

Alcohol-associated Liver Disease

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Terminology

- The term ‘alcoholic’ is stigmatizing
 - Undermines patient dignity and self-esteem

Previous term	Current term	Abbreviation
Alcoholic	Alcohol use disorder	AUD
Alcoholic liver disease	Alcohol-associated or alcohol-related liver disease	ALD
Alcoholic cirrhosis	Cirrhosis due to ALD	ALD cirrhosis
Alcoholic steatohepatitis*	Steatohepatitis due to ALD	ASH
Alcoholic fibrosis	Fibrosis due to ALD	ALD fibrosis
Alcoholic hepatitis	Alcoholic hepatitis†	AH

- Which of the following statements about the so-called '6-month abstinence rule' is accurate in relation to selection for and outcome of liver transplantation for patients with liver failure and alcohol use disorder in the US?

Answers:

- A. It is required by UNOS, and is a good predictor of alcohol use in the first 12 months after LT
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- C. It is required by UNOS, but is a weak predictor of alcohol use in the first 12 months after LT
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- **Stem:** A 23 years-old college student presents to student care with abdominal pain following a party in the house she shares with several other students. The family medicine resident working in the student care clinic orders urine ethyl glucuronide among many tests. The patient's serum gamma glutamyl transferase (GGT) is 5 times the upper limit of normal, and urine ethyl glucuronide is positive. Two days later the patient returns to student care. She reports that her pain is better, and that several of her housemates also had a GI upset. The medical resident asks the attending physician in the clinic for help on how to advise this patient. If you were the staff physician in the student clinic, which of the following approaches would you direct the medical resident to take with this patient?

Answers:

- Tell the patient that there are some more tests that you would like to order, and get a whole blood phosphatidylethanol (PEth)
- Tell the patient that the results show that she had had too much to drink, and to be more careful in the future
- Tell the patient that the results show that she had had too much to drink and she should see her family physician
- Administer the AUDIT screen, and based on the result advise changes in drinking behavior and refer for treatment of alcohol-use disorder.

Alcohol-Associated Liver Disease Practice *Guidance* 2019
Authors: David W. Crabb, Gene Y. Im, Gyongyi Szabo, Jessica L Mellinger, Michael R. Lucey

Nomenclature of Alcohol-Use Disorders

- **DSM-V refers to ‘alcohol-use disorders’ which replaces: alcoholism, alcohol abuse, alcohol dependency**
- **Craving: an internal prompt to use an addictive substance**
- **A slip is a temporary return to drinking, which is recognized by the patient as potentially harmful, and leads to renewed efforts towards abstinence.**
- **A relapse suggests a more sustained resumption of drinking. These events are sometimes characterized as ‘harmful’, ‘abusive’ or ‘addictive drinking’**
- **Loss of control: inability to stop at one drink**

Worldwide, ethanol accounts for...

- **3.3 million, or 5.9% of all global deaths, 5.1% of the global burden of disease**
- **493,000 deaths annually are attributable to ALD**
 - 47.9% of all cirrhotic deaths
 - ALD-associated liver cancer: 80,600 deaths

Based on WHO Report:

Rehm J et al. Global burden of alcoholic liver diseases. J. Hepatol 2013; 59: 160-168

Genetics of Lipid Droplet-associated Liver Fibrosis

- **Polymorphisms**
- **PNPLA3A (rs738409:G):** **Predisposes to steatosis; fibrosis; HCC**
- **TM6SF2 (rs58542926) :** **Predisposes to steatosis; fibrosis; HCC**
- **MBOAT7 (rs641738):** **Predisposes to steatosis; fibrosis**
- **HSD17B13 (rs72613567):** **Predisposes to steatosis; protects versus fibrosis, HCC**

