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Acute Alcoholic Hepatitis: Utilizing Prognostic Scores for Management

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Objectives

- Review prevalence and burden of alcohol associated liver disease (ALD)
- Discuss the natural history of ALD
- Describe how to diagnose alcoholic hepatitis (AH) and prognostic models
- Review treatment options for AH
What Is a Standard Drink?

12 fl oz of regular beer = 8–9 fl oz of malt liquor (shown in a 12 oz glass) = 5 fl oz of table wine = 1.5 fl oz shot of distilled spirits (gin, rum, tequila, vodka, whiskey, etc.)

Each beverage portrayed above represents one standard drink (or one alcoholic drink equivalent), defined in the United States as any beverage containing 0.6 fl oz or 14 grams of pure alcohol. The percentage of pure alcohol, expressed here as alcohol by volume (%vol), varies within and across beverage types. Although the standard drink amounts are helpful for following health guidelines, they may not reflect customary serving sizes.

Prevalence and Burden of Alcohol in US

88,129 alcohol-attributable deaths (71% males) in 2010

Annual alcohol misuse costs of $249 billion

Rising rates of any drinking, binge drinking, AUD diagnoses

Women
- Age > 65
- Minorities
- Lower socioeconomic status

CDC Alcohol and Public Health: Alcohol-Related Disease Impact (ARDI). Average for United States 2006–2010
Spectrum of ALD

- Injury resulting in hepatic steatosis to advanced forms
  - Alcoholic hepatitis (AH)
  - Alcohol-associated cirrhosis
  - Acute AH
    - Presents as acute on chronic liver failure
    - Often mis-labeled as “acute liver failure”
    - High short-term mortality if untreated

Dependent Factors of Progression

- Continued alcohol use
- Female
- Genetic susceptibility
- Diet
- Co-morbid liver disease
### NIAAA Diagnostic Criteria

<table>
<thead>
<tr>
<th>Definite</th>
<th>Probable</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Diagnosis + Biopsy</td>
<td>Clinical Diagnosis - Confounders</td>
<td>Clinical Diagnosis + Confounders</td>
</tr>
</tbody>
</table>

*Ischemia, DILI, uncertain alcohol use, atypical labs (+autoimmune or viral serologies, AST <50 or >400, AST/ALT <1.5)

Acute AH: Clinical Presentation

Rapid onset of jaundice
- Malaise, tender hepatomegaly
- Hepatic decompensation

Heavy alcohol use
- >6 months, typically more than 5 years
- >3 standard drinks per day in women (40-50 g/day) and >4 in men (50-60 g/day)
- <2 months of abstinence prior to onset of jaundice

Labs
- Serum bilirubin >3 mg/dL (often much higher)
- AST >50 (not greater than 400)
- AST/ALT ratio >1.5

Severe AH
- Maddrey discriminant function >32
Or
- MELD >20

Alcoholic Hepatitis Diagnosis

- Liver biopsy is confirmatory and prognostic
  - Macroversicular steatosis, neutrophilic infiltration, hepatocyte injury (balloon), Mallory-Denk bodies, chicken-wire fibrosis

- Cirrhosis often present (30-40%)

Histologic Scoring System

AHHS provides **prognostic stratification** in biopsy proven AH

**Table 3. AHHS for Prognostic Stratification of AH**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of fibrosis</td>
<td></td>
</tr>
<tr>
<td>No fibrosis or portal fibrosis</td>
<td>0</td>
</tr>
<tr>
<td>Expansive fibrosis</td>
<td>0</td>
</tr>
<tr>
<td>Bridging fibrosis or cirrhosis</td>
<td>+3</td>
</tr>
<tr>
<td>Bilirubinostasis</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Hepatocellular only</td>
<td>0</td>
</tr>
<tr>
<td>Canalicular or ductular</td>
<td>+1</td>
</tr>
<tr>
<td>Canalicular or ductular plus hepatocellular</td>
<td>+2</td>
</tr>
<tr>
<td>PMN infiltration</td>
<td></td>
</tr>
<tr>
<td>No/Mild</td>
<td>+2</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
</tr>
<tr>
<td>Megamitochondria</td>
<td></td>
</tr>
<tr>
<td>No megamitochondria</td>
<td>+2</td>
</tr>
<tr>
<td>Megamitochondria</td>
<td>0</td>
</tr>
</tbody>
</table>

**Figure 3.** Three-month survival probability of patients with AH according to the Histologic AHHS in the (A) study and (B) validation cohorts.

