Management of ALD including Acute Alcoholic Hepatitis

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Alcohol Basic Rules

- Readily absorbed in GIT
- 1 gm produce 7.1 Kcal
- 2%-10% eliminated via kidney and lungs
- 10-20% metabolized in stomach lining
  - (Men > women, leading to greater liver exposure in women)
- 80% of ETOH is oxidized primarily in liver
- No rate limiting mechanisms in the liver except Zero order metabolism
- Induce metabolic imbalances in the liver
  - Decrease fat oxidation by 79%
  - Decrease Protein oxidation by 39%
  - Decrease CHO Oxidation 100%
- Produces toxic metabolites via several pathways
Total Adult Per-capita Consumption of Pure Alcohol in Asia, Europe and North America

Liangpunsakul et al. Gastroenterology 2016 Vol. 150, No.8
Overall Alcohol-attributable Deaths Caused by Cirrhosis in Different Geographic Regions

Liangpunsakul et al. Gastroenterology 2016 Vol. 150, No.8
Epidemiology of ALD

- 50% of liver related deaths are due to alcohol induced liver disease, globally and in the US

NIAAAD Surveillance Report 2016
Outcomes Associated with Heavy Alcohol Use

NORMAL LIVER

FATTY LIVER

ALCOHOLIC HEPATITIS
A form of AoC LD
80-90% have cirrhosis

CIRRHOSIS

Death 30-50% at 3 months

90-100%
(drink more than 60 g/d)

10-35%*
Binge Drinking

8-20%
(>40 g/d)

*Hospitalized patients

Hepatology 2016 Mandrekar
Ethanol Metabolism: Oxidation in the Hepatocyte

Three Enzymes: Alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP2E1), and, of least importance, catalase.

The so-called hangover enzyme.

Acetylaldehyde is the agent responsible for the so-called “Oriental Flush Syndrome” via the ALDH2 allele.
Alcohol Metabolism

PATHWAYS
- Alcohol Dehydrogenase (ADH) (cytoplasm)
- Microsomal ethanol oxidizing system (MEOS) (microsomes) CYP2E1 / CYP1A2 / CYP3A4
- Catalase pathway (peroxisomes)
- Extrahepatic pathways
- Zero order metabolism

RESULTS
- Production of toxic metabolites
- Production of free radicals
- Cross induction of other microsomal enzymes
- Activation of carcinogenic metabolites
- Degradation of vitamin A
- Lipid peroxidation
- Depletion of glutathione
- Oxidative stress
LABORATORY ABNORMALITIES WITH ALCOHOL ABUSE

**Liver enzymes**
AST < ALT; AST usually ≤ 2 x ALT, both values usually less than 300 IU/dL
GGTP increased
Alkaline phosphatase increased

**Hepatic function panel**
Albumin decreased
Bilirubin usually increased
**INR**
INR: usually prolonged

**Complete blood count**
Leukocytosis
Thrombocytopenia
Mild anemia
Raised MCV

**Metabolic panel**
Hypertriglyceridemia
Hyperuricemia
Hypokalemia
Hypomagnesemia
Hypophosphatemia
**Alcoholic Hepatitis**

**Mechanisms of Inflammation**

- Ethanol
  - Alcohol dehydrogenase (ADH)
    - Peroxisomal Catalase
  - Miscrosomal ethanol-oxidising system (CYP 2E1)

- Acetaldehyde
  - Acetaldehyde dehydrogenase
  - Downregulated in chronic alcohol use
  - Altered membrane proteins
  - Neoantigens formation
  - Impaired cytoskeletal transport
  - Stimulation of HSC

- Acetate
  - Gultathione depletion
  - ROS & Free radicals

- Endotoxaemia

- Heat

- Kupfer cell activation
  - TNFα
  - IL-1, IL-8

- Gut Permeability

- Immunological injury
  - Damage to cell membranes

- Genetics
  - PNPLA3 Polymorphisms
  - Male vs Female Race

- TNFα
Mechanisms of Liver Fibrosis in ALD

Gao B et al. Gastroenterology 2011:141;1572-1585
Spectrum of ALD
Risk Factors and Comorbidity

Gao B et al. Gastroenterology 2011:141;1572-1585
Hypothesis
Hepatocyte

Kupffer cell

Nucleus

Lipid vesicle

DNA adducts

Lipid peroxides

ROS

Acetate

Acetaldehyde

Ethanol

ALD

AD

Intestinal lumen

Lipogenesis ↑

Fatty acid oxidation ↑

Lipid storage ↑

PPAR-γ

PNPLA3

TNFα

TNF-R1/2 ApoE-R

CD14

Endotoxin

ApoE

FFA

TG

Alcohol-induced barrier defect

Intestinal lumen

PNPLA3

CYP2

E1

Stickel & Hampe, GUT 2012;61:150-9
Alcoholic Liver Disease

1. Alcoholic Steatosis
   (a) Macrovesicular
   (b) Microvesicular (alcoholic foamy degeneration)
2. Alcoholic steatohepatitis (ASH)
3. Alcoholic hepatitis
4. Alcoholic cirrhosis (Compensated, ACLF)
Volumes

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 = 3-4 oz of fortified wine (such as sherry or port; 3.5 oz shown) = 2-3 oz of cordial, liqueur, or aperitif (2.5 oz shown) = 1.5 oz of brandy (a single jigger or shot) = 1.5 fl oz shot of 80-proof spirits ("hard liquor")

The percent of "pure" alcohol, expressed here as alcohol by volume (alcohol/vol), varies by beverage.
Pathogenesis of Alcoholic Hepatitis

Alcoholic Steatohepatitis

Macrosteatosis is obvious and two ballooned hepatocytes are shown containing Mallory-Denk bodies (top and bottom arrows). The arrowhead shows hepatocellular inflammation.
### New Histological Classification AAH

