Evaluation and Management of Alcohol-associated Liver Disease

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Disclosures

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• Consulting: TransMedics, Pfizer, Spruce
Outline

• Healthcare impact
• What is harmful/hazardous alcohol use?
• Spectrum & presentation
• Factors affecting risk
• Diagnosis
• Prognosis
• Management
Increasing alcohol-related mortality and liver transplant listing for ALD in US

Karaye IM et al. JAMA Open 2023
Increased rates of liver transplant listing for severe alcohol-associated hepatitis (AH) in the US

Cotter TG. Am J Transplantation 2021

Bittermann T et al. JAMA Open 2021
Rethinking harmful/hazardous alcohol use
Women are at higher risk for alcohol associated liver disease at lower levels of consumption than men.

Becker U et al. Hepatology 1996
Alcohol synergy with obesity increases the risk of fatty liver 
Metabolic dysfunction and alcohol-associated liver disease (MetALD)

What's hazardous/harmful alcohol use?

1 drink for women
2 drinks for men

One standard drink:
14 g of alcohol


GBD 2016 Alcohol Collaborators. Lancet 2018
Spectrum of ALD

Gomez-Medina C et al. Clinical and Molecular Hepatology 2023
ALD is usually detected late compared to other liver diseases

Shan ND et al. Clin Gastroenterol Hepatol. 2019

Aim for early screening in practice to detect early
Factors affecting ALD risk
PNPLA3 and coffee influence risk and severity of AH

**PNPLA3 RS738409**

<table>
<thead>
<tr>
<th></th>
<th>PNPLA3 CC</th>
<th>PNPLA3 GC/GG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>25%</td>
<td>52%</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>33%</td>
<td>54%</td>
</tr>
</tbody>
</table>

**P = 0.003**

** PNPLA3 CC PNPLA3 GC/GG **

<table>
<thead>
<tr>
<th></th>
<th>No coffee use</th>
<th>Coffee use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>33%</td>
<td>52%</td>
</tr>
<tr>
<td>PNPLA3 CC</td>
<td>25%</td>
<td>33%</td>
</tr>
<tr>
<td>PNPLA3 GC/GG</td>
<td>74%</td>
<td>52%</td>
</tr>
</tbody>
</table>

**P = 0.02**

Beaudoin JJ. Alcohol Clin Exp Res 2021

Samala N et al. GastroHep 2019
Metabolic and genetic risk factors are associated with severity of ALD

325 Danish patients with biopsy-proven ALD

**Steatosis**
- Active drinking
- BMI>30
- TG ≥1.7 mmol/L
- PNPLA3
- >20 years alcohol
- MBOAT7
- TM6SF2
- HSD17B13
- Age above 50
- Female sex

**Fibrosis**
- HOMA-IR >2.5
- LDL <2.6 mmol/L
- TM6SF2
- Age above 50
- PNPLA3
- >20 years alcohol

Israelsen M et al. Clin Gastroenterol Hepatol. 2022
Synergy of alcohol and the metabolic syndrome increases the risk of incident severe liver disease*, even with MAC

6732 Finnish persons, no baseline liver disease. * Hospitalization, liver cancer, or death. Mean follow-up 11.4 years

Aberg F et al. Hepatology 2018
ALD-Diagnosis
Is steatostic (fatty) liver disease alcohol-related?