**NOTE.** The AHHS categories are as follows: mild, 0–3; intermediate, 4–5; severe, 6–9. Histologic features included in the AHHS were the product of the multivariate logistic regression analysis (Table 2). Weighting of each histologic feature was based on the odds ratio of the updated model (training plus test set samples). See Supplementary Methods for information on model building.

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Severe AH

- Heavy alcohol use
- Cholestasis
- Coagulopathy (DIC)
- Portal hypertension
- Microbiota translocation (PAMPs, DAMPs, LPS)

Sepsis

- Dysregulated host immune response
- Leukocytosis
- Tachycardia
- Hypotension
- Cardiac dysfunction
- Kidney injury
- Encephalopathy
- Bacterial infection
- Fungal infection
- Respiratory failure/ARDS
- Burns
- Pancreatitis

TNFα
- ROS
- IL-1b
- IL-6
- IL-18

IL-6

ARDS
SIRS on Admission Predicts Mortality

Retrospective study in Spain, biopsy proven (n=162)

Fig 1. Ninety-day mortality according to (A) the presence of MOF, (B) the presence of SIRS, and (C) the SIRS-associated conditions. Michelena et al. *Hepatology*. 2015 Sep; 62(3):762-72.
Prognostic Scores

- Maddrey Discriminant Function (MDF)
- Model for End Stage Liver Disease (MELD) Score
- Lille Model
- Glasgow Alcoholic Hepatitis Score (GAHS)

All deaths had encephalopathy + asterixis on admission

CORTICOSTEROID THERAPY OF ALCOHOLIC HEPATITIS

WILLIS C. MADDOXY, M.D., JOHN K. BOITNOTT, M.D., MARSHALL S. BEDINE, M.D., FREDRICK L. WEBER, JR., M.D., ESTEBAN MEZEN, M.D., AND ROBERT I. WHITE, JR., M.D.

Departments of Medicine, Pathology and Radiology, The Johns Hopkins University School of Medicine, and The Johns Hopkins Hospital, Baltimore, Maryland

Fifty-five patients with alcoholic hepatitis were studied in a 28- to 32-day randomized double blind treatment trial comparing prednisolone (40 mg per day) with placebo therapy. Of 31 placebo-treated patients, 4 died during the study interval and 2 more died within 5 days of study completion. Only 1 of 24 prednisolone-treated patients died during the same interval (Fisher exact test; P = 0.10). Stepwise discriminant analysis of laboratory factors associated with death revealed independently significant associations with prolongation of prothrombin time and height of serum bilirubin at the initiation of the study. When treatment was included as a variable in this discriminant analysis, it was found that corticosteroid therapy significantly decreased mortality (P < 0.05). The corrected wedged hepatic venous pressure decreased to a similar extent in the two groups. These studies suggest that corticosteroid therapy does decrease early mortality in patients with severe alcoholic hepatitis, but has no short term effect on the development of portal hypertension.
Methylprednisolone Therapy in Patients with Severe Alcoholic Hepatitis
A Randomized Multicenter Trial

Robert L. Carithers, Jr., MD; H. Franklin Herlong, MD; Anna Mae Diehl, MD; Ellen W. Shaw, MD; Burton Combes, MD; Harold J. Fallon, MD; and Willis C. Maddrey, MD

Study Objective: To determine the efficacy of a corticosteroid in reducing the short-term mortality of patients with severe alcoholic hepatitis.

Design: Randomized, double-blind, placebo-controlled multicenter trial.

Setting: Four university teaching hospitals.