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

<table>
<thead>
<tr>
<th></th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage of fibrosis</strong></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><strong>Bilirubinostasis</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Hepatocellular only</td>
<td>0</td>
</tr>
<tr>
<td>Canalicuclar or ductular</td>
<td>+1</td>
</tr>
<tr>
<td>Canalicuclar or ductular plus hepatocellular</td>
<td>+2</td>
</tr>
<tr>
<td><strong>PMN infiltration</strong></td>
<td></td>
</tr>
<tr>
<td>No/Mild</td>
<td>+2</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
</tr>
<tr>
<td><strong>Megamitochondria</strong></td>
<td></td>
</tr>
<tr>
<td>No megamitochondria</td>
<td>+2</td>
</tr>
<tr>
<td>Megamitochondria</td>
<td>0</td>
</tr>
</tbody>
</table>

**NOTE.** The AHHS categories are as follows: mild, 0–3; intermediate, 4–5; severe, 6–9. Histologic features included in
New Histological Classification AAH

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

Acute Alcoholic Hepatitis

**Diagnosis**

- Subacute onset of fever
- Hepatomegaly
- RUQ Pain
- Manifestations of portal hypertension (ascites, hepatic encephalopathy, variceal bleeding).
Acute Alcoholic Hepatitis (AAH)

 Diagnosis

- Leukocytosis
- Increase AST (<500), AST/ALT>2
  - Leukocytosis
  - Marked impairment of liver function (jaundice, coagulopathy)
- Imaging: hepatomegaly and fatty liver by Abdominal US / CT
## Diagnostic Approach to Alcoholic Hepatitis

<table>
<thead>
<tr>
<th>Step</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen for Alcohol Abuse</td>
<td>• CAGE</td>
</tr>
<tr>
<td></td>
<td>• AUDIT</td>
</tr>
<tr>
<td>Confirm Diagnosis</td>
<td>• Suspected based on</td>
</tr>
<tr>
<td></td>
<td>• History and Physical</td>
</tr>
<tr>
<td></td>
<td>• Laboratory Tests AST/ALT ratio and level</td>
</tr>
<tr>
<td></td>
<td>Gold Standard is: <strong>Liver Biopsy</strong></td>
</tr>
<tr>
<td>Assess Illness Severity</td>
<td>• Scoring Systems - with treatment response</td>
</tr>
<tr>
<td>Rule out other causes of Liver Dysfunction</td>
<td>• History, Physical, Labs, +/- Liver Biopsy</td>
</tr>
</tbody>
</table>
Alcoholic Hepatitis
Histopathologic Features

- **Essential:**
  1. Parenchymal necrosis
  2. Mallory bodies
  3. Neutrophil infiltration (perivenular)

- **Common:**
  1. Bridging necrosis
  2. Fatty changes
  3. Bile duct proliferation
  4. Cholestasis
  5. Perivenular fibrosis
  6. Cirrhosis
  7. Sclerosing hyaline necrosis
ASSESSING ILLNESS SEVERITY

1. Maddrey’s Discriminant Function
2. Lille model: incorporates response to steroids
3. MELD Score
4. Glasgow Alcoholic Hepatitis Score
5. ECBL (early change in bilirubin levels): incorporates response to steroids
# Models Predicting Survival in Alcoholic Hepatitis

<table>
<thead>
<tr>
<th>Prognosticator</th>
<th>Parameter</th>
<th>Predictive Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modified DF</strong></td>
<td>$4.6 \text{ (Patient's PT - Control) + Serum bilirubin (mg/dL)}$</td>
<td>Modified DF $&gt; 32$ with hepatic encephalopathy predicts $&gt;50%$ mortality within 28 days</td>
</tr>
<tr>
<td><strong>MELD</strong></td>
<td>$9.57 \times \log [\text{Cr (mg/dL)}] + 3.78 \times \log [\text{Bilirubin (mg/dL)}] + 11.20 \times \log (\text{INR}) + 6.43$</td>
<td>MELD $\geq 21$ predicts 20% mortality in 90 days</td>
</tr>
<tr>
<td><strong>GAHS Score</strong></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Age</td>
<td>$&lt;50$</td>
<td>$\geq50$</td>
</tr>
<tr>
<td>WCC ($10^9$/L)</td>
<td>$&lt;15$</td>
<td>$\geq15$</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>$&lt;5$</td>
<td>$\geq5$</td>
</tr>
<tr>
<td>PT ratio</td>
<td>$&lt;1.5$</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>Bilirubin ($\mu$mol/L)</td>
<td>$&lt;125$</td>
<td>125-250</td>
</tr>
<tr>
<td><strong>Lille model</strong></td>
<td>$3.19 - 0.101 \times \text{Age (years)} + 0.147 \times \text{Albumin on day 0 (g/L)} + 0.0165 \times \text{Evolution in bilirubin level (µmol/L)} - 0.206 \times \text{Renal insufficiency} - 0.0065 \times \text{Bilirubin on day 0 (µmol/L)} - 0.0096 \times \text{PT (seconds)}$</td>
<td>Lille score $\geq 0.45$ predicts 75% morality within 6 months in patients who have received corticosteroid therapy</td>
</tr>
</tbody>
</table>

Tan HH et al, DOI:10.1002/MSJ
1. Maddrey’s Discriminant Function

- Most commonly used predictive model; developed to facilitate assessment of response to steroids in 1978; modified in 1989

**Discriminant function:**

\[(4.6 \times [PT - \text{control PT}]) + (\text{serum bilirubin})\]

**A DF ≥ 32** in the presence of HE predicts > 50% mortality at 28 days (in the absence of therapy); one month survival > 90% if DF < 32.

