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Acute Alcoholic Hepatitis: Utilizing Prognostic Scores for Management

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Disclosures

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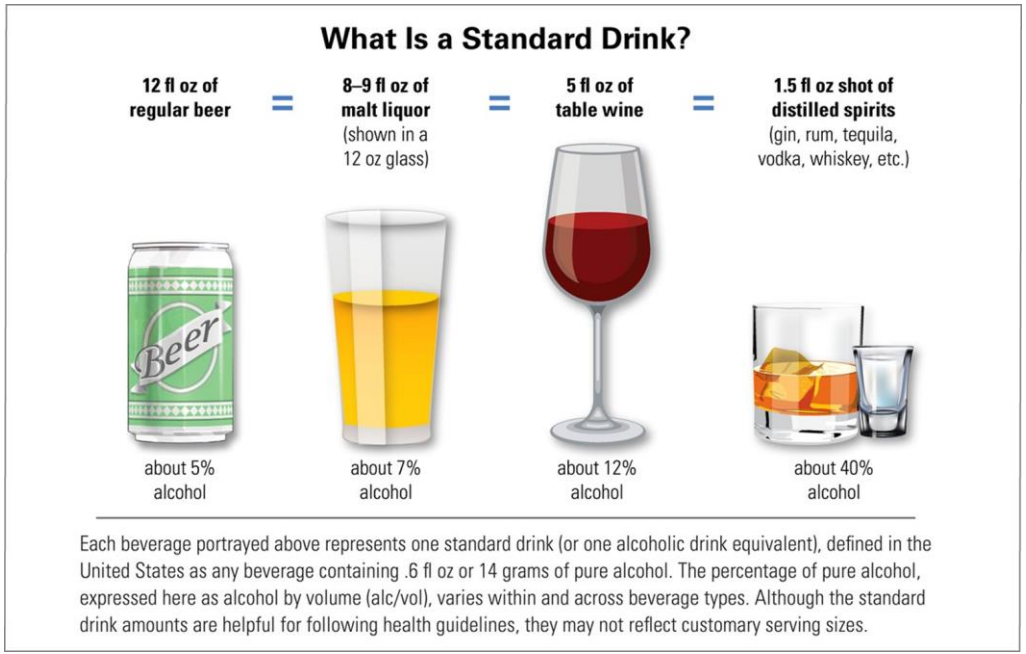
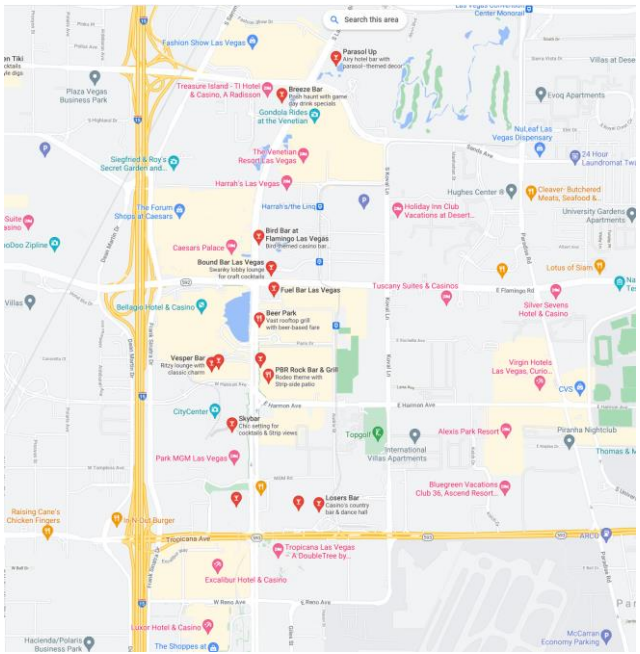
No financial relationships to disclose.

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

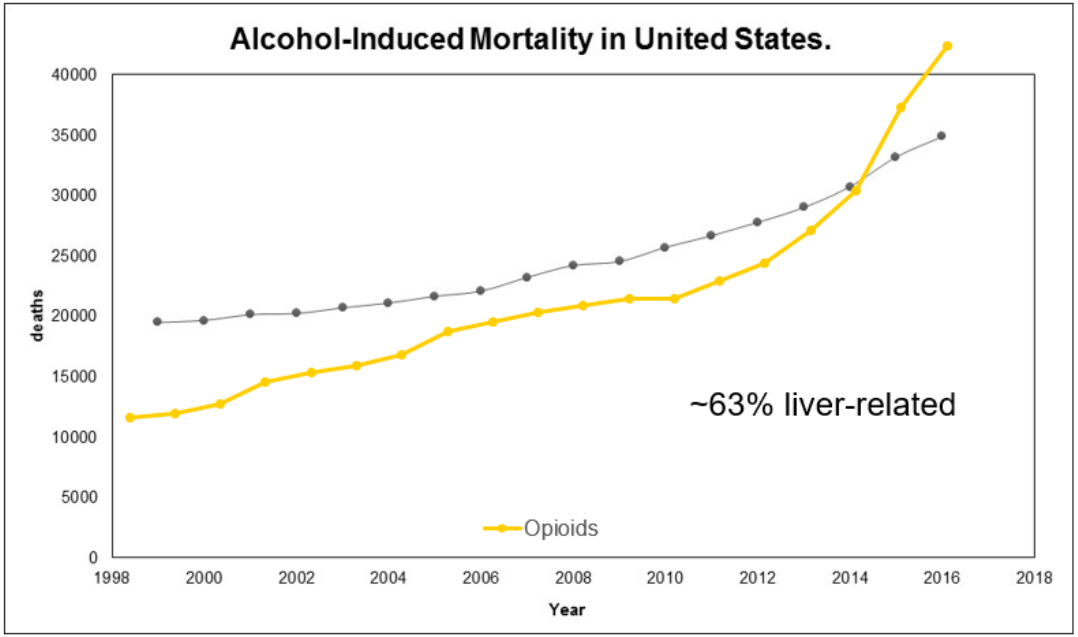
What Is a Standard Drink?