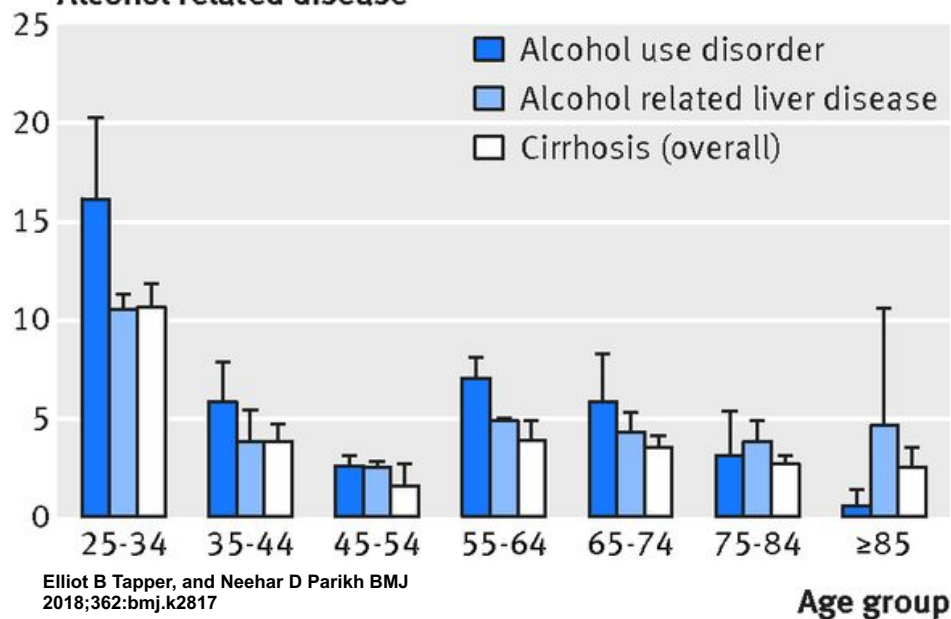
Alcohol the Health of the US

- 136 million Americans ages 18 and older drink alcohol, 17 million with alcohol abuse or dependence
- Excessive alcohol consumption:
 - 3rd leading cause of preventable death
 - kills 75,000 per year
 - reducing years lived by 30 years on average
- Alcoholic cirrhosis: 35,000 deaths per year
- Alcoholic liver disease is the 2nd most common indication for liver transplantation

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Trends in Mortality Due to Liver Disease by age group in the USA, 2009-16.
Alcohol related disease



Recognizing AUD in Clinical Practice

- Alcohol use disorder is often a hidden on account of stigma and shame. The key is recognizing excessive drinking and this starts with taking a drinking history.
- Most patients with ALD have had several previous contacts with medical professionals, at which AUD was not recognized.
- SBIRT
 - Screening
 - Brief Intervention
 - Referral for Treatment

Screening for AUD

- Here is a simple '3 question set' (called AUDIT C, when it is combined with a points score) to help you enquire about frequency and quantity of consumption and frequency of binge drinking:
- During the last 12 months:
 - how often did you usually have any kind of drink containing alcohol?
 - how many alcoholic drinks did you have on a typical day when you drank alcohol?
 - how often did you have ≥ 5 drinks of alcohol of any kind on one occasion?

2019 AASLD Guidance on Alcohol-related Liver Disease

(Crabb DW et al, Hepatology, 2019)

- **Gastroenterology/hepatology outpatient clinics, emergency departments, and inpatient admissions should be routinely screened for alcohol use using validated questionnaires.**
- **Brief intervention, pharmacotherapy, and referral to treatment should be offered to patients engaged in hazardous drinking (AUDIT-C ≥ 4 , AUDIT >8 , binge drinkers)**
- **Alcohol biomarkers can be used to aid in diagnosis and support recovery. Urine and hair ethyl glucuronide, urine ethyl sulfate, and phosphatidylethanol are not affected by liver disease, and therefore preferable.**

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2019 AASLD Guidance on ALD

(Crabb DW et al, Hepatology, 2019)

- **Referral to AUD treatment professionals is recommended for patients with ALD in order to ensure access to the full range of AUD treatment options.**
- **Multidisciplinary, integrated management of ALD and AUD is recommended and improves rates of alcohol abstinence amongst ALD patients.**
- **Based on limited data, the use of acamprosate or baclofen can be considered for the treatment of AUD in patients with ALD.**