Patients: We enrolled 66 patients with alcoholic hepatitis and either spontaneous hepatic encephalopathy or a discriminant function value greater than 32, calculated using the formula: 4.6(prothrombin time - control time) + serum bilirubin [in μmol/L]/17.1. Fifty-nine patients (89%) completed the study. Two patients withdrew from the trial. The other 64 patients were hospitalized for the duration of the trial; however, treatment was discontinued in 5 patients because of potential drug toxicity.

Interventions: Patients were randomly assigned to receive either methylprednisolone (32 mg) or placebo within 7 days of admission. Treatment was given for 28 days. The doses were then tapered over 2 weeks and discontinued.

Alcoholic hepatitis is a necrotizing inflammatory lesion that in its severe form is associated with high mortality and often leads to cirrhosis. There is no widely accepted, effective treatment for patients with alcoholic hepatitis. Abstinence from alcohol and management of associated alcohol-related problems are the most important elements of therapy. Several therapeutic agents including propylthiouracil, anabolic steroids, and corticosteroids have been evaluated in controlled trials, but none has been conclusively proved to be effective in decreasing mortality during the acute illness or decreasing the rate of progression of alcoholic hepatitis to cirrhosis (1,2).

The rationale for the use of corticosteroids in acute alcoholic hepatitis is based in part on evidence that immunologic factors may be important in the development of this complication of alcoholism. Corticosteroid therapy has been extensively studied in patients with alcoholic hepatitis. In three controlled clinical trials (3-5), the mortality of patients with severe alcoholic hepatitis and spontaneous hepatic encephalopathy...

Figure 1A. Cumulative survival in methylprednisolone and placebo recipients ($P = 0.0049$). Figure 1B. Cumulative survival in methylprednisolone and placebo recipients with hepatic encephalopathy at study entry ($P = 0.025$).

MELD Score: Predicts 30 & 90-Day Mortality

MELD = 0.957* ln(sCr) + 0.378*ln(TBILI) + 1.120*ln(INR) + 0.643*10

Fig. 1. Prediction of 90-day mortality in patients with AH based on MELD. The curve demonstrates probability of 90-day mortality in AH for given MELD (black line) with confidence intervals (gray shading). The probability of 90-day mortality in AH was calibrated using the data from logistic regression (P = e^{(-4.3 + 0.16 × MELD)} / [1 + e^{(-4.3 + 0.16 × MELD)}]). MELD, model for end-stage liver disease.


Fig. 2. Comparison of MELD and DF in predicting mortality in AH. Receiver operating characteristic curves and c-statistics were generated to compare MELD (black curve) and DF (gray curve) in predicting mortality rate in AH. Respective c-statistics and confidence intervals are indicated. MELD and DF were comparable regarding prediction of (A) 30-day mortality and (B) 90-day mortality (P > .05). MELD, model for end-stage liver disease; DF, Maddrey discriminant function; c-statistic, concordance statistic.
Glasgow Score

Multiple centers in UK
Test cohort: n=241
Clinical diagnosis validation: n=195
33% biopsy proven

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;50</td>
<td>&gt;50</td>
<td></td>
</tr>
<tr>
<td>WBC (10^9/L)</td>
<td>&lt;15</td>
<td>&gt;15</td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>&lt;42</td>
<td>&gt;42</td>
<td></td>
</tr>
<tr>
<td>PT/PT control</td>
<td>&lt;1.5</td>
<td>1.5-2.0</td>
<td>&gt;2.0</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;7.3</td>
<td>7.3-14.5</td>
<td>&gt;14.5</td>
</tr>
</tbody>
</table>

Table 7. Sensitivities (Sen), specificities (Spec), positive predictive values (PPV), negative predictive values (NPV), and overall accuracies (Acc) of the Glasgow alcoholic hepatitis score (GAHS), using validation dataset, relative to the modified discriminant function

