Blame it on the Alcohol: Management of Acute Alcoholic Hepatitis

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October 2015

Disclosure Statement

I have nothing to disclose related to the contents of this presentation

Objectives

Pharmacist Objectives:
- Identify acute alcoholic hepatitis (AH) using various scoring stratification schemes
- Compare and contrast literature surrounding treatment strategies of AH
- Formulate an evidence-based treatment regimen for a patient with AH

Technician Objectives:
- Define acute alcoholic hepatitis (AH)
- Provide examples of treatment strategies for AH
- Generalize differences between treatment regimens for AH

Alcoholic Liver Disease

- Top 10 leading cause of death
- Major risk factor for liver disease
- Excessive alcoholism increasingly common
- Increasing hospitalizations

Acute Alcoholic Hepatitis (AH)

Acute hepatic decompensation after longstanding alcohol abuse

Steatosis → Fibrosis → Liver failure → Cirrhosis → Hepatitis

Who is at risk?

- Women are more likely to develop AH
- Most AH-related hospitalizations are men
- Can occur even if alcohol consumption significantly reduced or stopped in last few weeks


AH Physiology

- CYP2E1
- ADH
- Kupffer cells activated
- Reactive O2 species, Acetaldehyde
- Oxidative degradation
- LPS from intestines
- Liver injury
- Cytokines, TNF, Interleukin

Diagnosis of AH

- Mainly clinical diagnosis, no specific lab marker
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma-glutamyl transpeptidase (GGT)
- Bilirubin
- Coagulopathy
- Hepatic encephalopathy, ascites

Role of liver biopsy: Gold standard, controversial

Diagnosis of Alcohol Hepatitis

- Scoring Assessment Tools
  - Maddrey
  - MELD
  - Glasgow
  - Lille

Maddrey’s Discriminant Factor (DF)

- Validated in 1978
- Retrospective review of biopsy proven AH
- Identified patients with 50% risk of mortality
- DF ≥ 32 merits drug therapy

Maddrey’s Discriminant Factor

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

MELD

\[ 9.57 \times \log_{10}(\text{SCr}) + 3.78 \times \log_{10}(\text{bili}) + 11.20 \times \log_{10}(\text{INR}) + 6.43 \]

Scorecard

<table>
<thead>
<tr>
<th>Retrospective Analysis</th>
<th>Pts</th>
<th>Comparison Assessment Tool</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheth, et al</td>
<td>34</td>
<td>Maddrey’s DF</td>
<td>Accurate predictor of 30-day mortality; MELD &gt;11</td>
</tr>
<tr>
<td>Dunn, et al</td>
<td>73</td>
<td>Maddrey’s DF</td>
<td>Accurate predictor of 30-day and 90-day mortality</td>
</tr>
<tr>
<td>Srikureja, et al</td>
<td>202</td>
<td>Maddrey’s DF, Child Pugh</td>
<td>Better predictor of 30-day and 90-day mortality; MELD &gt;18</td>
</tr>
</tbody>
</table>
### Glasgow (GAHS)
- Derived from 241 patients from Glasgow
- 144 patients with Maddrey’s DF ≥ 32 assessed
  - 64% found to have GAHS ≥ 9
- Accurate predictor of mortality

<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;50</td>
<td>≥50</td>
<td>--</td>
</tr>
<tr>
<td>WBC</td>
<td>&lt;15</td>
<td>≥15</td>
<td>--</td>
</tr>
<tr>
<td>BUN</td>
<td>&lt;5</td>
<td>≥25</td>
<td>--</td>
</tr>
<tr>
<td>PT ratio or INR</td>
<td>&lt;1.5</td>
<td>1.5-2.0</td>
<td>&gt;2.0</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;125</td>
<td>125-250</td>
<td>&gt;250</td>
</tr>
</tbody>
</table>


### Lille
- Predicts 6-month survival
- Performed 7 days after starting treatment
- Lille score >0.45 indicates non-responder to steroids

<table>
<thead>
<tr>
<th>Age</th>
<th>Albumin</th>
<th>Bilirubin (initial)</th>
<th>Bilirubin (day 7)</th>
<th>Creatinine</th>
<th>PT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>


### Scoring Assessment Tools

<table>
<thead>
<tr>
<th>DF</th>
<th>MELD</th>
<th>Glasgow</th>
<th>Lille</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>PT</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>INR</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>SCR</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Age</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>WBC</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Change in bilirubin between day 0 and day 7</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

### AH Physiology
- Block inflammation
- TNF inhibitor
- Avoid alcohol


### Corticosteroids
- 55 patients
- Prednisolone 40 mg PO Qday (n=24)
- Placebo (n=31)
- Outcome: Short-term mortality


### Corticosteroids
- Mortality: 1/24 in prednisolone group vs. 6/31 in placebo group (p = 0.10)

<table>
<thead>
<tr>
<th>Patients</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>Moderate</td>
<td>More severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Number</td>
<td>15</td>
<td>9</td>
<td>31</td>
</tr>
</tbody>
</table>

Corticosteroids

Over 15 trials investigating prednisolone vs. placebo in last 35 years

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Trials</th>
<th>Pts</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christensen (1995)</td>
<td>12</td>
<td>622</td>
<td>Does not support glucocorticoids in AH</td>
</tr>
<tr>
<td>Rambaldi (2008)</td>
<td>15</td>
<td>721</td>
<td>Does not support glucocorticoids in AH</td>
</tr>
</tbody>
</table>