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Factors Affecting the Risk of AALD

Enhancing the risk

- **Dose above minimal threshold:**
- **Pattern of consumption: daily drinking; drinking while fasting**
- **Smoking cigarettes**
- **Gender/Genetics:**
- **Increased body mass**
- **Co-morbid conditions: chronic viral hepatitis, hemochromatosis**

Ameliorating the risk

Genetics

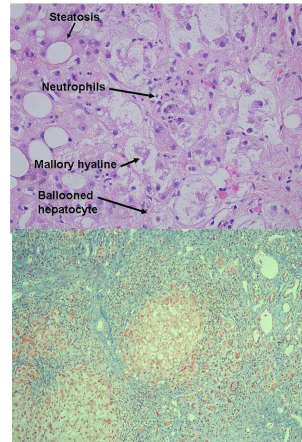
- **Coffee consumption**

Equivocal data

- **Type of alcohol consumed**
- **Influence of binge drinking**

Alcoholic Liver Disease

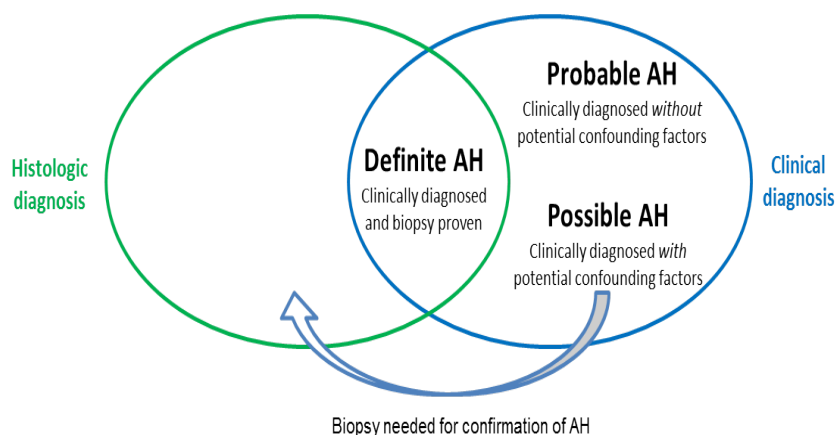
- Fatty liver
 - Hepatitis: ASH
 - Cirrhosis
- All three can coexist in the same biopsy



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2019 AASLD Guidance on Alcohol-related Liver Disease (Crabb DW et al, Hepatology, 2019)



2019 AASLD Guidance Statement: The diagnosis of AH (definite, probable, possible) should be made using the published consensus criteria

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Prognostic Scores for AAH

- **ABIC**
- **Maddrey Discriminant Function**
 - predicts 30-day mortality of AH
 - treatment of AH with corticosteroids
- **MELD**
- **Glasgow AH score**
 - Identify AH too ill for corticosteroids
- **Lille Score**
 - Response of AH at day 7
 - Identify AH too ill to continue corticosteroids

2019 AASLD Guidance on Alcohol-related Liver Disease (Crabb DW et al, Hepatology, 2019)

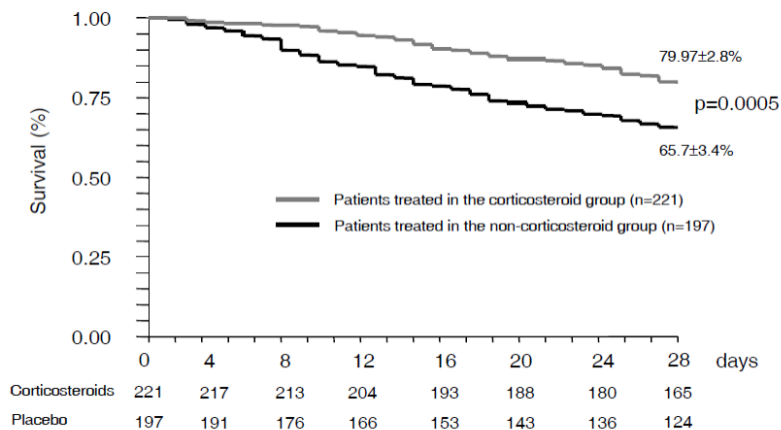
- **Lab-based prognostic scores should be used to determine prognosis in alcoholic hepatitis.**
- **The Maddrey Discriminant Function (≥ 32) should be used to assess the need for treatment with corticosteroids or other medical therapies.**
- **A MELD score >20 also should prompt consideration of steroid treatment.**
- **Abstinence from alcohol should be promoted to improve long-term prognosis in AH.**