https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink; Google Maps: 8/01/2021.

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

https://wonder.cdc.gov/mcd-icd10.html.
CDC Alcohol and Public Health: Alcohol-Related Disease Impact (ARDI). Average for United States 2006–2010
Alcohol-Attributable Deaths Due to Excessive Alcohol Use. Sacks et al. 2010. *American Journal of Preventive Medicine.* 49(5):e73–e79, 2015; Grant BF et al. *JAMA Psychiatry.* 2017;74(9):911–923.

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

Mathurin & Lucey et al. *Journal of Hepatology.* 2012. 56: S39-S45.

Dependent Factors of Progression

- Continued alcohol use
- Female
- Genetic susceptibility
- Diet
- Co-morbid liver disease

Lucey, Michael Ronan, et al. *Hepatology*. 2020. Vol 71, No.1.

NIAAA Diagnostic Criteria

Definite	Probable	Possible
Clinical Diagnosis + Biopsy	Clinical Diagnosis - Confounders	Clinical Diagnosis + Confounders

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

Crabb et al. *Gastroenterology*. 2016 Apr; 150(4): 785–790.

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

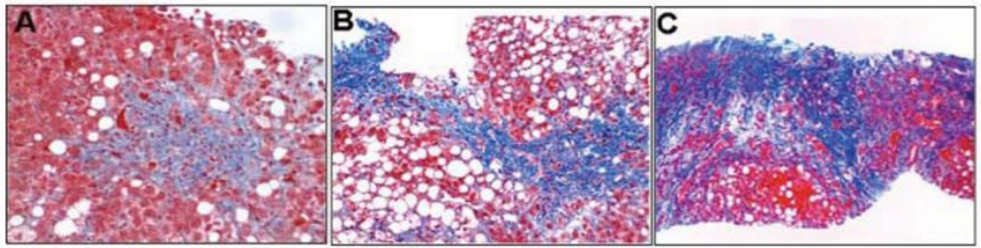
Or

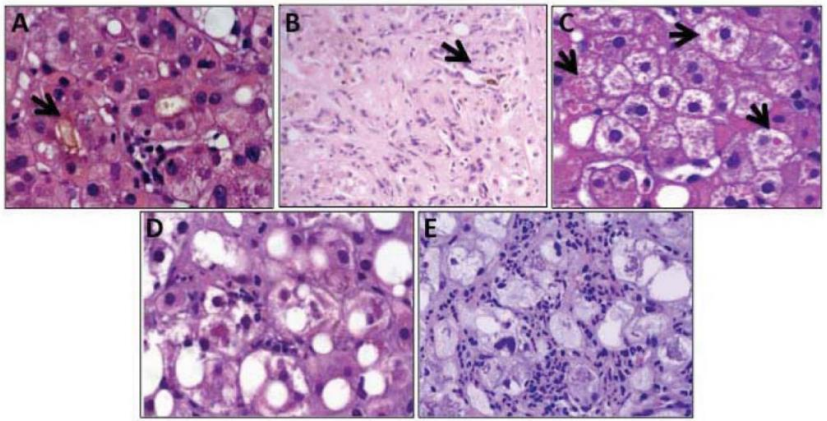
- MELD >20

Crabb et al. *Gastroenterology*. 2016 Apr; 150(4): 785–790.

Alcoholic Hepatitis Diagnosis

- Liver biopsy is confirmatory and prognostic
  - Macrovesicular steatosis, neutrophilic infiltration, hepatocyte injury (balloon), Mallory-Denk bodies, chicken-wire fibrosis
- Cirrhosis often present (30-40%)





Altamirano et al. *Gastroenterology.* 2014;146:1231–1239.

