Alcoholic Hepatitis

Paul J. Thuluvath, MD, MBBS, FACG
Professor of Medicine & Surgery

Alcoholic Hepatitis

- Diagnosis and Severity Assessment
- Treatment and Prognosis
- Role of Liver Transplantation
Global Impact of Alcoholism

- 3.3 million deaths/year
  - 5.9% of all deaths (7.6% male, 4.0% female)
  - 3rd leading preventable cause of death in high income countries
- 5.1% of global burden of disease is attributed to alcohol-related diseases
  - In 2012, alcohol accounted for 139 million disability adjusted life years (DALY)
  - Top 5 risk factors for disease, disability, and death

WHO 2014

Alcoholic Liver Disease

- Increased risk when alcohol intake is more than 30 grams per day
  - 1% prevalence in those who drink 30-60 grams per day
  - 6% prevalence in those who drink 120 grams per day
- In the USA, in 2003, 44% of all deaths from liver disease related to alcohol

Bellentani Gut 1997
JAMA 2004;291:1238
Confounding Factors

- Female gender
- Obesity
- Viral hepatitis
- Genetic predisposition
  - SNP of PNPLAe gene
  - Drinking habits may be influenced by fast ADH or slow ALDH enzymes

Alcoholic Liver Disease

- Alcoholism
  - Fatty Liver 90%
  - Normal Liver 10%
  - 20% Alcoholic Hepatitis
  - 15% Alcoholic Cirrhosis
  - 30%
Alcoholic Hepatitis

- A clinical syndrome characterized by rapid onset of jaundice and liver failure after decades of alcohol use
  - Age: 40-60 yrs, M>F (but women are more prone)
  - Symptoms: anorexia, fever, right upper quadrant pain, abdominal distension, proximal muscle weakness or confusion
  - Signs: jaundice, hepatomegaly, ascites, proximal myopathy or asterixis. Rarely malnutrition
Alcoholic Hepatitis

• Usually AST/ALT >2.0
  – AST usually not higher than 10 times, but may be higher in alcoholic foamy degeneration
• Elevated INR
• Moderate leukocytes, decreased lymphocytes, platelets & hemoglobin, elevated ESR
  – Rarely leukemoid reactions
• Macrocytosis
  – B12 or folate deficiency, alcohol toxicity, increased lipid on red cell membrane

Alcoholic Hepatitis

• Symptomatic alcoholic hepatitis
  – 50% will have concomitant cirrhosis
• Recidivism is common (67-81%)
• Medications that may reduce recidivism
  • Naltreoxone
  • Acamprosate
  • Baclofen
  • Gabapentin
Predictors of Outcome

– **Discriminant Function**: $4.6 \times PT \{\text{patient PT-control PT}\} + \text{serum total bilirubin (in mg/dL)}$
  - DF >32 associated with high mortality
  - 30-day mortality ~30% (versus less than 10% with mild to moderate disease)
  - Higher in the presence of encephalopathy

– **MELD score**
  - >21 associated with 20% 90-day mortality

– **Lille score calculated after 7 days of prednisolone**

Early Predictors on Treatment

**Lille Score**

- Decrease in serum bilirubin at day 7 from baseline is an excellent predictor of response on prednisolone
Early Predictors on Treatment Lille Score

• The model uses 6 variables: age, creatinine, albumin, PT, bilirubin (baseline, ie prior to treatment), and bilirubin at day 7
• Mortality at 6 months was higher in Lille score >0.45 (75%) when compared to those less than <0.45 (15%)
  – No advantage in continuing treatment if Lille score is more than 0.45

Is there a need for liver biopsy in alcoholic hepatitis?