All treatment of alcoholic liver disease begins with abstaining from drinking

Pharmacotherapy to Control Drinking

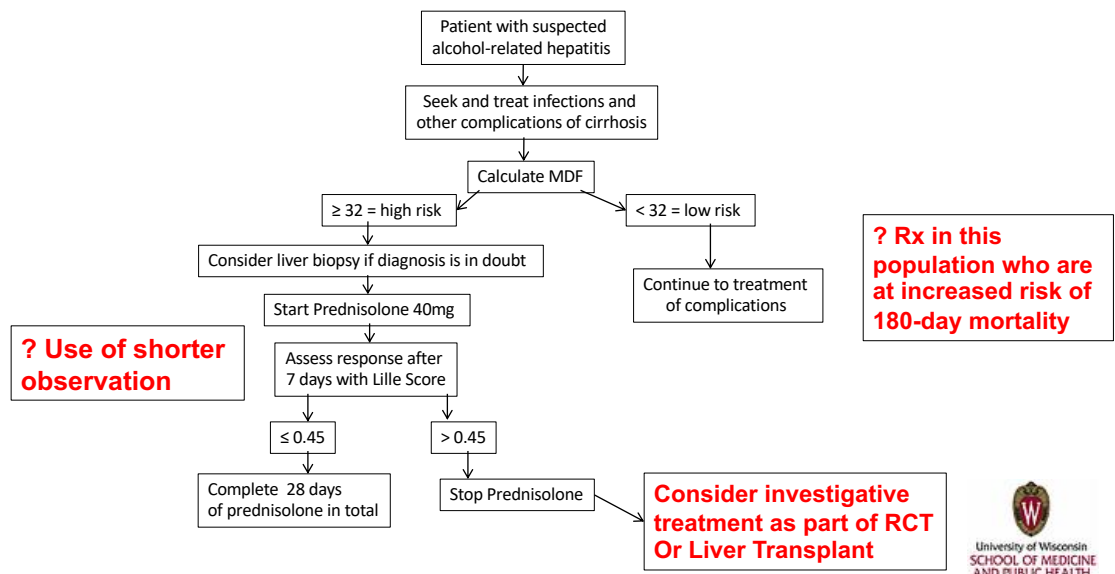
- **Disulfiram:** potentially toxic in cirrhosis
- **Naltrexone:** restores 'control'; black box warning
- **Acamprosate:** not studied in cirrhosis, doubts about efficacy
- **Topiramate:** not studied in cirrhosis
- **Baclofen:** goal to reduce craving. Improved abstinence in 1 RCT in cirrhosis

Meta Analysis of Individual Data from 4 RCTs of Corticosteroids in Patients with Severe Alcoholic Hepatitis. *Mathurin et al. GUT 2010*



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Treatment Algorithm for Severe Alcoholic Hepatitis



