Alcoholic Hepatitis: Routine Screening for Early Recognition and Management

Juan Guerrero, MD
Global Problem

- 1% of GNP of medium/high income countries
- Additional societal costs
- Disproportionately affects low SES/marginalized populations
- 48% of cirrhosis-related deaths in US

Rehm Lancet 2009.
Alcohol is a Major Burden

- 3.8% of **ALL** deaths worldwide in 2004
  - 6.3% for men vs. 1.1% for women
  - In population <70 yo: 15 per 10,000 men vs 3.5 per 10,000 women in Europe

Rehm Lancet 2009.
How Much is Too Much?

My Doctor said "Only 1 glass of alcohol a day". I can live with that.
# Standard Drinks

10-12 g ETOH

One mixed drink with:
- 1.5 fl oz (44 mL) of 80-proof liquor (such as vodka, gin, scotch, bourbon, brandy, or rum)
- 5 fl oz (148 mL) of wine
- 12 fl oz (355 mL) of beer or wine cooler

<table>
<thead>
<tr>
<th>Drink Type</th>
<th>Alcohol Content</th>
<th>Drink Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td></td>
<td>1 drink</td>
</tr>
<tr>
<td>Light</td>
<td></td>
<td>.8 drink</td>
</tr>
<tr>
<td>Ice</td>
<td></td>
<td>1.2 drink</td>
</tr>
<tr>
<td>Specialty / Micro-Brews</td>
<td></td>
<td>1.3 drink</td>
</tr>
<tr>
<td>Malt Liquor</td>
<td></td>
<td>1.3 to 2 drinks</td>
</tr>
<tr>
<td>Tequila</td>
<td>40%, 80 proof</td>
<td>1 drink</td>
</tr>
<tr>
<td>Rum</td>
<td>75.5%, 151 proof</td>
<td>1.9 drinks</td>
</tr>
<tr>
<td>Vodka</td>
<td>40%, 80 proof</td>
<td>1 drink</td>
</tr>
<tr>
<td>Wine Coolers 12 oz</td>
<td>6-8%, 12-16 proof</td>
<td>1 to 1.5 drinks</td>
</tr>
<tr>
<td>Everclear</td>
<td>95%, 190 proof</td>
<td>2 drinks</td>
</tr>
</tbody>
</table>
Long-term Consequences

- How much causes problems?
  - Men: 60-80 grams/day x 10 years
  - Women: 20-40 grams/day x 10 years

- How many alcoholics develop cirrhosis?
  - Only 15-20% of chronic alcoholics develop chronic liver disease
  - Genetics clearly important but poorly understood
Other Risk Factors

- **Sex**
  - Females increased risk

- **Drinking pattern**
  - Daily drinking from a young age > binge/episodic

- **Genetics**
  - PNPLA3

- **Co-factors**
  - Obesity – NASH – or malnutrition (common)
  - Chronic liver disease – HCV/HBV
  - Fe overload
  - Smoking
Only a Minority Progress

Reversal with abstinence
Clinical Features
Acute Alcoholic Hepatitis

• History
  • Alcohol intake – usually binge, usually honest (not always)
  • Fever
  • Weight loss – malnutrition

• Exam
  • Toxic looking, fever, tachycardia
  • Tender hepatomegaly +/- bruit
  • Signs of CLD & MALNUTRTION – often severe

Acute alcoholic hepatitis vs decompensated alcoholic cirrhosis?
No reliable indicator aside from recent alcohol intake
Lab Features

- **Liver Tests**
  - AST:ALT > 2:1
    - Rarely above 300 (never above 500 IU/L)
    - AST increased due to mitochondrial damage
  - GGT +/- ALP elevation – may appear very cholestatic
  - Bilirubin & INR increased, Albumin depressed

- **CBC**
  - WBC elevation with PMNs → but may be infection
  - Low plt → direct BM suppression vs portal HTN
  - Low Hb → nutritional deficiency, bleeding

- **Creatinine**
  - Predictor of outcome – very important
Discriminant Function

Maddrey’s (modified) discriminant function

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

\[mDF \geq 32\]

With encephalopathy 45% mortality
Without encephalopathy 35% mortality

More recent data → up to 100% survival <32 & 34% 28d mortality untreated cohorts

Glasgow Alcoholic Hepatitis Score

Range 5 - 12 points
≥ 9 = bad prognosis

Table 1 Glasgow alcoholic hepatitis score

<table>
<thead>
<tr>
<th>Parameter/score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>&lt; 50</td>
<td>≥ 50</td>
<td>-</td>
</tr>
<tr>
<td>Leucocytes (10^9/L)</td>
<td>&lt; 15</td>
<td>≥ 15</td>
<td>-</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>&lt; 5</td>
<td>≥ 5</td>
<td>-</td>
</tr>
<tr>
<td>INR</td>
<td>&lt; 1.5</td>
<td>1.5-2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Bilirubin (μmol/L)</td>
<td>&lt; 125</td>
<td>125-250</td>
<td>&gt; 250</td>
</tr>
</tbody>
</table>

