defenses (e.g., low levels of vitamins, selenium, mitochondrial glutathione), can lead to liver injury
• Oxidant stress also leads to stellate cell activation causing steatosis and fibrosis
Liver Injury - Endotoxins

- Bacterial endotoxin is a toxic lipopolysaccharide (LPS) present in the cell wall of some intestinal bacteria.
- When bacteria die, the endotoxin is released and enters the portal and systemic circulation.
- Excess EtOH leads to increased intestinal permeability (disruption of the mucosal barrier) and increased endotoxemia.
- Ultimately leads to upregulation of proinflammatory cytokines (notably TNF α).
Figure 2
Alcoholic Hepatitis

• Acute hepatic inflammation associated with significant morbidity and mortality that occurs in a subset of patients who consume excessive amounts of alcohol
• Clinical syndrome of jaundice and liver failure that generally occurs after decades of heavy alcohol use (mean intake, approximately 100 g per day)
  • Can occur several weeks after alcohol abstinence
  • Usually age 40-60,
  • Female sex an independent risk factor for AH
  • Cardinal sign is rapid onset of jaundice
Alcoholic Hepatitis

- Severe cases, mortality 30-50%
- Spectrum from mild to severe
- Often times on background of cirrhosis
Presentation

- Fever, tachycardia
- Encephalopathy
- Physical Exam: jaundice, enlarged and tender liver, hepatic bruit, parotid enlargement, Dupuytren contracture, spider nevi, ascites
- Labs: ↑AST(2x) > ALT (usually <300 IU/ml), Tbili > 5, Leukocytosis, thrombocytopenia, elevated INR,
  - Hypokalemia, hypomagnesemia, hyperuricemia, elevated ferritin hypertriglyceridemia, low zinc level, hypoalbuminemia, elevated MCV.
  - Elevated Cr (ominous)
**TABLE 84-2  Symptoms and Signs in Hospitalized Patients with Alcoholic Liver Disease**


<table>
<thead>
<tr>
<th>SYMPTOM OR SIGN</th>
<th>Patients Affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MILD DISEASE ($n = 89$)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>84.3</td>
</tr>
<tr>
<td>Jaundice</td>
<td>17.4</td>
</tr>
<tr>
<td>Ascites</td>
<td>30.3</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>27.3</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>18.0</td>
</tr>
<tr>
<td>Fever</td>
<td>18.0</td>
</tr>
</tbody>
</table>
Differential Diagnosis

- Decompensated cirrhosis,
- Acute or chronic viral hepatitis,
- Drug-induced liver injury,
- Fulminant Wilson’s disease,
- Autoimmune liver disease,
- Alpha-1 antitrypsin deficiency,
- Pyogenic hepatic abscess,
- Ascending cholangitis,
- Decompensation associated with hepatocellular carcinoma
Work-up

• Screen for bacterial infections
  • Blood culture, CXR, spontaneous bacterial peritonitis, and urinary tract infection

• Hepatic ultrasonography
  • hepatic abscess, hepatocellular carcinoma, and biliary obstruction, each of which may mimic alcoholic hepatitis.
Assessing Disease Severity

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>Variables</th>
<th>Severe disease</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>mDF\textsuperscript{24}</td>
<td>$4.6 \times \text{(patient's PT-control PT in seconds)} + \text{serum bilirubin}$</td>
<td>32</td>
<td>Simple to use, validated internationally, and guides treatment initiation</td>
<td>Does not guide treatment response</td>
</tr>
<tr>
<td>MELD\textsuperscript{29}</td>
<td>SB, INR, serum creatinine</td>
<td>21</td>
<td>Validated internationally</td>
<td>Variable cutoff across studies</td>
</tr>
<tr>
<td>GAHS\textsuperscript{32}</td>
<td>Age, BUN, WBC, SB, and INR each scored 1-3</td>
<td>9</td>
<td>Simple to use and stratifies DF $&gt;32$ patients for treatment</td>
<td>Not validated worldwide and needs day 7 laboratory values</td>
</tr>
<tr>
<td>ABIC\textsuperscript{33}</td>
<td>Age, SB, INR, serum creatinine</td>
<td>9</td>
<td>Stratifies patients to low, intermediate, and high risk</td>
<td>Only validated in Spain</td>
</tr>
<tr>
<td>Lille\textsuperscript{35}</td>
<td>Age, SB, serum albumin, PT, change in SB at day 7</td>
<td>0.45</td>
<td>Identifies nonresponders to steroids</td>
<td>Complex to use and does not guide treatment initiation</td>
</tr>
<tr>
<td>Web site: <a href="http://gihep.com/calculators/hepatology/lille-model">gihep.com/calculators/hepatology/lille-model</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BUN, blood urea nitrogen; PT, prothrombin time; SB, serum bilirubin.
Maddrey’s Discriminant Function

