An Integral Approach to Treat Alcohol-Induced Liver Disease

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NATURAL HISTORY OF ALD

- Normal liver
- Steatosis: 80-90%
- Fibrosis: 20-40%
- Cirrhosis: 8-20%
- HCC: 3-10%
- Alcoholic steatohepatitis (Alc Hep)
- Decompensation (+ infections): 20-40%
COLD WEATHER AND SUNLIGHT HOURS AND ALCOHOL ABUSE

VENTURA-COTS M ET AL, HEPATOLOGY 2018
The Scientific Reason We Want To Drink More Alcohol When It Gets Colder And Darker

A new study from the US has found a direct link between decreasing temperatures and hours of sunlight with alcohol consumption.

A bottle of Merlot shared over a takeaway with a friend. A round of pale ales in the pub on a Saturday night. Several rum and cokes at a work Christmas party.
Prevalence of liver fibrosis in 1,358 subjects in France:
7.5%

Underlying cause of liver fibrosis:

- **Fatty liver**: 88%
- **NAFLD**: 60%
- **ALD...**: 1/3 have both
- **PBC-PSC**: 1%
- **HBV**: 5%
- **HCV**: 6%
- **DAFLD/DASH**

Roulot et al, Gut 2010
Worldwide Lack of Early Referral of Patients with Alcoholic Liver Disease: Results of the Global Alcoholic Liver Disease Survey (GLADIS)

Neil D. Shah¹, Meritxell Ventura Cots¹, Nerma Zahiragic², Mohamed Yacoub¹⁰, Andrew Wandera³, Julio Vorobioff¹³, Edna Solange Dos Santos Traquino¹¹, Prem Harichander Thurairajah⁶, Sanjin Sprečić⁷, Enrique R Arus Soler¹¹, Nadja Sivač⁵, Way Siow⁸, Christoph Scheurich⁴, Federico Sáez-Royuela¹², Agustina Rodí³¹³, Daniela Reis¹⁶, Suzane Ono¹², Mariana Nabeshima¹², Mercy Karoney³, Marlen Castellanos Fernández¹¹, Alberto Farias¹², Caridad Ruens Domech¹¹, Pedro Marques Costa¹⁶, Marina Biryukova⁶, Ahmad Alfadhli¹³, Fatma Some³, Johannes Kluwe⁴, Won Kim⁴, Vasily Isakov⁶, Azra Husić-Selimovic⁷, John Hsiang⁸, Jacob George⁶, Mohamed El-Kassas¹⁰, Zaily Dorta¹¹, Flair J. Carrilho¹², Fernando Bessone¹³, Ester Badia Aranda¹⁴, Mohamed Alboraie¹⁵, Helena Cortez-Pinto¹⁶, Ramon Bataller³
EARLY ALD IS THE MOST OVERLOOKED PHENOTYPIC IN CLINICAL HEPATOLOGY

CAMPAIGNS AIMED AT DETECTING SILENT FORMS OF ALD WITH ADVANCED FIBROSIS ARE URGENTLY NEEDED AT A GLOBAL LEVEL
Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease

Carolin Lackner\textsuperscript{1,*,*}, Walter Spindelboeck\textsuperscript{2,*}, Johannes Haybaeck\textsuperscript{1}, Philipp Douschan\textsuperscript{2}, Florian Rainer\textsuperscript{2}, Luigi Terracciano\textsuperscript{3}, Josef Haas\textsuperscript{4}, Andrea Berghold\textsuperscript{5}, Ramon Bataller\textsuperscript{6}, Rudolf E. Stauber\textsuperscript{2}
MANAGEMENT OF MODERATE-SILENT ALD

**clinical-biological picture**

- AST > ALT, GGT, MCV, other organs, physical exam
- Self-report (AUDIT), family, biomarkers
- Rule out other causes:
  - ANA, ferritin, HCV, HBV
- Non-invasive techniques (US, ASHtest®®, Fibroscan, RNM)
- Biopsy (if diagnosis uncertainties)

**vs**

**ALD**

**Motivational interviewing**

**Vitamin B-D + folic acid**

**Antioxidants (?)**

- Treat AUD pharmacologically (Disulfiram, Baclofen, Naltrexone)
- Antifibrogenic therapies (?) (Losartan, Pentoxifylline)
FIBROSCAN IN PATIENTS WITH ASYMPTOMATIC ALD

F01 vs F234: varies from 0.89 to 0.96
F0123 vs F4: varies from 0.90 to 0.94

PRIMARY CARE CENTERS  ADDICTION CENTERS

Melin et al. Alcohol Addicto 2005
Nahon et al. J Hepatol 2008
N’Guyen-Khac et al. Alimen Pharmacol Therap 2008
Mueller S. W J Gastroenterol 2010
NORMAL HISTORY OF ALD