28-DAY SURVIVAL OF PATIENTS WITH DF ≥ 32: Individual Data Analysis of the Three RCTs

Cumulative survival

- Prednisolone-randomized patients, n=113
- Placebo-randomized patients, n=102

Days

100%

84.6±3.4%

p = 0.001

65.1±4.8%
2. Lille Model

- Six variables used to identify patients with severe AH (DF ≥ 32) not responding to steroids
- Lille score calculated after 7 days of steroids:
  \[ \text{Score} = 3.19 - 0.101 \times \text{Age (years)} + 0.147 \times \text{Albumin on day 0 (g/L)} + 0.0165 \times \text{Evolution in bilirubin level (μmol/L)} - 0.206 \times \text{Renal insufficiency} - 0.0065 \times \text{Bilirubin on day 0 (μmol/L)} - 0.0096 \times \text{PT (seconds)} \]
- [http://www.lillemode](http://www.lillemode.com/)
- Score ≥ 0.45 associated with marked decrease in 6 month survival (25% vs 85%)
- Superior to CTP, DF, GAHS, and MELD at predicting prognosis

Louvet A et al. Hepatology 2007; 45: 1348-54
Lille Model

![Survival probability vs. time in days graph](image)

- Lille score < 0.45
- Lille score ≥ 0.45
- \( p < 0.0001 \)

Louvet A et al. Hepatology 2007; 45: 1348-54
Bilirubin response to corticosteroids in acute alc hep

- 37 pts with AH, DF >32
- Prednisone 40 mg QD X 4 weeks, reduced by 5 mg increments Q 5 days
- In CS group, there was mean decrease in serum concentration of bilirubin after 6-9 days of 23
- CS response was defined as a fall in serum bilirubin of 25% after 6-9 days of treatment
- Sepsis developed in 59% of CS treated pts

Fig. 1

Dot plot of 28-day outcome relative to percentage fall in serum bilirubin after 6-9 days of corticosteroid treatment.
Twenty-eight and 56 day mortality of corticosteroid responders and non-responders. ■ Responders; □ non-responders.
3. MELD SCORE

- MELD derived to predict 3 month survival in cirrhosis patients
- MELD score >11 comparable to DF >32; although studies have suggested MELD cutoffs of 18, 19 and 21 for predicting prognosis
- MELD score on admission ≥ 18, MELD at 1 week ≥ 20 or rise in MELD ≥ 2 have been shown in a retrospective study to be more sensitive (91%) and specific (85%) than DF or CTP score in predicting mortality

4. EARLY CHANGE IN BILIRUBIN LEVEL

**Identification of responders**

**Early change in bilirubin levels (ECBL)**

ECBL: defined as bilirubin level at 7 days lower than bilirubin level on the first day of treatment. ECBL is an independent prognostic factor: Odds ratio 0.18 (0.08 - 0.37), p=0.000005

![Bar graph showing percentage of patients with and without ECBL](chart.png)

P. Mathurin, Abdelnour M, Ramond MJ, Carbonell N et al., Hepatology 2003
TREATMENT:

I) GENERAL MEASURES:

- Abstinence
- Toxicology Screen Move to lab section
- Treat: Signs and symptoms of: Alcohol Withdrawal
- Correct: Electrolyte Abnormalities Esp Mg++, K+, Na+
- Diagnostic Confirmation
- Enteral NUTRITIONAL SUPPLEMENTATION
- OTHERS: ECHO, ASCITES, AKI
Current Therapies in Acute Alcoholic Hepatitis

Prednisolone/ Prednisone: Yes
- Potent inhibitor of inflammatory cascade
- Cannot be used with active GI bleed or infection
- May increase risk for infection

Pentoxifylline: No
- Nonselective phosphodiesterase inhibitor, modulates TNF-α transcription and reduces the formation of IL-5, IL-10, and IL-12.
- Can cause GI upset, also rare complications (arrhythmias, hypotension, bleeding, and aseptic meningitis)
Nutrition management:

- Aggressive caloric intake (35-40 kcal/kg/day) and protein intake (1.2-1.5 grams/kg/day)
- Use of naso-enteric tube
- Consider intravenous lipids, 500 ml/day (~1000 kcal/day), as an adjunctive means of nutrition support in those with large caloric requirement and severe AH.
- Treat nutritional deficiencies
- S/C Vitamin K administration x3 days
- IV Magnesium, provided that the GFR is >40 ml/Hr

(Plauth 2009)
Near Universal Malnutrition in Alcohol Hepatitis

Mortality Correlates With Low Calorie Intake

Approaches
- Enteral
- Parenteral
- Medium Chain TGs
- Branched Chain A.A
Nutrition VS prednisolone

- Multicenter prospective randomized study
- Compared enteral nutrition (nasoduodenal TF 2000 kcal/day, (n=35) for 28 days and prednisolone 40 mg/day (n=36)
- No significant difference in 28-day mortality between the pts receiving steroids and those receiving total enteral nutrition (25 vs 31% respectively) but the mortality rate during f/u was higher with steroid treatment (27% vs 8%, p=0.04). Early deaths were more frequent with enteral nutrition but deaths weeks after treatment more frequent with steroids, mainly because of infections
<table>
<thead>
<tr>
<th>Component</th>
<th>Amount per 2,000 kcal</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>72 g</td>
<td>Whole milk protein with added amino acids; 31% of amino acid composition as branched-chain amino acids</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>345 g</td>
<td>As maltodextrin</td>
</tr>
<tr>
<td>Fat</td>
<td>36 g</td>
<td>35% as medium-chain triglycerides, 45% as Oleic acid, 15% as essential fatty acids*</td>
</tr>
<tr>
<td>Sodium</td>
<td>40 mmol</td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>1,000 mL</td>
<td></td>
</tr>
<tr>
<td>Caloric density</td>
<td>1.3 kcal/mL</td>
<td></td>
</tr>
<tr>
<td>Vitamins and trace elements</td>
<td>Recommended dietary allowances ×2</td>
<td></td>
</tr>
</tbody>
</table>