- DF: 4.6 (PT-control)+TB
- DF >32 indicates a poor prognosis
- Mortality up to 44-62%

Limitations
- Not used to guide therapy. DF < 32 are still at risk for mortality
- Results can vary among laboratory
MELD Score

- MELD Score = $3.8 \times \log_e(\text{bilirubin in mg/dL}) + 11.2 \times \log_e(\text{INR}) + 9.6 \times \log_e(\text{creatinine mg/dL}) + 6.4$

- MELD ≥ 21, estimated 90 day mortality of 20%
- Increase in MELD ≥ 2 in first week has been shown to predict in hospital mortality
Glasgow Alcoholic Hepatitis Score

- age, leukocyte count, serum urea level, PT ratio (ratio of patient-to-control PT), and serum bilirubin level
- A score > 8 predicts poor prognosis
- Score > 9
  - 78% 28-day survival with corticosteroids vs. 52% without
  - 59% vs. 38%, 84 day survival
- Rarely used clinically
ABIC

• most recent scoring system, includes age, serum bilirubin, INR, and serum creatinine.
• It stratifies risk of mortality from AH as low (score < 6.71), intermediate (score:6.71-8.99), and high (score ≥ 9.0), with 90 d mortality at 0%, 30%, and 75%, respectively (P < 0.0001)
• Rarely used clinically & Not validated externally
Treatment - Abstinence

- Current therapy focuses on supportive care & complete EtOH abstinence
- AH may persist for months after cessation, and may worsen during the first weeks of abstinence.
- Inpatient: measures for decompensated cirrhosis in many cases
- Thiamine, MVI, folate, pyridoxine
- Watch for DTs and EtOH withdrawal
Treatment - Nutrition

• Protein calorie malnutrition
• Vitamin deficiencies
• Risk of death correlated with malnutrition

• AASLD: 1.2 – 1.5 g/kg protein and 35-40 kcal/kg total calories
Treatment - Nutrition

- Randomized, controlled clinical trial compared enteral tube feeding (2000 kcal per day) with prednisolone therapy (40 mg of prednisolone per day) for 28 days in 71 patients with severe alcoholic hepatitis.
- The survival rate in the two groups was similar at 28 days
- Overall lower mortality in nutrition group at 1 year (p=ns)
- Nutritional support may be as effective as corticosteroids in some patients
Treatment - Corticosteroids

- Rationale is to decrease the immune and pro-inflammatory cytokine response.
- There have been 13 randomized, controlled trials evaluating corticosteroids in alcoholic hepatitis
  - Inconsistent results with 5 showing reduction in mortality, and the remainder showing no benefit
-significant increase in short-term survival among treated patients compared to control patients: 84.6% versus 65%.
-30% relative risk reduction, and translates into a number needed to treat of 5,
Treatment - Corticosteroids

- Active infections, gastrointestinal bleeding, pancreatitis, renal failure, and non-compliance are excluded, because corticosteroids treatment may adversely affect these conditions
  - Prednisolone 40mg/d for 4 weeks then tapered over 2-4 weeks
  - Active form of prednisone, and not metabolized by liver
- Still, 40% of patients unresponsive
**Lille Score**

- Predicts 6 months survival in patients treated with corticosteroids
- based on pretreatment data plus the response of serum levels of bilirubin to a 7-day course of corticosteroid therapy
- A score < 0.45 predicts 15% mortality, whereas a score ≥0.45 predicts 75% mortality ($P < 0.0001$).
- Alternative therapies should be considered when the score is ≥ 0.45 at day 7 of corticosteroid therapy
Treatment – TNF α inhibitors

- Pentoxifylline (PTX), a nonselective phosphodiesterase inhibitor that inhibits TNF synthesis
- One prospective, randomized, double blind clinical trial in 101 patients who had severe alcoholic hepatitis (mDF score ≥ 32)
  - PTX 400mg PO TID vs placebo
  - In-hospital mortality lower (24.5% vs 46.1%)
Treatment – TNF α inhibitors

- The survival benefit of PTX seemed to result from a significant decrease in the risk of death from hepatorenal syndrome
  - PTX group 6 of 12 deaths (50%)
  - Placebo group 22 of 24 deaths (92%)
- The mechanism by which PTX decreased the development of hepatorenal syndrome is not clearly explained in this study
- Most authorities advocate PTX for patients with contraindications to using corticosteroids
Jaurigue MM et al. Therapy for ALD