Histologic Scoring System

AHHS provides prognostic stratification in biopsy proven AH

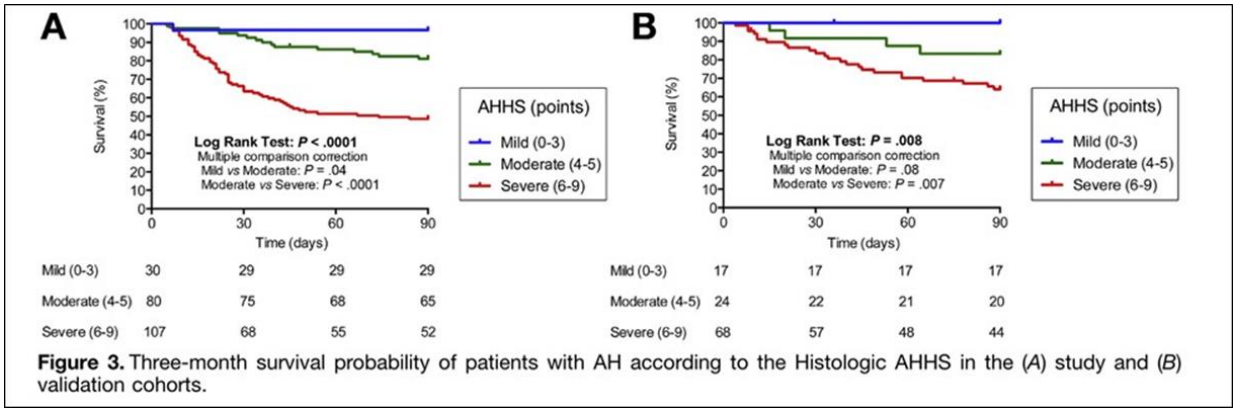


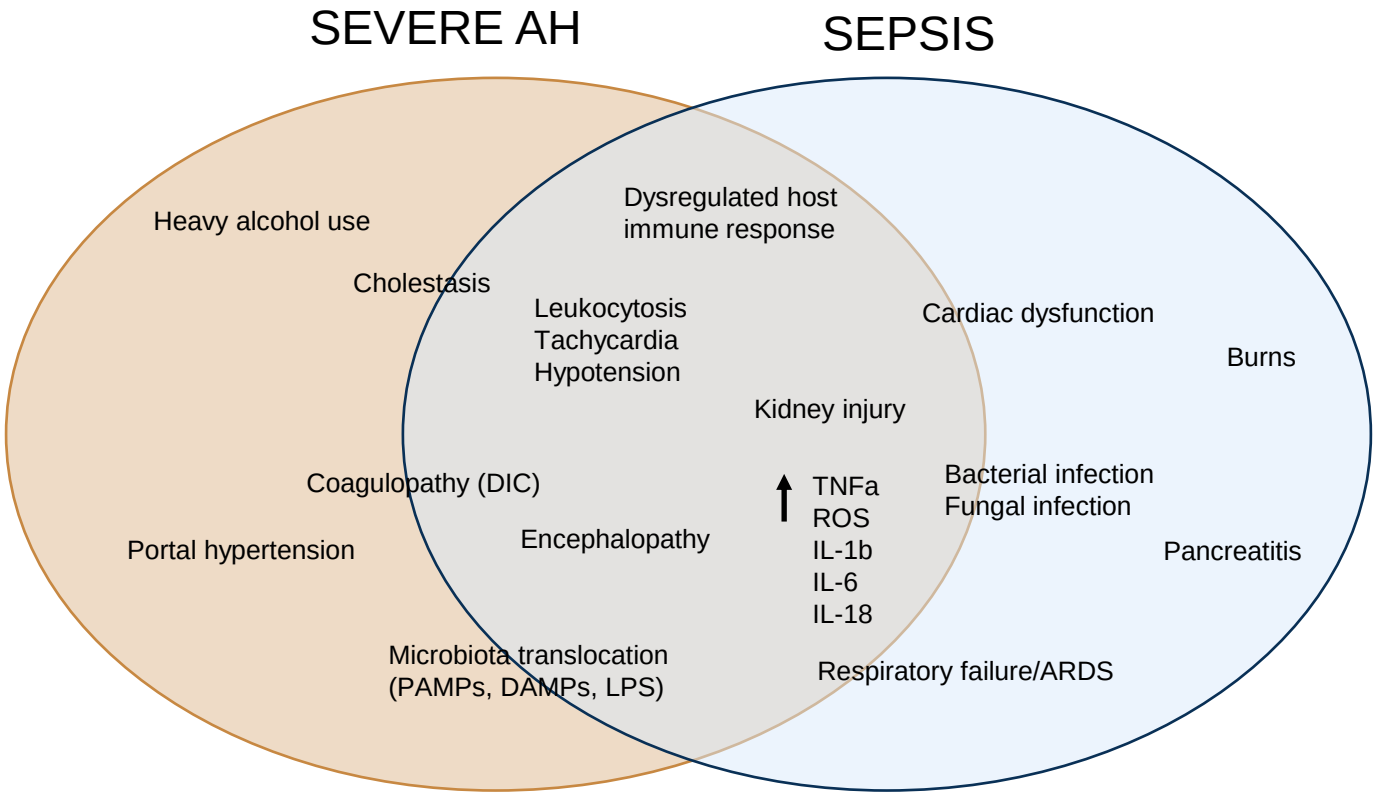
Figure 3. Three-month survival probability of patients with AH according to the Histologic AHHS in the (*A*) study and (*B*) validation cohorts.