• ~20% misdiagnosis
• Useful when diagnosis is in doubt or clinical trials
• Could be beneficial for prognostic purposes
Mortality based on Liver histology

- Alcoholic Hepatitis Histologic Score (AHHS) on the basis of 4 histological parameters
  - degree of fibrosis
  - degree of neutrophil infiltration
  - presence of megamitochondria
  - type of bilirubinostasis (hepatocellular, ductular, both)

Altamirano J et al Gastroenterology 2014
90-day Mortality
Score 0-3: 3%;  Score 4-5: 19%; Score 6-9: 55%

Altamirano J et al Gastroenterology 2014

Test Validation Cohort

Causes of Death in Alcoholic Hepatitis

- Liver failure (55%)
- GI bleeding (21%)
- Sepsis (7%)
- Others

Imperiale TF 1990
Treatment of Alcoholic Hepatitis

Alcoholic Hepatitis - Treatment

- Nutritional supplements (enteral + supplements)
  - Discordant results on survival
    - Improved liver tests and histology reported
  - Encourage good nutrition (multiple meals and snacks), high protein (1.5 g/kg) and high calories (35-40 kcal/kg)
  - Vitamin supplements: thiamine, pyridoxine, folate
  - Mineral supplements: phosphate, magnesium
- Surveillance for infection
  - Cultures of body fluid and sputum if infection suspected
Alcoholic Hepatitis - Treatment

• Mild to moderate alcoholic hepatitis: only supportive care and alcohol abstinence
• Severe alcoholic hepatitis (DF ≥32)
  – prednisolone 40 mg daily for 28 days followed by rapid taper
  – non-responders (~40% do not respond) have a 6-month mortality of 70%

Steroid Treatment – Meta-analysis

• Rambaldi et al 2008
  – 15 randomized studies, 721 patients
  – Survival advantage only if DF ≥32 (RR 0.37)
• Mathurin P et al 2011
  – 5 randomized studies, 418 patients
  – 28-day mortality 34% on placebo (n=197) and 20% on steroid (n=221) in severe AH (p =0.0005)
  – Survival advantage only if Lille score <0.56
Pentoxifylline

- Cochrane meta-analysis (Whitfield 2009)
  - 5 trials, 336 patients
  - Mortality reduced, RR 0.64 (CI 0.46-0.89)
  - Not significant after adjustment, and there was heterogeneity and bias of trials
- Hepatorenal syndrome is lower in treated group compared to placebo
  - Meta-analysis (910 trials, N=884), RR 0.47 (CI 0.26-0.86) (Parker R et al 2013)

---

**Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH trial)**

Severe AH (n=1092)
DF ≥ 32

- Placebo/Placebo N=272
- Placebo/Prednisolone N=274
- Pentox/Placebo N=273
- Pentox + Pred N=273

- Primary endpoint: mortality at 28 days
- Secondary endpoints: mortality at 90 days and 1 year

Thursz M et al NEJM 2015;372:1619-28
Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH trial)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Placebo/Placebo N=272</th>
<th>Placebo/Prednisol N=274</th>
<th>Pentox/Placebo N=273</th>
<th>Pentox + Pred N=273</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day Mortality</td>
<td>17%</td>
<td>14%</td>
<td>19%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Thursz Mret al NEJM 2015;372:1619-28

Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH trial)

- Prednisolone group (n=526)
  - 28 day mortality: 0.72 (0.52-1.01, P=0.06)
    - Significant on effect multivariate analysis (p=0.02)
  - Infections more common (13% vs. 7%, p=0.007)
- Pentoxifylline group (n=518)
  - 28 day mortality: 1.07 (0.77-1.49, P=0.87)

Both drugs had no effect on 90-day or 1-year mortality

Thursz Mret al NEJM 2015;372:1619-28
STOPAH Summary

- Prednisolone improves 28-day mortality
  - No benefit after this time
- Pentoxifylline offers no benefit
- Combination is not beneficial
- Abstinence is a major determinant of survival after 90 days

Pentoxifylline in Non-responders To Prednisolone

- Corticosteroids: Prednisolone 40 mg/day
- Pentoxifylline: 400mgx3/day
- Interruption of pentoxifylline after 28 days