- Normal liver
  - $80-90\%$
- Steatosis
  - $20-40\%$
- Fibrosis
  - $8-20\%$
- Cirrhosis
  - $3-10\%$
- Alcoholic steatohepatitis
- HCC
  - $20-40\%$
  - Decompensation (+ infections)

HCC
ALCOHOLIC HEPATITIS

IS THERE ANYTHING NEW IN THE DIAGNOSIS OR MANAGEMENT?
• Vital signs: BP 90/60 mmHg, HR 105, RR 22, T 37.8°C

• Biochemical data at admission:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (10⁹/l)</td>
<td>13.2</td>
</tr>
<tr>
<td>Hemoglobin (gr/dl)</td>
<td>11.7</td>
</tr>
<tr>
<td>Platelets (10⁹/l)</td>
<td>100</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>24</td>
</tr>
<tr>
<td>AST (UI/l)</td>
<td>159</td>
</tr>
<tr>
<td>ALT (UI/l)</td>
<td>74</td>
</tr>
<tr>
<td>GGT</td>
<td>653</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.8</td>
</tr>
<tr>
<td>Albumin (gr/dl)</td>
<td>2.7</td>
</tr>
<tr>
<td>PT /control PT (seg)</td>
<td>45/15</td>
</tr>
<tr>
<td>INR</td>
<td>3.7</td>
</tr>
<tr>
<td>Na (mEq/l)</td>
<td>134</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>46</td>
</tr>
<tr>
<td>HBsAg, Anti-HCV Abs, HIV</td>
<td>negative</td>
</tr>
</tbody>
</table>

• Abdominal US: steatosis, signs of cirrhosis, no HCC, no PVT, ascites
Mean arterial pressure at admission predicts mortality in patients with alcoholic hepatitis independently of MELD.

Meritxell Ventura-Cots¹, Carlos Fernández-Carrillo¹, JosepMaria Argemi¹, Juan G Abraldes², Francisco Bosques³, Robert S Brown Jr⁴, Guadalupe Garcia-Taso⁵, Juan Genesca⁶, Samuel Ho⁷, Phillipe Mathurin⁸, Alexander Louvet⁸, Michael Lucey⁹, Debbie Shawcross¹⁰, Victor Vargas⁶, Elisabeth Verna¹¹, Ramon Bataller¹.
Can we establish a definitive diagnosis of alcoholic hepatitis based on clinical/analytical parameters?
Are there **confounding** factors?

What is the **certainty** of the diagnosis without a liver biopsy?
**CLINICAL FEATURES OF ALCOHOLIC HEPATITIS**

- Suspicion ischemic hepatitis (hypotension, cocaine)
- Atypical labs (i.e. GOT or GPT more 500, similar GOT - GPT, etc).
- Sepsis at admission
- Uncertain alcohol assessment
- Use of any potential hepatotoxic substance in the last month

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**DIAGNOSIS OF AH**

**CONFIRMATORY FEATURES**

- All negative
  - Clinically diagnosed AH
  - PROBABLE AH

- Any positive
  - Biopsy-proven AH
  - DEFINITIVE AH

**TJB**

- Other diagnoses
- Not possible
- Uncertain AH
- POSSIBLE AH
How can we assess the severity of the episode and the need for specific therapy?
<table>
<thead>
<tr>
<th>Model</th>
<th>Bilirubin</th>
<th>PT/INR</th>
<th>Creatinine</th>
<th>Urea</th>
<th>Age</th>
<th>Leucocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maddrey DF*</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAHS*</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ABIC*</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

**Severe vs non-severe**

Maddrey DF: 32
MELD: 21
GAHS*: 9
ABIC*: 6.7
• Patient underwent TJB (INR 3.0) at day 2
  – Diagnosis of ASH was confirmed
    • Histological features
      • Fibrosis Stage : F4
      • Moderate PMN infiltration
      • Megamitochondria neg
    • Hepatocanalicular/Ductular Bilirubinostasis

AHHS: 7

• Scoring Systems
  – Maddrey’s DF: 62
  – MELD: 33
  – GAHS: 9
  – ABIC: 10.2

  \[\text{Severe Episode of Alcoholic Hepatitis}\]

• Prednisolone 40 md/day for 1 week (Lille: no responder). Developed nosocomial infection, MOF and death. He was considered a suboptimal candidate for early liver transplantation.
Early Liver Transplantation in Acute Alcoholic Hepatitis