Table 3. AHHS for Prognostic Stratification of AH

	Points
Stage of fibrosis	
No fibrosis or portal fibrosis	0
Expansive fibrosis	0
Bridging fibrosis or cirrhosis	+3
Bilirubinostasis	
No	0
Hepatocellular only	0
Canalicular or ductular	+1
Canalicular or ductular plus hepatocellular	+2
PMN infiltration	
No/Mild	+2
Severe	0
Megamitochondria	
No megamitochondria	+2
Megamitochondria	0

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.

Altamirano et al. *Gastroenterology.* 2014;146:1231–1239.


SEVERE AH
SEPSIS
Heavy alcohol use
Cholestasis
Dysregulated host immune response
Leukocytosis
Tachycardia
Hypotension
Cardiac dysfunction
Burns
Kidney injury
Coagulopathy (DIC)
TNFa
ROS
IL-1b
IL-6
IL-18
Bacterial infection
Fungal infection
Portal hypertension
Encephalopathy
Pancreatitis
Microbiota translocation
(PAMPs, DAMPs, LPS)
Respiratory failure/ARDS

SIRS on Admission Predicts Mortality

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

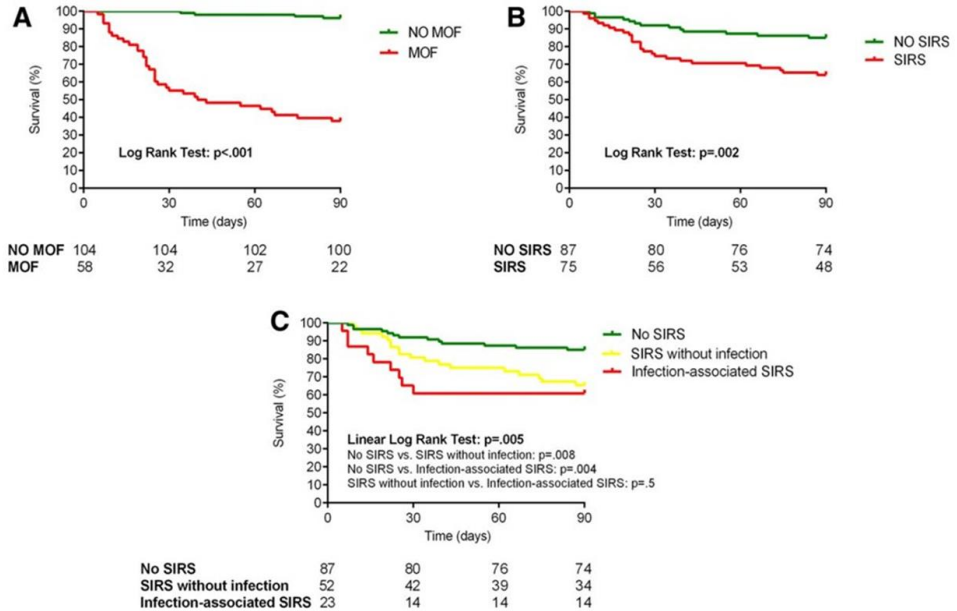


Fig 1. Ninety-day mortality according to (A) the presence of MOF, (B) the presence of SIRS, and (C) the SIRS-associated conditions. Michelena et al. *Hepatology*. 2015 Sep; 62(3):762-72.

Prognostic Scores

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

Mitchell et al. Clin *Gastroenterol Hepatol*. 2017 January ; 15(1): 5–12.

0016-5085/78/7502-0193$02.00/0
GASTROENTEROLOGY 75:193–199, 1978

All deaths had encephalopathy
+ asterixis on admission

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CORTICOSTEROID THERAPY OF ALCOHOLIC HEPATITIS

WILLIS C. MADDREY, M.D., JOHN K. BOITNOTT, M.D., MARSHALL S. BEDINE, M.D., FREDRICK L. WEBER, JR., M.D., ESTEBAN MEZEY, 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.

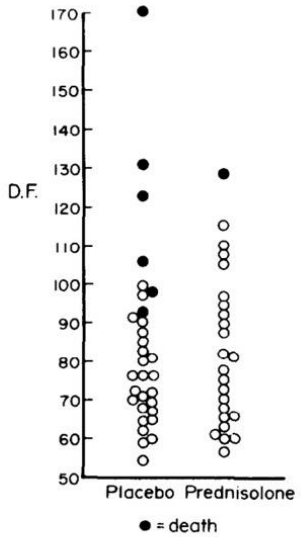


FIG. 7. Discriminant function (*D.F.*) (4.6 × prothrombin time sec) + serum bilirubin (mg per dl) at onset in two treatment groups.