Billirubine at Day 7 ≥ day 0: Non-responders to corticosteroids

Pentoxifylline is ineffective in non-responders to corticosteroids

Combination of Prednisolone and Pentoxifylline

- STOPAH study (N=273): no benefit when compared to placebo
- Corpox study (n=137): no benefit
  - No differences in response assessed by Lille score or the incidence of HRS
Steroid + N-acetyl cysteine (NAC) vs. Steroids alone

• 174 patients with DF >32 + histology consistent with alcoholic hepatitis were randomized from 11 centers in France
  – Group 1: Prednisone 40 mg daily for 4 weeks
  – Group II: Prednisone 40 mg daily for 4 weeks +
    NAC for 5 days

• Prednisone group
  – Day1-5:
    • 1000 mL of D5 in 24 hours
• N-Acetyl Cysteine + Prednisone
  – Day1:
    • 150 mg/kg (in 250 mL of 5% dextrose) in 30 minutes followed by 50 mg/kg in 4 hrs (500 mL D5), 100 mg/kg in 16 hrs (1000 mL D5)
  – Day 2-5
    • 100 mg/kg in 1000 mL D5 over 24 hrs


Mortality
4 weeks: 24% vs 8%, p <0.01
12 weeks: 34% vs. 22%, p=0.06
24 weeks: 38% vs. 27%, p=0.07)
Unproven treatment options

- Granulocyte colony stimulating factor (GCSF) with or without prednisolone or pentoxifylline
- Metadoxine (anti-oxidant) with or without prednisolone or pentoxifylline

Optimal treatment of AH based on current evidence

- Supportive care and abstinence for mild-to-moderate hepatitis
- Supportive care and prednisolone for 28 days + NAC for 5 days for severe AH \( (DF > 32) \)
- Stop prednisolone if Lille score >0.56
- Consider liver transplantation in selected cases if Lille score >0.45
Long term survival in severe alcoholic hepatitis

• 272 with severe alcoholic hepatitis treated with steroids
• 6 month survival
  – responders (Lille <0.45) 82.7%
  – non-responders (Lille >0.45) 27.6%

Louvet A et al Hepatology 2010;52:381a

Long term survival in severe alcoholic hepatitis treated with steroids

• Recidivism
  – heavy drinking 53.6% after median time of 180 days (60-180 days)

Louvet A et al Hepatology 2010;52:381a
5-year survival in severe alcoholic hepatitis treated with steroids

- Responders to steroids:
  - responders & abstinent: 80.4%
  - responders and not abstinent 39%
- Non-responders to steroids
  - non-responders who drank 0%
  - Non-responders & abstinent 0-20%

Louvet A et al Hepatology 2010;52:381a

Liver Transplantation?

- Organ shortage
- Recidivism
- Long term outcomes
- Moral and ethical issues
Liver Transplantation for Alcoholic Hepatitis

- Case control study of LT in patients with non-response to steroids (NRS) at day-7 (Lille score 0.88)
- 26 listed within 13 days of NRS
  - Selected by consensus (social, co-morbidities..)
  - Less than 2% of patients admitted with alcoholic hepatitis were selected.
  - 6 month survival (77% vs. 23%)
  - Three patients resumed drinking at 720, 740 and 1140 days


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

Alcoholic Hepatitis

DF >32 and no obvious infection

Treat with NAC for 5 days + prednisolone

<0.45

Continue prednisolone for 28 days

>0.45 or worsening liver failure

Lille Score on day-7

Consider LT in selected cases

Conclusions

• Severe alcoholic hepatitis (DF >32) should be given a trial of corticosteroids
  – combination of prednisone and NAC is an option
  – Enteral nutrition is encouraged
  – Pentoxifylline does not appear to be effective

• Those who do not respond at day-7 should be considered for alternate treatment strategies
  – In selected cases, liver transplantation may be considered