- Thorough alcohol use history
- Laboratory parameters (MCV, AST/ALT, GGT)
- Mayo’s ALD/NAFLD Index (ANI)*

* Dunn W et al. Gastroenterology 2006
Biomarkers of alcohol use

<table>
<thead>
<tr>
<th>Test</th>
<th>Source</th>
<th>Detection Time</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDT/%CDT</td>
<td>Blood</td>
<td>2-3 weeks</td>
<td>21%-50%</td>
<td>50%-100%</td>
<td>64%-100%</td>
<td>86%-93%</td>
</tr>
<tr>
<td>EtG</td>
<td>Urine</td>
<td>3-7 days</td>
<td>76%-89%</td>
<td>93%-99%</td>
<td>81%-90%</td>
<td>91%-99%</td>
</tr>
<tr>
<td>EtG</td>
<td>Hair</td>
<td>Months</td>
<td>81%-100%</td>
<td>83%-98%</td>
<td>68%-95%</td>
<td>86%-100%</td>
</tr>
<tr>
<td>EtS</td>
<td>Urine</td>
<td>3 days</td>
<td>82%</td>
<td>86%</td>
<td>70%</td>
<td>93%</td>
</tr>
<tr>
<td>PEth</td>
<td>Blood</td>
<td>2-4 weeks</td>
<td>97%-100%</td>
<td>66%-96%</td>
<td>85%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Modified from Crabb DW et al. Hepatology 2020
Non-invasive tests are useful for evaluation of significant fibrosis, inflammation and steatosis in asymptomatic ALD.

Significant fibrosis ≥F2

≥ mild inflammation

Mild steatosis ≥S1

Niu L et al. Nat Med 2022
Clinical diagnosis of AH: NIAAA definition

- Onset of jaundice within prior 8 weeks
- Ongoing consumption of >40 (female) or 60 (male) g alcohol/day for > 6 months, with <60 days of abstinence before the onset of jaundice
- AST >50, AST/ALT >1.5, and both values <400 IU/L Serum total bilirubin >3.0 mg/dl

ALD- Prognosis
Major determinants of survival in patients with AH

Severity

- Survival Probability
- Log Rank < 0.001

Relapse to alcohol use

- Survival (%)
- Log Rank p < 0.001
- Number At Risk:
  - No Relapse: 456, 293, 209, 142, 98, 72, 47, 31, 18, 11, 8, 1, 0, 0
  - Relapse: 214, 138, 99, 69, 48, 31, 17, 9, 4, 1, 0, 0

Lille response to steroids*

- Survival probability
- Lille score < 0.45
- Lille score ≥ 0.45

*Survival for US Lille non-responders is different

Gaurnizo-Ortiz M et al. Liver Int. 2024
Patidar KR et al. Hepatol Commun. 2023
Louvet A et al. Hepatology 2007
Causes of death in patients with AH

Gaurnizo-Ortiz M et al. Liver Int. 2024
Predicting AH severity and prognosis: MELD superior to MDF and other scores

Mortality at 28 days & 90 days

Morales-Arráez D et al. Am J Gastroenterol. 2022
ALD-Management Rx
Integrated management of ALD and AUD

- Screen for AUD at every encounter
- Offer brief motivational interviewing
- Manage cirrhosis complications similar to other liver diseases
- Consider AUD Rx to prevent alcohol relapse for those with AUD
- Involve AUD specialists in care of those with moderate-severe AUD
- Refer eligible candidates to LT
  Those with < 6 months of abstinence can be evaluated for early LT if at low risk for relapse and otherwise meet LT eligibility criteria

Based on ACG guidance. Jophlin LL et al. Am J Gastroenterol 2024
Steroids with Lille stopping rule result in superior survival to anakinra+zinc in patients with severe AH

Overall 90-day survival

Transplant free 90-day survival

Gawrieh S et al. In press, J Hepatol 2024
Steroids with Lille stopping rule result in lower rates of AKI to anakinra+zinc in patients with severe AH

Gawrieh S et al. In press, J Hepatol 2024
Who are the patients with severe AH most likely to respond to corticosteroids?