Christine E. Haugen, MD, PhD\(^1\) Andrew M. Cameron, MD, PhD\(^1\)

**Table 1** Recent studies of early liver transplantation for severe acute alcoholic hepatitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Mathurin</th>
<th>Im</th>
<th>Lee</th>
<th>ACCELERATE-AH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant recipients, N</td>
<td>26</td>
<td>9</td>
<td>17</td>
<td>147</td>
</tr>
<tr>
<td>Center(s)</td>
<td>France, Belgium</td>
<td>Mount Sinai</td>
<td>Johns Hopkins</td>
<td>United States</td>
</tr>
<tr>
<td>Comparison group</td>
<td>Severe AAH, medical treatment</td>
<td>Severe AAH, medical treatment</td>
<td>Alcoholic cirrhosis, LT with (\geq 6) mo abstinence</td>
<td>–</td>
</tr>
<tr>
<td>Age, years(^a)</td>
<td>47</td>
<td>41</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Abstinence prior to LT, days(^a)</td>
<td>&lt; 90</td>
<td>30</td>
<td>40</td>
<td>55</td>
</tr>
<tr>
<td>6-mo survival, %</td>
<td>77</td>
<td>89</td>
<td>100</td>
<td>94(^b)</td>
</tr>
<tr>
<td>Any alcohol use post-LT, %</td>
<td>12</td>
<td>22</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Harmful alcohol use post-LT, %</td>
<td>8</td>
<td>11</td>
<td>24</td>
<td>11</td>
</tr>
</tbody>
</table>
Does alcohol relapse influence long-term survival?

How can I help the patient?
• MI during hospitalization
• Early follow-up outpatient clinic
• Multidisciplinary team in the clinic
• All team members should be trained

60% relapse
TREATING AUD IN A PATIENT-CENTERED MANNER

GENETIC-ENVIRONMENTAL FACTORS
- Family history
- Genetic risk
- Other addictions

SOCIOECONOMIC FACTORS
- Isolation
- Stigma
- Transportation
- Insurance

COMMON ASSOCIATED CONDITIONS
- PTSD
- Sexual abuse
- Depression
- Anxiety
- Sleep
- Pain

MULTIDISCIPLINARY ALD CLINIC
- Specialized APP & nurse
- Addiction therapist
- Social worker
- Hepatologist
In a recent VA study led by Shari Rogal, we show that treatment of alcoholism in patients with cirrhosis improves outcomes. At UPMC, we now have great addiction specialists seeing all hospitalized ALD patients.

#ALDcure

Rogal S et al, Hepatology 2020 (in press)
Alcohol-related Liver Disease
The *Candida albicans* exotoxin Candidalysin promotes alcohol-associated liver disease

**Aim:**
To evaluate the contribution of *Candida albicans* and its exotoxin Candidalysin on ALD

**Methods:**
*C. albicans* and *ECE1* were analyzed in fecal samples from 11 non-alcoholic controls, 42 patients with alcohol use disorder (AUD) and 91 alcoholic hepatitis (AH), and mice colonized with different and genetically manipulated *C. albicans* strains were subjected to the chronic-plus-binge ethanol diet model.

**Conclusions:**
Candidalysin contributes to progression of ethanol-induced liver disease in preclinical models, and is associated with worse clinical outcomes in patients with alcoholic hepatitis.

Mice colonized with Candidalysin positive *C. albicans* displayed more severe ethanol-associated liver injury(A), steatosis(B and C) and inflammation(D-F). Candidalysin was significantly associated with MELD score(G), and an increased 90 day mortality in alcoholic hepatitis patients(H).

Chu HK, et al., Abstract 29
Keratin 18 is a biomarker for the diagnosis and prognosis in acute alcoholic hepatitis

**Hypothesis:**
K18M65:ALT ratio may assist in distinguishing acute alcoholic hepatitis (AAH) from non-alcoholic steatohepatitis patients (NASH); K18 concentrations are potentially robust biomarkers for predicting mortality in severe AAH.

**Methods:**
173 participants; 84 AAH patients were classified as severe (n=57, MELD ≥20), or moderate (n=27, 12≤ MELD <19); 38 Alcohol Use Disorder (AUD) patients had mild (n=28, ALT >40) or no liver injury (n=10, ALT ≤40); 34 were NASH patients; and 17 were healthy controls in this single time-point 90-day mortality assessment study.

**Main Findings:**
ROC curve for K18M65:ALT distinguishes AAH significantly from NASH.

**Conclusions:**
Keratin 18 appears to reflect the degree of hepatocyte death and liver disease severity better than AST, ALT, or other traditional biomarkers in AAH.

Vatsalya V, et al., Abstract 270