*Linoleic and α-linolenic.
## Causes of death during the treatment

<table>
<thead>
<tr>
<th>(A) Treatment Phase (28 days)</th>
<th>Steroids (n = 9)</th>
<th>TEN (n = 11)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hepatic failure (n = 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hepatic failure + sepsis (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hepatic failure + SBP + bleeding gastric ulcer (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia + sepsis (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massive limb hematoma + hypovolemic shock (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hepatic failure (n = 5)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hepatic failure + hepatorenal syndrome (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hepatic failure + terminal variceal bleeding (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatorenal syndrome (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatorenal syndrome + sepsis (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatorenal syndrome + SBP (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOF + sepsis (n = 1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Causes of death during the follow up period

<table>
<thead>
<tr>
<th>(B) Follow-up Phase</th>
<th>Steroids (n = 10)</th>
<th>TEN (n = 2)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia + sepsis + MOF (n = 3)</td>
<td></td>
<td>Massive variceal bleeding (n = 1)</td>
</tr>
<tr>
<td>Bronchopneumonia + sepsis (n = 1)</td>
<td></td>
<td>SBP + MOF (n = 1)*</td>
</tr>
<tr>
<td>Pneumonia (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis by MRSA (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hepatic failure + sepsis (n = 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hepatic failure + cachexia (n = 1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Infections during the 28 day treatment period

14/36 accounted for death in 5 pts

<table>
<thead>
<tr>
<th>Patient</th>
<th>Infection</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SBP</td>
<td><em>Streptococcus viridans</em></td>
</tr>
<tr>
<td>2</td>
<td>SBP</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SBP + bacteremia</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>4</td>
<td>SBP</td>
<td><em>Klebsiella oxytoca</em></td>
</tr>
<tr>
<td></td>
<td>Oesophagitis</td>
<td><em>Candida albicans</em></td>
</tr>
<tr>
<td>5</td>
<td>Sepsis</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>6</td>
<td>Sepsis</td>
<td><em>MRSA</em></td>
</tr>
<tr>
<td>7</td>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Urinary tract infection</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>10</td>
<td>Urinary tract infection</td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>11</td>
<td>Respiratory infection</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Acute gastroenteritis</td>
<td><em>Probably viral</em></td>
</tr>
<tr>
<td>13</td>
<td>Cellulitis of the limb</td>
<td><em>Str. viridans</em></td>
</tr>
<tr>
<td>14</td>
<td>Persistent fever†</td>
<td></td>
</tr>
</tbody>
</table>
Infections during the 28 day treatment period

15/35, accounted for death in 3 pts

<table>
<thead>
<tr>
<th>Patient</th>
<th>Infection</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SBP</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>SBP</td>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td></td>
<td>Respiratory infection</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Sepsis</td>
<td><em>Str. viridans</em></td>
</tr>
<tr>
<td>4</td>
<td>Sepsis</td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>5</td>
<td>Urinary tract infection</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>6</td>
<td>Urinary tract infection</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>7</td>
<td>Urinary tract infection</td>
<td><em>Str. agalactiae</em></td>
</tr>
<tr>
<td>8</td>
<td>Pneumonia</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>Aspirative pneumonia</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>Respiratory infection</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>Respiratory infection</td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td></td>
<td>Perianal abscess</td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td>12</td>
<td>Bacteremia</td>
<td><em>Enterococcus faecalis</em></td>
</tr>
<tr>
<td>13</td>
<td>Dental phlegmon</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>Persistent fever†</td>
<td>—</td>
</tr>
<tr>
<td>15</td>
<td>Fever and chills after transjugular liver biopsy</td>
<td>—</td>
</tr>
</tbody>
</table>
Probability of survival during the entire study period ($t + f/u$) - INTENTION TO TREAT analysis in both TEN (thick line) and steroids (thin line). Numbers in the boxes below indicate the number of at-risk patients at the beginning of each time period in either group.

\[ \text{TEN: 62\%} \]
\[ p = 0.26 \]
\[ \text{STE: 39\%} \]
Probability of survival during the entire study period (t-t + f/u) PER PROTOCOL in both TEN (thick line) and steroids (thin line). Numbers in the boxes below indicate the number of at-risk patients at the beginning of each time period in either group.
Conclusions

- total enteral nutrition is as effective as steroid t-t in the short-term treatment of severe alcoholic hepatitis.
- Combination of steroids and TEN
1. Steroids

- Prednisolone 40mg daily recommended in pts with DF ≥ 32 or HE for 28 day course +/- taper 2-3 weeks (guided by Lille score < 0.45), discontinue if LILLE threshold not meet

- CONTRAINdications:
  - Infection/sepsis
  - GI bleed
  - Renal insufficiency
Prednisolone for Severe Alcoholic Hepatitis

Survival (%)

Day

Corticosteroids

Placebo

Ramond, 1992
Short-term effect of corticosteroids

Phillips et al., J Hepatol 2006
2. Pentoxifylline

- Pentoxifylline is no longer used for the treatment of alcoholic hepatitis. Journal of Hepatology Volume 61, Issue 4, Pages 792–798, October 2014
The STOPAH trial for alcoholic hepatitis

- 1103 patients were randomized to one of four treatment groups: prednisolone and pentoxifylline, prednisolone and placebo, pentoxifylline and placebo, or double placebo

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Patients (n = 1103)</th>
<th>Percent mortality at 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone and pentoxifylline</td>
<td>274</td>
<td>13.5</td>
</tr>
<tr>
<td>Prednisolone and placebo</td>
<td>277</td>
<td>14.3</td>
</tr>
<tr>
<td>Pentoxifylline and placebo</td>
<td>276</td>
<td>19.4</td>
</tr>
<tr>
<td>Double placebo</td>
<td>276</td>
<td>16.7</td>
</tr>
</tbody>
</table>

5. TNF-INHIBITORS

- Infliximab and etanercept, were evaluated for treatment of AH **but did not show benefit**.\(^{60}\) Naveau, S., Chollet-Martin, S., Dharancy, S. et al. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis.