MELD 25-39

Baseline Neutrophil-to-Lymphocyte ratio 5-8

K18 fragments (M30) >5kIU/L

Validation in US studies is necessary

Arab JP et al. J Hepatol 2020

Forrest EW et al. Aliment Pharmacol Ther 2019

Atkinson SR et al. Am J Gastroenterol 2020
Infections and antibiotics use in patients with severe AH

- Infections are a major cause of death
- Screen for infection on admission
- Treat proven infections
- Controlled infections are generally not a contraindication to steroids use

Prophylactic antibiotics are not recommended

- No effect on mortality
- Lower infection rates
- No effect of HRS

Louvet A et al. JAMA 2023
Effective nutrition is essential part of AH management

- Screen for adequacy of protein-calorie oral intake on admission
- Offer oral nutritional supplements when needed
- Place NJ for enteral feed early when needed

Moreno C et al. Gastroenterology 2016
Liver transplantation for alcohol-associated hepatitis in the US

Profound geographic variation in frequency

Excellent patients’ outcomes

Cotter TG. Am J Transplantation 2021
# Relapse prevention therapy in patients with ALD & AUD

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Metabolism (M) and Excretion (E)</th>
<th>Mechanism of Action</th>
<th>ALD Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Naltrexone</strong></td>
<td>50 mg/d orally or 380 mg monthly sq</td>
<td>M: HepaticE: Mostly renal, fecal 2%-3%</td>
<td>Opioid receptor antagonist</td>
<td>1. Not studied in ALD 2. Hepatotoxicity concerns</td>
</tr>
<tr>
<td><strong>Acamprosate</strong></td>
<td>666 mg tid</td>
<td>M: NoneE: Renal</td>
<td>NMDA receptor antagonist</td>
<td>1. Not studied in ALD 2. No reported instances of DILI</td>
</tr>
<tr>
<td><strong>Gabapentin</strong></td>
<td>600-1,800 mg/d</td>
<td>M: NoneE: Renal 75%, fecal 25%</td>
<td>Modulates GABA activity at presynaptic calcium channels</td>
<td>1. Not studied in ALD 2. Monitor closely for renal dysfunction and worsening mental status/sedation</td>
</tr>
<tr>
<td><strong>Baclofen</strong></td>
<td>30-60 mg/d</td>
<td>M: Hepatic, limitedE: Renal</td>
<td>GABA-B receptor agonist</td>
<td>Single RCT in patients with ALD showed benefit</td>
</tr>
<tr>
<td><strong>Topiramate</strong></td>
<td>75-400 mg/d</td>
<td>M: Not extensively metabolizedE: Renal</td>
<td>GABA action augmentation, glutamate antagonism</td>
<td>Not studied in ALD</td>
</tr>
</tbody>
</table>

*Disulfiram is not included on this list because it is not recommended for use in patients with ALD.*

Crabb DW et al. Hepatology 2020
Approach to AUD therapy in patients presenting with ALD to Indiana University

Approach:
- Patient agrees to AUD treatment in outpatient setting and less than 1 year sobriety
- Screen for high-risk features with HRAR score and AUDIT-C
  - HRAR score < 4:
    - Seek behavioral therapy:
      - 12 Step Program
      - Smart Recovery
      - Celebrate Recovery
  - HRAR score > 4 AUDIT-C > 8:
    - Refer to chemical dependency program
- Pharmacotherapy:
  - Compensated disease: Naltrexone 50mg QD
  - Decompenesed disease: Acamprosate 666 mg TID if GFR >30
  - Decompenesed & GFR < 30, Baclofen 10 mg TID
- Labs 2 - 4 weeks, then every 3 months including PEth and ethylgluc
- Follow up in 3 months to determine if effective

HRAR: High-Risk Alcohol Relapse score
Take-home messages

- ALD is a leading and rising cause of liver disease in the US
- Screen early for AUD
- Integrate AUD management with ALD management
- Offer steroids with Lille stopping rule for those with severe AH
- Nutritional support is essential part of ALD management
- Referral for early (< 6 months of abstinence) LT evaluation
  - Select patients with severe AH not responding to steroids
  - Patient with decompensated ALD-related cirrhosis and/or early HCC
Thank you