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 alco-

Discriminant Function = 4.6 * (Pt's PT - Control PT) + serum bilirubin

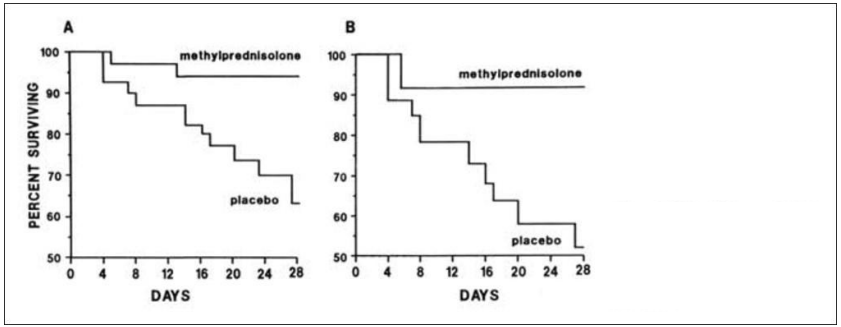


Figure 1A. Cumulative survival in methylprednisolone and placebo recipients (P = 0.0049). Figure 1B. Cumulative survival in methylprednisolone and placebo recipients with hepatic encephalopathy at study entry (P = 0.025).

Carithers et al. *Ann Intern Med*. 1989 May 1;110(9):685-90.

MELD Score: Predicts 30 & 90-Day Mortality

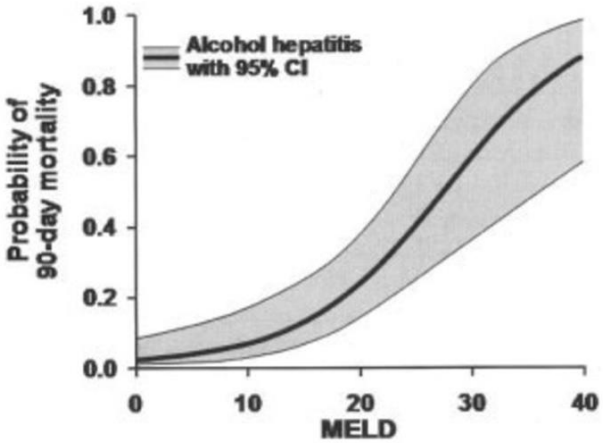


Fig. 1. Prediction of 90-day mortality in patients with AH based on MELD. The curve demonstrates probability of 90-day mortality in AH for given MELD (**black line**) with confidence intervals (**gray shading**). The probability of 90-day mortality in AH was calibrated using the data from logistic regression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

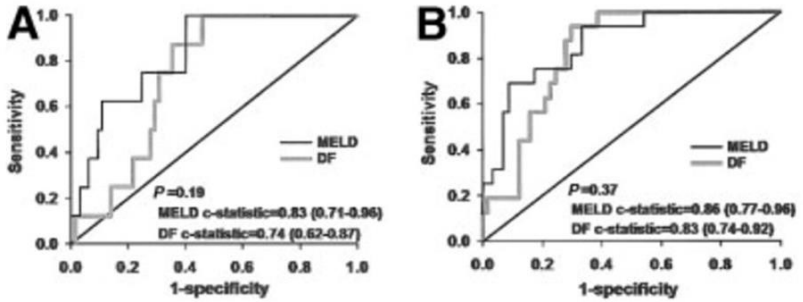


Fig. 2. Comparison of MELD and DF in predicting mortality in AH. Receiver operating characteristic curves and c-statistics were generated to compare MELD (**black curve**) and DF (**gray curve**) in predicting mortality rate in AH. Respective c-statistics and confidence intervals are indicated. MELD 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.

$$\text{MELD} = 0.957 * \ln(\text{sCr}) + 0.378 * \ln(\text{TBILI}) + 1.120 * \ln(\text{INR}) + 0.643 * 10$$

Dunn et al. *Hepatology*. 2005 Feb;41(2):353-8.

Glasgow Score

	1	2	3
Age	<50	>50	
WBC (10^9/L)	<15	>15	
BUN (mg/dL)	<42	>42	
PT/PT control	<1.5	1.5-2.0	>2.0
Bilirubin (mg/dL)	<7.3	7.3-14.5	>14.5

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

	Day 28 outcome (%) (Sen/Spec; PPV/NPV; Acc)	Day 84 outcome (%) (Sen/Spec; PPV/NPV; Acc)
Day 1 score		
GAHS </≥ 9	81/61; 47/89; **67**	78/66; 61/81; **71**
mDF </≥ 32	96/27; 36/93; **48**	95/31; 48/90; **57**
Day 7 score		
GAHS </≥ 9	93/68; 51/97; **75**	82/71; 60/88; **75**
mDF </≥ 32	90/45; 36/93; **56**	88/48; 88/62; **62**

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

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

	Day 28 outcome (%) (Sen/Spec; PPV/NPV; Acc)	Day 84 outcome (%) (Sen/Spec; PPV/NPV; Acc)
Day 1 score		
GAHS </≥ 9	75/68; 45/88; **70**	69/67; 45/85; **67**
MELD </≥ 11	92/29; 31/91; **46**	92/29; 31/91; **46**
Day 7 score		
GAHS </≥ 9	86/83; 54/96; **83**	86/83; 54/96; **83**
MELD </≥ 11	100/28; 23/100; **41**	100/28; 23/100; **41**

Forrest et al. *Gut*. 2005 Aug; 54(8): 1174-79.