<table>
<thead>
<tr>
<th></th>
<th>Day 28 outcome (%) (Sen/Spec; PPV/NPV; Acc)</th>
<th>Day 84 outcome (%) (Sen/Spec; PPV/NPV; Acc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 score</td>
<td>GAHS ≤9 mDF ≥32</td>
<td>GAHS ≤9 MELD ≥11</td>
</tr>
<tr>
<td></td>
<td>81/61; 47/89; 67</td>
<td>75/68; 45/88; 70</td>
</tr>
<tr>
<td></td>
<td>96/27; 36/93; 48</td>
<td>92/29; 31/91; 46</td>
</tr>
<tr>
<td>Day 7 score</td>
<td>GAHS ≤9 mDF ≥32</td>
<td>GAHS ≤9 MELD ≥11</td>
</tr>
<tr>
<td></td>
<td>93/68; 51/97; 75</td>
<td>86/83; 54/96; 83</td>
</tr>
<tr>
<td></td>
<td>90/45; 36/93; 56</td>
<td>100/28; 23/100; 41</td>
</tr>
</tbody>
</table>

Table 8. Sensitivities (Sen), specificities (Spec), positive predictive values (PPV), negative predictive values (NPV), and overall accuracies (Acc) of the Glasgow alcoholic hepatitis score (GAHS), using validation dataset, relative to the MELD score

<table>
<thead>
<tr>
<th></th>
<th>Day 28 outcome (%) (Sen/Spec; PPV/NPV; Acc)</th>
<th>Day 84 outcome (%) (Sen/Spec; PPV/NPV; Acc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 score</td>
<td>GAHS ≤9 MELD ≥11</td>
<td>GAHS ≤9 MELD ≥11</td>
</tr>
<tr>
<td></td>
<td>75/68; 45/88; 70</td>
<td>69/67; 45/85; 67</td>
</tr>
<tr>
<td></td>
<td>92/29; 31/91; 46</td>
<td>92/29; 31/91; 46</td>
</tr>
<tr>
<td>Day 7 score</td>
<td>GAHS ≤9 MELD ≥11</td>
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<td>100/28; 23/100; 41</td>
<td>100/28; 23/100; 41</td>
</tr>
</tbody>
</table>

Lille Model: Assessing Treatment Response

Fig. 1. Receiver operating characteristic curve for survival at 6 months in the exploratory cohort using the Lille model.

Fig. 4. Kaplan-Meier survival analysis according to 0.45 cutoff of the Lille model.

Age, bilirubin day 0, creatinine day 0, albumin day 0, INR day 0, bilirubin day 7

N-Acetylcysteine Reduces Infection and HRS

- NAC potent antioxidant that reduces oxidative stress, improves liver blood flow, reduces lactate levels
- Multi-center (France), randomized trial (n=180, unblinded) of IV NAC for 5 days + prednisolone vs. prednisolone alone
- 1 month mortality: 8% in NAC+Pred (7/85) and 24% in pred alone (21/89) p=0.006 CI 0.14-0.76
- NAC group had less infections (12 vs 37), HRS (10 vs 22)
- Safe, no study-related SAEs

Management of AH

Clinical diagnosis of AH
- Recent onset of jaundice
- History of heavy alcohol consumption

Consider liver biopsy if diagnosis is uncertain (DILI...)

Perform systematic extensive screening for infection

Assessment of disease severity
(prognostic scores)

mDF ≥32 or GAHS ≥9
Prednisolone 40 mg/day ± NAC
Assess treatment response at day 7 (Lille score)

Lille score <0.45
Continue treatment for 28 days

Lille score ≥0.45
Stop treatment* and assessment for early liver transplantation in highly selected patients

MELD >20

mDF <32 and GAHS <9
No specific therapy

2-week taper

Treatment of alcohol dependence

Steroids Do Not Improve Mortality

STOP-AH Trial

Multi-center, randomized, double-blinded, placebo-controlled trial

Clinical AH diagnosis, MDF >32 (biopsy not necessary)

Primary outcome: 28-day all-cause mortality

Secondary outcome: death or LT at 90 days and 1 year, infections

Criticisms: no biopsy, lower death rates in placebo arm than previous studies

Strengths: large sample size, trial design

Summary

• Alcohol misuse is an epidemic in the US with rising mortality

• Acute AH is a serious form of acute decompensation of ALD with high short-term mortality

• Prognostic scores should be used to determine prognosis in AH

• Corticosteroid therapy in AH is well studied but benefit in severe AH is minimal
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