- In fact, the study assessing etanercept had to be closed prematurely because of **increasing number of deaths in** the treatment arm, mostly from superimposed infections.

**Hepatology. 2004; 39: 1390–1397**
3. G-CSF

- G-CSF is safe and effective in the mobilization of hematopoietic stem cells and improves liver function as well as survival in patients with severe alcoholic hepatitis. Granulocyte Colony-Stimulating Factor in Severe Alcoholic Hepatitis: A Randomized Pilot Study Virendra Singh AJG 2014
4. NAC-Antioxidants

- One study of nutrition support with or without IV NAC x 14 days found no survival benefit or biochemical improvement with the addition of NAC.

- Recent trial, 28 days of prednisolone 40mg with or without 5 days of IV NAC (regimen shown below) demonstrated significantly improved short-term (1 month) survival as well as lower rates of infection and hepatorenal syndrome in the group treated with NAC. No difference was observed in longer term survival (6 months).
6. REFRACTORY CASES:

- Use of **oxandrolone 40mg PO daily x 30 days only** (longer duration should be avoided due to increased risk of prostate cancer and HCC with androgen therapy) in patients who present with DF ≤ 80 or a lack of improvement in DF or MELD score (Mendenhall 1984; Orr 2004; Amini 2010).

- **S-adenosyl methionine (SAMe)** 400 mg TID is thought to be a potentially important mediator in alcoholic liver disease and is currently being studied for treatment of AH (Mato 1999; Lee 2004)
COMBINATION THERAPIES IN THE NEAR FUTURE?
NAC alone is ineffective

Sewart S, J Hepatol 2007

Moreno C, J Hepatol 2010
Glucocorticoids plus N-Acetylcysteine in Severe Alcoholic Hepatitis

Eric Nguyen-Khac, M.D., Ph.D., Thierry Thevenot, M.D.

No. at Risk
Prednisolone only 89 69 61 60 56 55 46
Prednisolone—in N-acetylcysteine 85 78 73 66 63 63 48

P=0.07 by log-rank test
NAC + Steroids: the near future?

- **N+C group**
  - Death at 1 month: 0% (p=0.005)
  - Death at 2 months: 33.1%
  - Death at 3 months: 34.1%
  - Death at 6 months: 38.1%

- **C group**
  - Death at 1 month: 24.1%
  - Death at 2 months: 15.3%
  - Death at 3 months: 22.4%
  - Death at 6 months: 27.1%

NS (not significant)

AASLD 2009 – Nguyen-Khac E, Amiens, Abstract 91 actualisé
Early Liver Transplantation for Severe Alcoholic Hepatitis

Philippe Mathurin, M.D., Ph.D., Christophe Moreno, M.D., Ph.D.,

Figure 2. Kaplan–Meier Estimates of Survival among the 26 Study Patients and Randomly Selected Matched Controls.
Liver Transplantation

- AH is typically considered a contraindication to transplantation.
- Historically, 6 months of abstinence is recommended as minimal listing criterion by tradition.
- Recidivism rates range from 11-50% at 3-5 years post-transplantation.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Purpose</th>
<th>Dose</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotherapy</td>
<td>Maintain abstinence</td>
<td>Optimum approach and frequency not determined</td>
<td>No clear evidence of benefit in patients with alcoholic liver disease; has not been studied in patients with alcoholic hepatitis⁶⁵</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Reduce inflammation</td>
<td>40 mg of prednisolone orally, once a day for up to 28 days</td>
<td>Reduces short-term mortality in selected patients with severe alcoholic hepatitis¹⁷,¹⁸,⁶⁶-⁷⁰</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Ablate TNF-α, help maintain kidney function, and many other actions</td>
<td>400 mg orally, three times daily</td>
<td>Improves in-hospital survival in patients with severe alcoholic hepatitis; fewer instances of the hepatorenal syndrome in group receiving pentoxifylline⁷¹</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Ablate TNF-α</td>
<td>Most effective dose has not been determined</td>
<td>May increase risks of infection and death⁷²</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Ablate TNF-α</td>
<td>Most effective dose has not been determined</td>
<td>May increase risks of infection and death⁷³</td>
</tr>
<tr>
<td>Nutritional support</td>
<td>Reverse malnutrition</td>
<td>35–40 kcal/kg of body weight per day, including 1.2–1.5 g protein/kg/day</td>
<td>Improves nutritional status but does not improve short-term survival in patients with severe alcoholic hepatitis⁷⁴-⁷⁶</td>
</tr>
<tr>
<td>Oxandrolone</td>
<td>Increase muscle mass</td>
<td>Most effective dose has not been determined</td>
<td>Does not improve short-term survival in patients with severe alcoholic hepatitis⁷⁷</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Ablate oxidant-mediated liver injury</td>
<td>Most effective dose has not been determined</td>
<td>Does not improve survival in patients with severe alcoholic hepatitis⁷⁸</td>
</tr>
<tr>
<td>Silymarin (milk thistle extract)</td>
<td>Ablate oxidant-mediated liver injury</td>
<td>Most effective dose has not been determined</td>
<td>Does not improve survival in patients with severe alcoholic hepatitis⁷⁹</td>
</tr>
</tbody>
</table>

* TNF-α denotes tumor necrosis factor α.
ALGORITHM FOR AH:

As modified from: Am J Gastroenterol 2010; 105:14–32;
NEWER THERAPEUTIC TARGETS
TO SUMMARIZE...

**Therapeutic Algorithm for the Long-term Management of ALD**

1. **Emphasize Abstinence**
2. **Evaluate and treat Co-morbidities**
   - Need for Rehabilitation +/− drug treatment?
   - Determine Stage of Disease
     - Fatty Liver
     - Alcoholic Hepatitis
     - Fibrosis / Cirrhosis
   - Nutritional Assessment / Intervention
     - Frequent feeding / night-time snacks micronutrient & vitamin replacement
     - Consider Clinical Trials
     - Manage Complications of Liver Disease

Fig. 2. Proposed therapeutic algorithm for the long-term management of alcoholic liver disease.