Lille Model: Assessing Treatment Response

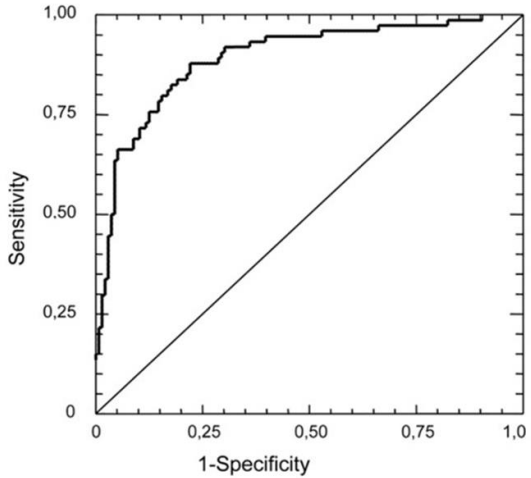


Fig. 1. Receiver operating characteristic curve for survival at 6 months in the exploratory cohort using the Lille model.

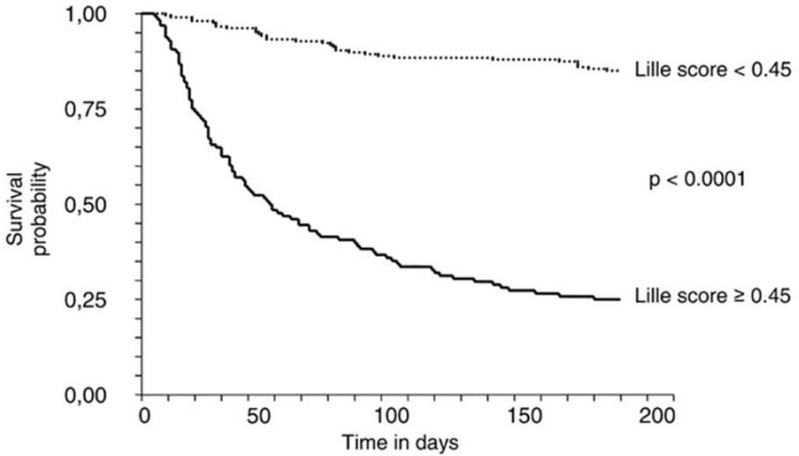


Fig. 4. Kaplan-Meier survival analysis according to 0.45 cutoff of the Lille model.

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

Louvet et al. *Hepatology*. 2007 Jun;45(6):1348-54; http://www.lillemodel.com/score.asp.