<table>
<thead>
<tr>
<th>Ref.</th>
<th>n</th>
<th>Duration of treatment with pentoxifylline 400 mg PO tid</th>
<th>Mortality in placebo</th>
<th>Mortality in pentoxifylline</th>
<th>Relative risk or hazard ratio</th>
<th>95% CI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akriviadis et al(^1), 2000</td>
<td>101</td>
<td>28 d</td>
<td>24/52 (46)</td>
<td>12/49 (24)</td>
<td>RR = 0.59</td>
<td>0.35-0.97</td>
<td>Positive study (P = 0.037)</td>
</tr>
<tr>
<td>Fernández-Rodriguez et al(^1), 2008</td>
<td>24</td>
<td>28 d</td>
<td>Not reported(^1)</td>
<td>Not reported(^1)</td>
<td>HR = 1.46</td>
<td>0.5-4.28</td>
<td>Negative study (P = 0.48)</td>
</tr>
<tr>
<td>Tyagi et al(^2), 2011</td>
<td>61</td>
<td>6 mo</td>
<td>2/31 (6)</td>
<td>1/30 (3)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Negative study (P = 0.15)</td>
</tr>
<tr>
<td>Sidhu et al(^3), 2012</td>
<td>50</td>
<td>28 d</td>
<td>10/25 (40)</td>
<td>5/25 (20)</td>
<td>RR = 0.5</td>
<td>0.19-1.25</td>
<td>Negative study (P = 0.216)</td>
</tr>
</tbody>
</table>

\(^1\)Fernandez-Rodriguez et al\(^1\) reported no statistically significant difference in short-term or long-term survival based on actuarial survival curve; \(^2\)Tyagi et al\(^2\) randomized 70 patients, but only 61 completed follow-up and were included in the analysis. The study did not show a significant difference in mortality, but showed a significant difference in the occurrence of hepatorenal syndrome. PO: Per oral survival; RR: Relative risk; HR: Hazard ratio.
Treatment – TNF α inhibitors

- **Infliximab** (chimeric human/mouse TNF α antibody) infusion
  - Trials with no benefit, one with no survival advantage
  - Another with infliximab + prednisolone vs prednisolone alone stopped prematurely because of higher death rate related to severe infections

- **Etanercept** (p75-soluble TNF receptor:FC fusion protein)
  - RCT, mod-sev AH
  - Compared with placebo, etanercept was associated with significantly higher mortality (mainly due to infections) after six months (58 versus 23 percent)
Management Algorithm

Alcoholic liver disease

- Alcoholic fatty liver (steatosis)
- Alcoholic hepatitis
- Liver cirrhosis

Abstinence
- Psychotherapy (e.g., brief intervention and psychiatric consultation)
- Pharmacological treatment (e.g., baclofen)

Nutritional therapy
- 1.2-1.5 g/kg per day of protein and 35-40 kcal/kg per day (depending on the state of disease)

Alcohol withdrawal syndrome
- Thiamine, benzodiazepines, and other drugs

General management
- Fluids, electrolytes (e.g., magnesium), vitamins, or admission (depending on the state of disease)

Pharmacological treatment according to severity

Management of complications
**Management Algorithm**

**Clinical suspicion of alcoholic hepatitis**
- History of alcohol use
- New-onset jaundice
- Hepatic encephalopathy, ascites, fever
- Enlarged, tender liver
- Elevated aspartate aminotransferase

**Assess severity**
- Maddrey Discriminant Function (MDF) score
- Model for End-stage Liver Disease (MELD) score

- MDF score ≥ 32 or MELD score ≥ 21
- MDF score < 32 or MELD score < 21

**Consider corticosteroids**
- Gastrointestinal bleeding?
- Active infection?
- Hepatorenal syndrome?

- No
- Prednisolone 40 mg daily
  - Assess at 1 week of treatment
    - Lille score ≤ 0.45
      - No
      - Stop prednisolone
        - Consider early liver transplantation in carefully selected patients
        - May enroll in clinical trials of novel agents
      - Yes
        - Continue prednisolone for 3 more weeks
  - Yes
  - Pentoxifylline 400 mg orally three times daily

**Supportive care**
- Management of alcohol withdrawal
- Nutritional supplementation (enteral)

**FIGURE 2. Management algorithm for alcoholic hepatitis.**

ADAPTED FROM THE GUIDELINES OF THE AASLD AND EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER.
- 1103 patients with severe acute alcoholic hepatitis DF >32
- randomized to placebo, Prednisolone, PTX, or combination
- 28 day mortality
- Prednisolone vs. placebo (14% vs 17%, ns)
- PTX vs. placebo (19% vs 17%)
- study limitations
References


O'Shea RS. Alcoholic Liver Disease. AASLD guidelines. *Hepatology* 2010