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STOPAH Mortality at 28 Days

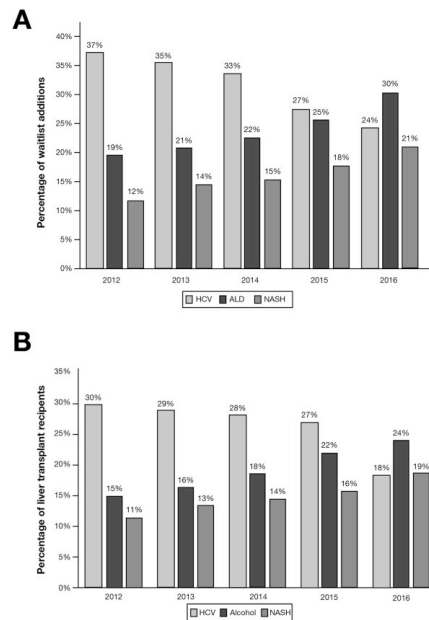
- 1103 adult subjects 66% male; 95% white
- Clinical diagnosis of alcoholic hepatitis; Maddrey DF = 32.
- Mean daily alcohol: females: 142 to 157 g in women; males; 195 to 210 g.
- Mean interval to treatment : 6 days

Treatment Group	Patients (n = 1103)	Percent
Pred/pentoxi	274	13.5
Pred/placebo	277	14.3
Pentoxi/placebo	276	19.4
Double placebo	276	16.7

>28 days, neither drug was associated with a survival benefit

Factor	Odds Ratio	P Value
Prednisolone	0.609	.015
PT ratio	1.380	.002
Bilirubin	1.002	.003
Age	1.050	<.001
WCC	1.030	.037
Urea	1.065	.037
Creatinine	1.564	.028
HE	3.073	<.001

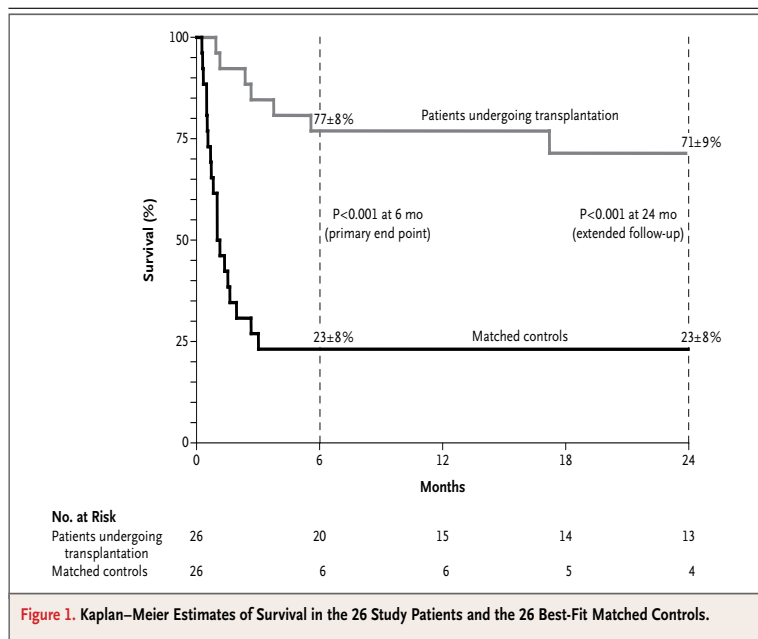
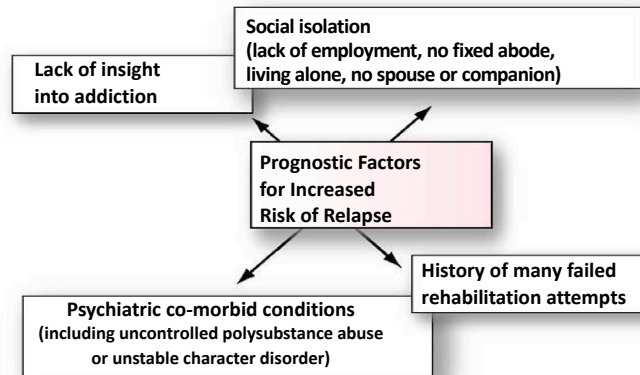
Alcoholic Liver Disease Replaces Hepatitis C Virus Infection as the Leading Indication for Liver Transplantation in the United States
Cholankeril G, Ahmed A. Clinical Gastroenterology and Hepatology, 2018, 16, 1356-1358,



The 6-Month Abstinence Rule

- The utility of the six-month rule as a predictor of long-term sobriety is controversial
- ALD patients with less than 6 months abstinence are more likely to drink after transplantation
- admits patients who will relapse after transplantation and excludes patients who will not drink after transplantation
- It is not required by UNOS, nor advocated in the 2019 AASLD guidance
- Assessment by an addiction specialist that combines sobriety with assessment of other indicators of relapse risk is advisable.