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

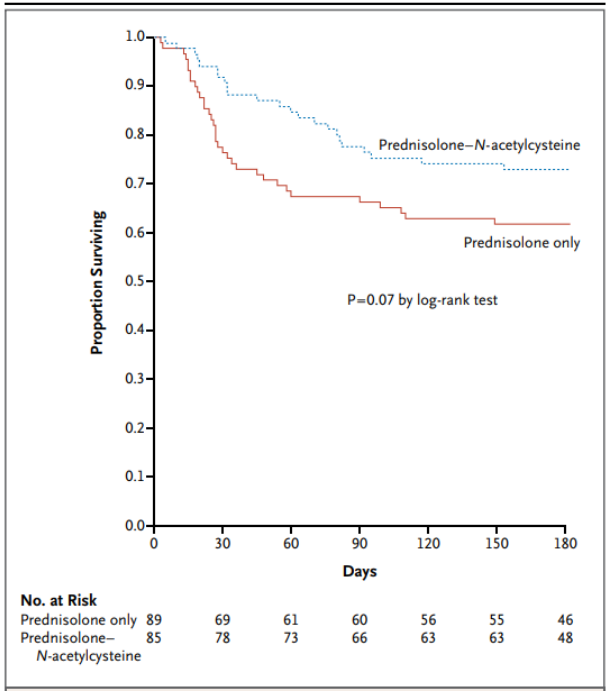
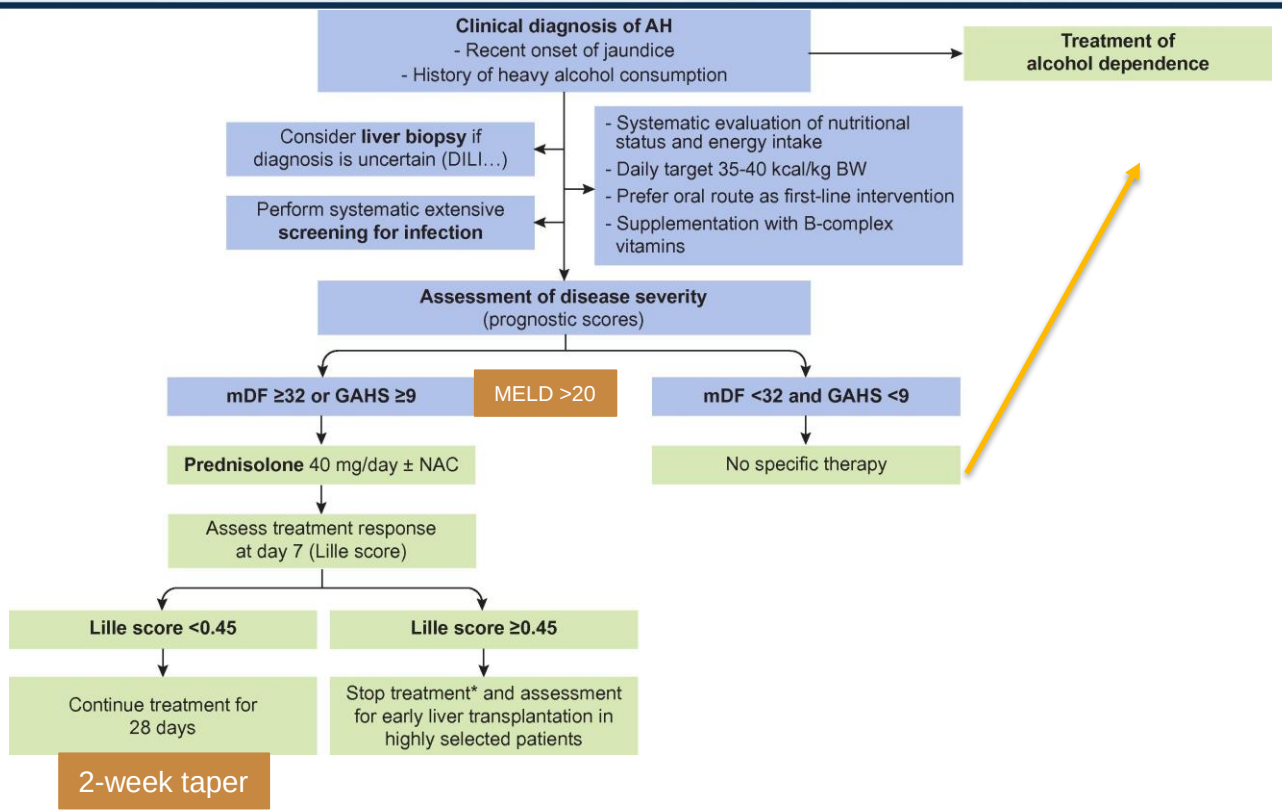


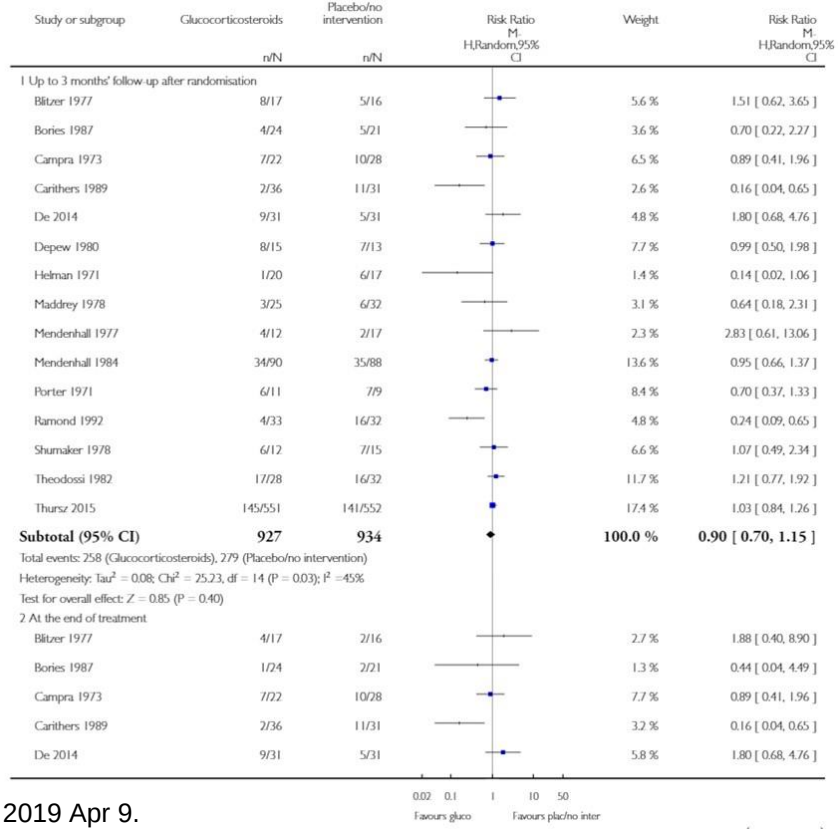
Figure 2. Kaplan-Meier Curves for 6-Month Survival in the Intention-to-Treat Population. Nguyen-Khac et al. *N Engl J Med*. 2011 Nov 10;365(19):1781-9.