MELD Works Too

- MELD factors include: INR > creatinine > bilirubin
- MELD > 21 associated with higher mortality
  - Particularly those with ascites and/or encephalopathy
- 30 day mortality
  - MELD sensitivity 75%, specificity 75%
  - DF sensitivity sensitivity 75%, specificity 69%
- 90 day mortality
  - MELD sensitivity 75%, specificity 75%
  - DF sensitivity sensitivity 88%, specificity 65%
- Similar data other studies

Lille Score

- Formula allows predicting improved mortality after 7 days of steroid therapy
- Heavily weighted on change in bilirubin
- A score of >0.45 associated with ~25% 6 month survival vs 85% if <0.45
- Allows for decision making of steroid discontinuation and/or exploration of alternative txs
Treatment
Resuscitation

• Sick patients!
• Address other issues:
  • Ascites → tap to r/o SBP
  • Infection → very low threshold for antibiotics, culture often
  • Renal function → make sure fluid replete, no NSAIDs, careful with diuretics and contrast dye, albumin, albumin, albumin
  • Encephalopathy → lactulose, Xifaxan
  • Alcohol withdrawal → benzodiazepines
• Nutrition
  • Vitamins B complex (Wernicke’s)
  • Protein
  • Calories
Nutrition – CRITICAL!!

• 71 patients randomized:
  Prednisone 40 mg/d x 30 d vs
  Total Enteral Nutrition 2000 Kcal/d x 30 d
• Similar 30 d mortality – 9/36 vs 11/35
• 1 year mortality HIGHER with steroids
  • 10 of 27 vs 2 of 24 (p=0.025)
  • 9 of 10 steroid deaths due to infection
Specific Therapies

- Lots of things evaluated…
  - Anabolic steroids
  - Insulin/glucagon
  - Colchicine
  - PTU
  - SAMe
  - Anti-TNF (infliximab/etanercept)

- Nutrition

- Steroids

- Pentoxyfilline
  - Both

No benefit

Let’s discuss…
What About Steroids?

- Lots of trials
- Meta-analysis…15 RCTs (but ? good ones)
  - Mortality benefit if DF>32 or encephalopathy
    - RR 0.37 (0.16-0.86)
- 5 most recent RCTs…
  - N=418 → 80% vs 66% 28-day survival
- Prednisone 40 mg/day x 30 d
- **Exclude:** Active GI bleed,
  - Renal failure
  - Coma
  - Active uncontrolled infection

Pentoxyfilline

Pentoxyfilline 400 mg PO TID vs placebo

- Deaths – 25% vs 46%
- Main benefit in reduction in mortality due to HRS
- Fairly well tolerated

This single study led to widespread adoption of PTX!

• Alc hep with DF>32, bili>4 with no active GI bleed or untreated infection
  • Prednisone – n=277
  • PTX – n=276
  • Pred + PTX – n=274
  • Placebo – n=276
28 Day Survival – Primary Endpoint

Pred vs no Pred

PTX vs no PTX

Trend toward benefit for prednisone
No benefit of PTX
Lower mortality than expected in placebo arm (17%)

### Table 3. Analysis of Factors Associated with Mortality at 28 Days.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Prednisolone vs. no prednisolone</td>
<td>0.61 (0.41–0.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pentoxifylline vs. no pentoxifylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discriminant function</td>
<td>1.02 (1.02–1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GAHS</td>
<td>2.17 (1.86–2.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MELD</td>
<td>1.15 (1.12–1.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lille§</td>
<td>1.03 (1.02–1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prothrombin ratio or INR</td>
<td>3.07 (2.32–4.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.05 (1.03–1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White cells</td>
<td>1.06 (1.03–1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urea</td>
<td>1.06 (1.01–1.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>3.07 (2.32–4.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0.66 (0.37–1.16)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1.20 (0.79–1.83)</td>
<td>0.39</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1.09 (0.71–1.65)</td>
<td>0.70</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>1.00 (1.00–1.00)</td>
<td>0.37</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.99 (0.96–1.02)</td>
<td>0.41</td>
</tr>
<tr>
<td>Alkaline phosphate</td>
<td>1.00 (1.00–1.00)</td>
<td>0.07</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.07 (1.05–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>3.70 (2.59–5.29)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Adjusting for baseline factors – modest benefit to steroids**
Beyond 28 d, only abstinence associated with survival
Take Home Messages

- PTX of no benefit
- Prednisone likely has a modest EARLY benefit but no long-term benefit
- ABSTINENCE is key (and the only thing that probably matters)

Consider using prednisone because you need to get them through the first month to give them a chance to be abstinent!
Would NAC help?

Alc Hep with DF>32 → Pred + NAC vs Pred alone x 30 d

- Fewer infections in Pred + NAC group
- Improved bilirubin at day 7 = 90% 6 m survival vs 10% with no change!

Nguyen. NEJM. 2011.
Summary

- Alcoholic liver disease causes a huge burden of illness worldwide
- Only a minority of heavy drinkers develop cirrhosis
- Acute alcoholic hepatitis has a poor prognosis
- Multiple scoring systems – all useful
  - mDF most widely used
  - Lille helps guide therapy
- Treatment: NUTRITION, supportive care, steroids, +/- NAC → ABSTINENCE!
- Assess response at day 7 and stop if no response
- Long-term – abstinence is EVERYTHING!
Roundtable/Q&A

Drs. Poordad, Alkhouri and Guerrero