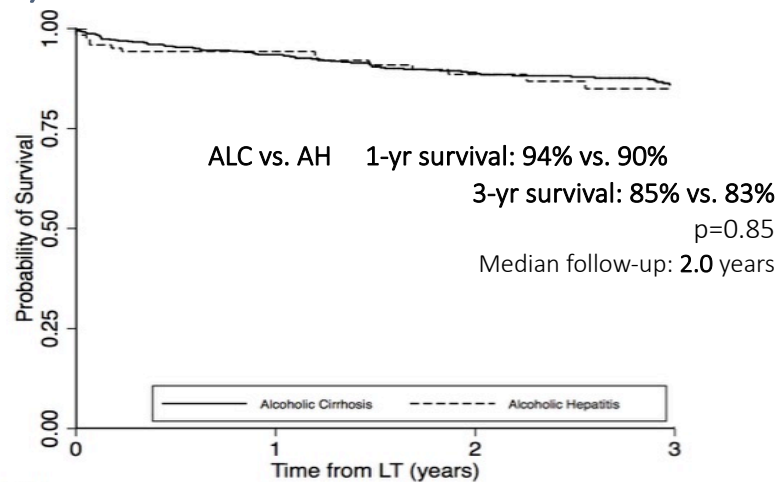
Alcoholic Relapse



Patient Survival in Alcoholic Cirrhosis (ALC) vs. Alcoholic Hepatitis (AH)

Limited to 12
ACCELERATE-AH sites

N=147 AH
N=699 ALC



Number at risk
Alcoholic Cirrhosis 699
Alcoholic Hepatitis 123

Time from LT (years)
1 2 3
564 366 251
93 58 38

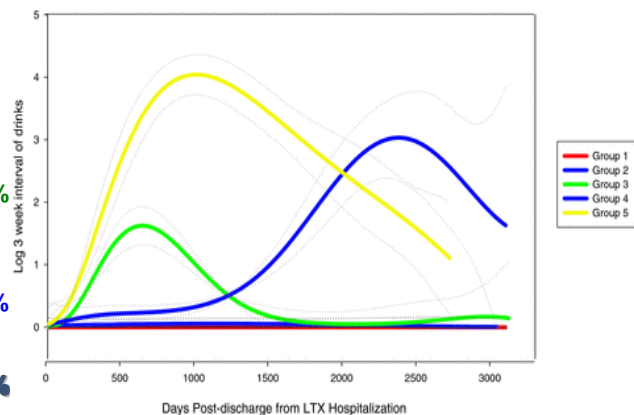


Trajectories of Alcohol Use after Liver Transplantation for Alcoholic Cirrhosis

DiMartini et al, ATJ 2010

Pattern of use % cohort

None 51.3%
Occasional, low level 28.6%
Early onset, accelerates and declines 6.4%
Delayed increase to moderate use 7.9%
Early onset, increasing heavy use 5.8%



2019 AASLD Guidance on Alcohol-related Liver Disease (Crabb DW et al, Hepatology, 2019)

- **Patients with decompensated alcohol-associated cirrhosis, Child-Pugh class C or MELD-Na ≥ 21 should be referred and considered for LT**
- **Candidate selection should not be solely based on a fixed interval of abstinence**
- **LT may be considered in carefully selected patients with favorable psychosocial profiles in severe AH not responding to medical management**

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Take Home Points

- **Patients with ALD have two diseases**
- **The nomenclature of alcohol use has changed.**
- **SBIRT, AUDIT-C**
- **All interventions for ALD start with alcohol cessation**
- **Corticosteroids may provide benefit to some with severe AH, but not all patients respond**
- **Many new treatments, but designing RCTs is difficult.**
- **LT is established for life-limiting ALD, including some patients with short intervals of sobriety.**