Management of AH



Journal of Hepatology. 2018 vol. 69.154–181.

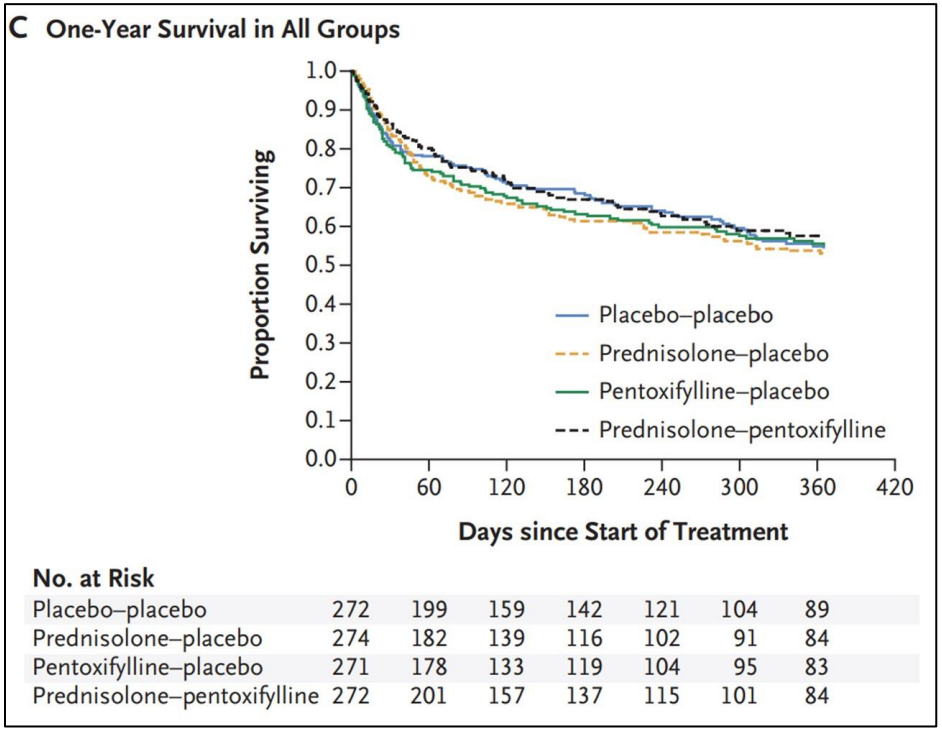
Steroids Do Not Improve Mortality



Study or subgroup	Glucocorticosteroids n/N	Placebo/no intervention n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Up to 3 months' follow-up after randomisation					
Blitzer 1977	8/17	5/16		5.6 %	1.51 [0.62, 3.65]
Bories 1987	4/24	5/21		3.6 %	0.70 [0.22, 2.27]
Campra 1973	7/22	10/28		6.5 %	0.89 [0.41, 1.96]
Carithers 1989	2/36	11/31		2.6 %	0.16 [0.04, 0.65]
De 2014	9/31	5/31		4.8 %	1.80 [0.68, 4.76]
Depew 1980	8/15	7/13		7.7 %	0.99 [0.50, 1.98]
Helman 1971	1/20	6/17		1.4 %	0.14 [0.02, 1.06]
Maddrey 1978	3/25	6/32		3.1 %	0.64 [0.18, 2.31]
Mendenhall 1977	4/12	2/17		2.3 %	2.83 [0.61, 13.06]
Mendenhall 1984	34/90	35/88		13.6 %	0.95 [0.66, 1.37]
Porter 1971	6/11	7/9		8.4 %	0.70 [0.37, 1.33]
Ramond 1992	4/33	16/32		4.8 %	0.24 [0.09, 0.65]
Shumaker 1978	6/12	7/15		6.6 %	1.07 [0.49, 2.34]
Theodossi 1982	17/28	16/32		11.7 %	1.21 [0.77, 1.92]
Thursz 2015	145/551	141/552		17.4 %	1.03 [0.84, 1.26]
Subtotal (95% CI)	**927**	**934**		**100.0 %**	**0.90 [0.70, 1.15]**
Total events: 258 (Glucocorticosteroids), 279 (Placebo/no intervention)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 25.23$, df = 14 (P = 0.03); $I^2 = 45\%$					
Test for overall effect: Z = 0.85 (P = 0.40)					
2 At the end of treatment					
Blitzer 1977	4/17	2/16		2.7 %	1.88 [0.40, 8.90]
Bories 1987	1/24	2/21		1.3 %	0.44 [0.04, 4.49]
Campra 1973	7/22	10/28		7.7 %	0.89 [0.41, 1.96]
Carithers 1989	2/36	11/31		3.2 %	0.16 [0.04, 0.65]
De 2014	9/31	5/31		5.8 %	1.80 [0.68, 4.76]

Pavlov et al. *Cochrane Database Syst Rev.* 2019 Apr 9.

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

Thursz et al. *N Engl J Med*. 2015 Jul 16;373(3):282-3.

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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