Statistically significant reduction when DF ≥ 22

Corticosteroids

Assessed incidence of infection before and after initiating corticosteroids

Baseline Infection Screen

- Chest X-ray
- Blood cultures
- Urine culture
- Ascites culture

Resolution Criteria

- No need for O₂
- Neg blood cx
- Clear urine
- 50% ↓ PMN

Corticosteroid Controversies

- Choice of corticosteroid
- Need for taper
- IV administration
Pentoxifylline

- Phosphodiesterase inhibitor
- FDA approved for intermittent claudication
- Adverse events – nausea, vomiting, headache, bleeding
- Clinical pearls

Pentoxifylline in AH

- Hepatorenal syndrome as cause of death
  - 6/12 (50%) vs. 22/24 (91.7%); p=0.009
- Lab values did not improve in either group
- Only 77.6% completed PTX due to ADRs
- Non-survivors had higher TNF levels than survivors
  - PTX did not have appreciable decrease in TNF
  - Less pronounced increase in TNF in PTX group

Pentoxifylline vs. Prednisolone

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>68</td>
<td>121</td>
</tr>
<tr>
<td>Inclusion</td>
<td>DF ≥ 32</td>
<td>DF ≥ 32</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Infection, GI bleed</td>
<td>Infection, GI bleed</td>
</tr>
<tr>
<td>Outcome</td>
<td>Higher mortality in</td>
<td>Higher mortality in</td>
</tr>
<tr>
<td></td>
<td>prednisolone group</td>
<td>prednisolone group</td>
</tr>
<tr>
<td></td>
<td>(p=0.04)</td>
<td>(p=0.08)*</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>6 receiving prednisolone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 receiving pentoxifylline</td>
<td></td>
</tr>
<tr>
<td>Conclusion</td>
<td>Pentoxifylline is superior to prednisolone</td>
<td>Pentoxifylline is non-inferior to prednisolone</td>
</tr>
</tbody>
</table>

Combination of Treatment

- Pentoxifylline 400mg TID + Prednisolone 40mg Qday
- Outcomes: 6-month survival, Hepatorenal syndrome, Response to therapy
- No additional survival advantage of combination therapy
- Combination therapy did not result in improved 6-month survival compared with prednisolone alone
Comparison Study

• Primary outcome: Mortality at 28 days
• Secondary outcomes: Mortality or liver transplant at 90 days, 1 year; adverse events


Endpoints Prednisolone No Prednisolone p-value
28-day mortality 85/526 (14) 95/527 (18) 0.056
90-day mortality or transplant 139/478 (29) 141/490 (29) NS
1-year mortality or transplant 210/371 (57) 211/376 (56) NS


Early switch

121 pts with AH given prednisolone

No benefit in early switch to pentoxifylline


AASLD Recommendations

Therapeutic Algorithm for the Management of Acute Liver Failure


Alternative Therapies

Etanercept

• Pilot study with 13 pts showed success (92% survival rate at 30 days)
• 48 patients randomized to etanercept vs. placebo
• Similar 30-day mortality, significantly higher 6-month mortality in the etanercept arm


Infliximab

• 36 patients given infliximab vs. placebo, both groups received prednisolone
• Similar 2-month mortality, statistically higher incidence of severe infection in infliximab group
• Study discontinued due to potential harm


Inclusion 71 patients with severe AH (DF ≥ 32)

Primary outcome Short-term and long-term survival

Secondary outcome Incidence of infection, side effects

Results Similar incidence of mortality during treatment
Early mortality seen in enteral tube feeding group (p=0.025)
Greater incidence of infection in prednisolone group
Higher mortality rate seen after treatment in the prednisolone group


Alternative Therapies

174 patients

Prednisolone 40 mg PO Qday (n=89)

Prednisolone + N-acetylcysteine (n=85)

28 days duration

Significantly lower mortality at 1-month, not at 3-month or 6-month mortality


Alternative Therapies

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxandrolone</td>
<td>Not currently recommended</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Not currently recommended</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Not currently recommended</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>No significant survival benefit seen in AH in six studies</td>
</tr>
<tr>
<td>SAM</td>
<td>Possible benefit, two NIH funded trials studying effect in AH</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Not currently recommended</td>
</tr>
</tbody>
</table>


Role of Liver Transplant

• 6-month abstinence rule prior to transplant
• High 6-month mortality regardless of drug therapy
• Concern of alcohol relapse rate post-transplant without 6-month rule
• Subset of AH patients may be candidates for early transplant


Clinical Trials in Pipeline

<table>
<thead>
<tr>
<th>New therapies</th>
<th>Mechanism of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMM 124-E</td>
<td>Hyperimmune bovine colostrum enriched with immunoglobulin G</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Interleukin 1 receptor antagonist</td>
</tr>
<tr>
<td>Emrinasan</td>
<td>Oral caspase protease inhibitor</td>
</tr>
<tr>
<td>Interleukin 22</td>
<td>Hepatoprotective cytokine</td>
</tr>
</tbody>
</table>

• Diagnosis via breath biomarkers
• Prednisolone effect in mice models


Conclusion

• High incidence of mortality in AH, controversial management
• Recommended to give prednisolone 40 mg Qday x 28 days if DF ≥ 32
• If contraindicated, consider pentoxifylline
• Combination therapy not shown to have additive benefits
• Role of liver transplant may be considered in non-responders


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April 2015

References

12. Christensen E, Gluud C. Glucocorticoids are ineffective in alcoholic hepatitis: a randomized controlled trial. Gastroenterology 2000;119:1637-1648.