VII. Long-Term Management of ALD

Reduction in the frequency of ALD hospitalizations for infections over a 1-year period.
**AAH: Indications For Steroid Therapy**

- DF $\geq$ 32
- Presence of hepatic encephalopathy
- Absence of infection, GI bleeding, renal failure

| Modified DF | 4.6 (Patient’s PT – Control) + Serum bilirubin (mg/dL) | Modified DF $> 32$ with hepatic encephalopathy predicts $>50\%$ mortality within 28 days |
Acute Alcoholic Hepatitis

Additional Management

Abstinence

Critical Threshold

MOF

Time

SMT
Nutrition, Vits, Prednisolone, Pentoxifylline,

ECAD
ELAD

Tx

Death

Hassanein T et al, Crit Care 2011
Corticosteroids in AAH

- Candidates For Corticosteroids:
  - DF > 32
  - Presence of hepatic encephalopathy
  - ECBL
  - Lille Score <0.45

- Most patients are not candidates:
  - DF <32; No HE
  - Lille Score >0.45; No ECBL
  - Presence of GI bleeding, infection or renal failure
Steroids or pentoxifylline for alcoholic hepatitis?:
Results of the STOPAH trial

STOPAH evaluated therapeutic benefit of both prednisolone (Pred, 40 mg QD for 4 wks) and pentoxifylline (PTX, 400 mg three times daily for 4 wks) in Tx of severe alcoholic hepatitis

1,103 patients randomized

Primary endpoint: Mortality at 28 days

- Prednisolone: OR = 0.72 (0.52–1.01), p=0.056
- No Prednisolone: OR = 1.07 (0.77–1.49), p=0.686

Prednisolone is of marginal benefit in alcoholic hepatitis

Thursz MR, et al. NEJM 2016
Lille Score

prednisone/prednisolone stopping rules

- Lille score decline of <30% at 7 days
Extra Corporeal Albumin Dialysis: MARS

- Selective hemodiafiltration
- Removes both water-soluble and protein bound molecules
- Low and middle weight molecules (50 kd)
ECAD for Alcoholic Hepatitis
Long Term Survival

ELAD® System Schematic

- Glucose Pump
- ECMO Heater
- Heat Exchanger
- Oxygenator
- Reservoir
- Quick Disconnects
- In-Line Gas Analyzer
- ELAD® Cartridges
- Centrifugal Pump
- Cell Filter
- Gas Blender
- Dual lumen catheter
- Blood Return Line
- Air Detector
- Blood Withdrawal Line
- Heparin Pump
- Ultrafiltrate Return
- Ultrafiltrate In line
- UF Pump
- Blood Pump
- Ultrafiltrate Generator
- P - Pressure Sensor

Extracorporeal Liver Assist Device
Severe Alcoholic Hepatitis
ELAD Trial

ITT Population with minimum follow-up of 91 days

Secondary Endpoints: Proportion of Survivors

<table>
<thead>
<tr>
<th></th>
<th>ELAD (%)</th>
<th>Control (%)</th>
<th>p-value (Pearson’s chi-squared)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days</td>
<td>76.0</td>
<td>80.4</td>
<td>0.46</td>
</tr>
<tr>
<td>91 days</td>
<td>59.4</td>
<td>61.7</td>
<td>0.74</td>
</tr>
</tbody>
</table>

p=0.90
HR=1.027
ELAD N=96
Control N=107
Total N=203

Thompson, J. AASLD LB-15. 2015
Pre-Specified Subgroup Analysis: MELD

Pre-specified subgroup analysis reveals MELD-dependent ELAD response

- **83** patients ITT with MELD ≥28
  - **ELAD N=45**
  - **Control N=38**
  - p=0.146
  - HR=1.503

- **120** patients ITT with MELD <28
  - **ELAD N=51**
  - **Control N=69**
  - p=0.077
  - HR=0.575

Overall, no significant difference in OS
Trend towards improved survival in low MELD (<28) and younger patients (<47)

Baseline parameters were balanced between ELAD and Control in both subgroups.

Thompson, J. AASLD LB-15. 2015
Pre-specified Subgroup Analysis: Age

Pre-specified subgroup analysis reveals age-dependent ELAD response
102 patients ITT with Age >47yrs

101 patients ITT with Age <47yrs

Baseline parameters were balanced between ELAD and Control in both subgroups.
The Next Trial: VTL-308

- Eligibility guided by earlier data (MELD <>28 and Age <>median) and then refined here to accommodate MELD <30 (plus INR ≤2.5, creatinine <1.3 mg/dL, age < 50 and bilirubin ≥16 mg/dL)
- 60 subjects with hazard ratio of 0.28; p <0.01 (if predefined)
- 91-day survival: ELAD 93% versus Control 61%
- 180-day survival: ELAD 89% versus Control 48%

- US and Europe (40 sites enrolled subjects)
- Anticipate enrolling a minimum of 150 subjects
  - ~ 99% powered assuming hazard ratio of 0.30
  - > 95% powered assuming hazard ratio of 0.40
  - > 85% powered assuming hazard ratio of 0.50
- Timeline
  - First enrollment in H1:2016
  - Anticipate data mid-2018
Acute Alcoholic Hepatitis

Management

Abstinence

Critical Threshold

SMT
Nutrition, Vits, Prednisolone, Pentoxifylline,

MOF

Low Risk Patients

ECAD
ELAD

Time

Tx

Death

Hassanein T et al, Crit Care 2011
Potential Targeted Therapies in AAH or chronic ALD

Loupert A. Rev. Gastroenterol. Hepatol. 12, 231-242 (2015); published online 17 March 2015
Experimental Treatment of Acute Alcoholic Hepatitis

In Trials

- Glucocorticoids
- Pentoxifylline
- ECAD
- Anti TNFα
- ELAD
- Obeticholic acid
- G-CSF
- GS-4997 (oral molecule that inhibits Apoptosis Signal-regulating Kinase 1 (ASK1))
Deeper DETAILS

- Phenotypes and Genotypes of ALD
Alcoholic Liver Disease – Phenotypes may vary...
Alcoholic Liver Disease (ALD)

- Healthy Liver
- Alcohol
- Alcoholic Fatty Liver / Fibrosis / Hepatitis
- Alcohol
- Liver Cirrhosis

90-100% of alcoholics reveal steatosis
10-35% show signs of alcoholic fibrosis / hepatitis
10% develop cirrhosis

Only a minority of heavy drinkers develop severe liver disease!
Factors Influencing the Progression of ALD

Environmental Factors

+ Drinking pattern (amount, continuity, type of beverage ?, relation to meals)
+ Metabolic syndrome
+ Coinfection with hepatitis C (and B ?) virus
+ Age (cirrhosis)
+ High fat diets
+ Smoking ?
+ Cannabis ?
- Coffee

Genetic factors ?

Rotily et al. 1990
Klatsky et al. 1992
Becker et al. 1996
Bellentani et al 1997
Becker et al. 2002
Raynard et al. 2002
Hezode et al. 2005
Johansen et al. 2006
Klatsky et al. 2006
Genetic risk of alcoholic liver disease

Evidence from epidemiology

- Females are more susceptible towards equal amounts of alcohol \( (Pares \ et \ al. \ 1986, \ Sato \ et \ al. \ 2001) \)

- Hispanics are more prone to developing ALD than Blacks and Whites \( (Wickramasinghe \ et \ al. \ 1995, \ Stinson \ et \ al. \ 2001) \)

- Monozygotic twins have a 3-fold higher prevalence of alcoholic cirrhosis than dizygotic twins \( (Hrubec \ et \ al. \ 1981, \ Reed \ et \ al. \ 1996) \)
Genetics of ALD: Why Bother?

Identify causal gene(s)/genetic variant(s)

Diagnostic/Prognostic Testing

Better Insight to Pathophysiology

Prevention

Drug therapy

Gene therapy
Mendelian vs. Complex Diseases

Mendelian Inheritance
- Mutation
- Genotype
- Phenotype

Dominant, recessive, X-linked inheritance

Complex Inheritance
- Genetic variant
- Gene A
- Gene B
- Genetic variant
- Environment / Behavior

Phenotype
Types of Genomic Variation

1. Single Nucleotide Polymorphism (SNP)

ggc tgc at\textbf{A/C} aat gtc ttc ttt

2. Microsatellite

tac aca cat gta \textit{CACACACACACACACACACACA} cca tga cct

3. Insertion

AGG CC $\rightarrow$ AGG \textbf{ATA} CC

4. Deletion

AGG TCC $\rightarrow$ AGCC

Exonic – coding
Intronic – non-coding
Promoter – transcription
Intergenic – splicing
Types of Genetic Studies

- Twin studies
- Family linkage studies
- Genetic association studies (case control studies)
  - Candidate gene association studies
    *Hypothesis-driven*
  - Genome-wide association studies
    *Hypothesis-free/-generating*
Genetics of Alcohol-Related Liver Damage

Twin Studies

- 15.924 Twin pairs (National Academy of Sciences-National Research Council, USA)
- Prevalence of alcoholic cirrhosis 17.7/1,000
- Rate of concordance: monozygotic 16.9, dizygotic 5.3 (p < 0.001)
- Genetics contribute to 50% of variability to develop alcoholic liver cirrhosis

## Candidate Gene Association Studies in ALD

Pubmed: "alcoholic liver disease" and "polymorphism" 1,358 hits

<table>
<thead>
<tr>
<th>Candidate genes already tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH1B, ADH1C, ALDH2, CYP2E1,</td>
</tr>
<tr>
<td>CYP1A1, NAT2, GSTA1, GSTM1,</td>
</tr>
<tr>
<td>GSTM3, GSTT1, GSTP1, ApoE,</td>
</tr>
<tr>
<td>SLC6A4, MnSOD, IL-10, IL-1R and</td>
</tr>
<tr>
<td>ET-R, TGFbeta1, IL-1beta,</td>
</tr>
<tr>
<td>CD14-ET-R, CTLA-4, MPO, HFE, UCP..</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Candidate genes that could be tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMPs, TIMPs, collagens, CTGF, leptin,</td>
</tr>
<tr>
<td>leptin-R, adiponectin, CPT1A,</td>
</tr>
<tr>
<td>SREBP-1, MTP, acyl-CoA oxidase, 11beta-HSD, SCD-1, PEMT,</td>
</tr>
<tr>
<td>angiotensinogen, TLRs, MCP, CYP4A,</td>
</tr>
<tr>
<td>RAR, MAT1, insulin-R, etc....</td>
</tr>
</tbody>
</table>

**No confirmed genetic risk factor for ALD!**
Genetic Association Studies: Problem of replication validity

Ioannidis et al., Nature Genetics 2001;29:306-9
Meta-analysis

- SNPs of ADH1B, ADH1C, CYP2E1, ALDH2 and the risk of alcoholism and alcoholic liver disease
- 50 association studies (1990-2004)
- Exploration of heterogeneity, bias, power, compliance with Hardy-Weinberg equilibrium, subgroup analyses (ethnicity, gender)
- Associations for ADH1B*1, ADH1C*2 and ALDH2*1 and the risk of alcoholism (ORs 1.89, 1.32, and 4.35, respectively)
- Subgroup analysis: associations of ALDH2*2 and ADH1C*2 with alcoholism restricted to Asian men
- No associations for any of the tested genetic variants with regard to alcoholic cirrhosis
Genes associated with alcohol dependence
Genes associated with alcohol dependence

Chromosome 4

No association with ALD!

Fehr et al. Psychiatr Genetics 2006;16:9-17
## Genome-wide association studies in liver diseases

<table>
<thead>
<tr>
<th>Author</th>
<th>Disease</th>
<th>Patients (n)</th>
<th>Risk variant(s)</th>
<th>Genome-wide significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buch et al. 2007</td>
<td>Gall stones</td>
<td>2,280 cases 2132 controls</td>
<td>ABCG8</td>
<td>1.4 x 10^{-14}</td>
</tr>
<tr>
<td>Romeo et al. 2008</td>
<td>Fatty liver</td>
<td>9,229</td>
<td>PNPLA3 (I148M)</td>
<td>5.9 x 10^{-10}</td>
</tr>
<tr>
<td>Huang et al. 2007</td>
<td>Hepatitis C - progression</td>
<td>574 patients</td>
<td>7-gene signature</td>
<td>na</td>
</tr>
<tr>
<td>Ge et al. 2010</td>
<td>Hepatitis C – response to therapy</td>
<td>2,612 patients</td>
<td>IL28B</td>
<td>1.37 x 10^{-28}</td>
</tr>
<tr>
<td>Fellay et al. 2010</td>
<td>Hepatitis C - side-effects (RBV)</td>
<td>1,286 patients</td>
<td>ITPA</td>
<td>1.1 x 10^{-45}</td>
</tr>
<tr>
<td>Melum et al. 2011</td>
<td>PSC</td>
<td>1,740 cases 5,136 controls</td>
<td>MST1, BCL2L11</td>
<td>1.1 x 10^{-16}</td>
</tr>
<tr>
<td>Mells et al. 2011</td>
<td>PBC</td>
<td>1,840 cases 5,163 controls</td>
<td>STAT4, DENND1B, CD80, IL7R, CXCR5, TNFRSF1A, CLEC16A and NFKB1</td>
<td>5 x 10^{-8}</td>
</tr>
</tbody>
</table>
Steatosis in NAFLD
PNPLA3 (Adiponutrin) rs738409 (G/C → I148M) and liver injury

- Genome-wide association study in patients with NAFLD (n=9,229)
- 2-fold higher hepatic fat content in homozygous carriers of PNPLA3 rs738409 (G) allele

*Romeo et al. Nature Genetics 2008;40:1461-5*
PNPLA3 Variation – rs738409 C>G (I148M)
PNPLA3 variation and protein function

- Localised between membranes and lipid droplets

- PNPLA3 hydrolyses triglycerides *in vitro* (Lake *et al*, *J Lipid Res* 2005)

- PNPLA3 rs738409 (G/G) reduces triglyceride hydrolysis *in vitro* (*He et al*, *J Biol Chem* 2010;285:6706-15)

- PNPLA3 rs738409 (G/G) overexpressing mice reveal more steatosis than wild types (*He et al*, *J Biol Chem* 2010;285:6706-15)
PNPLA3 variation – Steatogenesis?

PNPLA3 variation and ALD

Multi-center cohort (alcoholics)

- Recruitment between 2000-2009
- Alcohols (n=1043; German/Swiss ancestry) from
  - GI/Hepatology (Bern, Kiel, Erlangen, Heidelberg, Regensburg, Frankfurt, Homburg)
  - Addiction Medicine units (Bern, Regensburg, Mannheim)
- Inclusion criteria: heavy alcohol consumption (>60g/day♀; >80g/day♂ for >10 years)
- Standard laboratory (ALT, AST, GGT, AP, bilirubin, INR, albumin, platelets), US
- Exclusion of CHB+C, hemochromatosis, autoimmune hepatitis
- Cirrhosis as per (1) biopsy (Ishak 4-6), (2) complications of cirrhosis, (3) unequivocal US or CT imaging and/or esophageal varices

Population-based cohort (at-risk drinkers)

- SHIP cohort (n=376 / 4319; recruitment 1996)
- At-risk drinkers (median alcohol consumption 300g/day)
- Standard laboratory; US

Genotyping / Statistics

- TaqMan PCR (Applied Biosystems; Foster City, CA) (Hampe et al; Bioinformatics 2001;17:654-55)
- Case-control design; Chi² test; Fisher exact test
- Population-attributable risk

\[
PAR\% = \frac{f_{GT} (RR - 1)}{f_{GT} (RR - 1) + 1} \cdot 100
\]
PNPLA3 rs738409 (G) allele frequency

**Clinical Alcoholics**
- N=1,043
- P=1.6×10^{-5}
- NS (0.03*)
- P=0.0042

**At Risk Drinkers**
- N=376
- P=0.02
- NS (0.03*)

*Stickel et al. Hepatology 2011;53:86-95*
PNPLA3 rs738409 GG and alcoholic cirrhosis

N=3,746

- Tian et al.: OR, P=1.7 x 10^{-10}, p=0.0012
- Seth et al.: OR, P=4.7 x 10^{-5}
- Trepo et al.: OR, p=0.02
- Stickel et al.: OR, p=1.18 x 10^{-5}, p=0.04
Summary

- Environmental and host factors modulate evolution and progression of ALD

- Genetic background important modulator of susceptibility

- Quest for genetic risk factors if ALD has only identified/confirmed few candidate genetic variants

- Carriage of PNPLA3 rs738409 (G) allele and GG genotype first confirmed genetic risk factor

- Genome-wide association studies are under way to search for yet unknown genetic variants
Summary

- Alcoholic Liver Disease (ALD) # 1 cause of liver disease world-wide
- Alcoholic hepatitis: common disease
- Prednisone: use for 7 days if no GI bleeding, active infection or renal failure
  - Stop prednisone if Lille score does not decrease by 30% at 7 Days
- Liver transplant for Alc Hep remains controversial but is increasing in use
Thank You

to all Participants and Supporters