Non-viral Hepatitis: AIH and ETOH

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Objectives – Autoimmune Hepatitis (AIH)

• Define the diagnostic criteria for AIH
• Describe typical treatment for AIH & overlap syndromes
• Describe situations for cessation of therapy for AIH
Objectives – Alcoholic Liver Disease

• Describe the spectrum of alcoholic liver disease
• Understand the treatments for alcohol use disorder, alcohol withdrawal, and alcoholic hepatitis
• Understand the role of liver transplant in alcoholic liver disease

Autoimmune Hepatitis (AIH)

– Elevated aminotransferases
  • 70-80% chronic hepatitis
  • 1/3 cirrhosis on presentation
  • Rare Acute Liver Failure
– Women ~70%
– Fatigue, arthralgias, 1/3 asymptomatic
– Immunoglobulins (IgG)
– Autoantibodies
  • ANA, ASMA, Anti-LKM Ab
Type 1 and Type 2 AIH

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female:Male</td>
<td>4:1</td>
<td>10:1</td>
</tr>
<tr>
<td>Demographic</td>
<td>All ages</td>
<td>Child-young adult</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Usually indolent, rare ALF</td>
<td>More severe, rare ALF</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>ANA, SMA, anti-F-actin,</td>
<td>Anti-LKM1, anti-LC1, anti-LKM3</td>
</tr>
<tr>
<td>Response to steroids</td>
<td>Excellent for most</td>
<td>Excellent in minority, failure common</td>
</tr>
<tr>
<td>Need for long term immune suppression</td>
<td>Most require long term</td>
<td>Nearly all require long term</td>
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</tbody>
</table>


“Interface hepatitis”

Selected AIH Autoantibodies

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Disease &amp; Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>Type 1 AIH, also other chronic liver disease</td>
</tr>
<tr>
<td>SMA</td>
<td>Type 1 AIH</td>
</tr>
<tr>
<td>LKM-1</td>
<td>Type 2 AIH, CHC</td>
</tr>
<tr>
<td>Soluble liver antigen</td>
<td>Type 1 or 2 AIH, Severe disease &amp; ↑ relapse</td>
</tr>
<tr>
<td>(SLA)</td>
<td></td>
</tr>
<tr>
<td>Actin</td>
<td>AIH, young pts, aggressive disease</td>
</tr>
<tr>
<td>Liver cytosol-1 (LC)</td>
<td>Type 2 AIH, liver specific</td>
</tr>
<tr>
<td>Asialoglycoprotein</td>
<td>Type 1 or 2 AIH, Severe disease, ↑ relapse potential</td>
</tr>
<tr>
<td>receptor (ASGPR)</td>
<td></td>
</tr>
<tr>
<td>AMA</td>
<td>PBC, up to 1/3 AIH pts</td>
</tr>
</tbody>
</table>

13% AIH patients lack antibodies

Drug induced auto-immune like hepatitis

- Acute idiosyncratic reaction (d/c med → resolves)
- Well described
  - Minocycline or Nitrofurantoin = 90% cases
  - Dihydralazine, Halothane, Methyldopa
- Probable
  - Atorvastatin, Diclofenac, Infliximab, Adalimumab,
    Natalizumab, Isoniazid, Prophythiouracil, Liraglutide
- Supplements
  - Black cohosh, Germander, Hydroxycut, Ma huang,
    Melatonin, Green tea extract
Overlap syndromes

- 14-20% frequency
- Primary sclerosing cholangitis
- Primary biliary cirrhosis
  - Paris criteria for diagnosis
- IgG4-associated AIH
- Treat both/predominant disease

Simplified Diagnostic Criteria

<table>
<thead>
<tr>
<th>Autoantibodies:</th>
<th>≥1:40</th>
<th>≥1:80</th>
<th>≥1:40 Positive</th>
<th>+1</th>
<th>+2</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA or SMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LKM-1 Anti-SLA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1:40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1:80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1:40 Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunoglobulin Level IgG or γ-Globulin</th>
<th>&gt;ULN</th>
<th>&gt;1.1xULN</th>
<th>+1</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LKM-1 Anti-SLA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA or SMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histologic features:</th>
<th>Compatible w AIH</th>
<th>Typical AIH</th>
<th>+1</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Score

- ≥7 Definite
- ≥6 Probable

### Treatment regimens

<table>
<thead>
<tr>
<th></th>
<th>Prednisone monotherapy (mg/day)</th>
<th>Pred + azathioprine (mg/day)</th>
<th>Budesinide + azathioprine (mg dosing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>60</td>
<td>30 + 50</td>
<td>3 TID + 50 (1-2 mg/kg)</td>
</tr>
<tr>
<td>Week 2</td>
<td>40</td>
<td>20 + 50</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>30</td>
<td>15 + 50</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>30</td>
<td>15 + 50</td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>≤20</td>
<td>10 + 50</td>
<td>~3 mg/day + 50</td>
</tr>
</tbody>
</table>

**Goals of remission:**
1) Normal AST, ALT, Bili, immunoglobulins
2) Absence of inflammatory activity on liver biopsy

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### TPMT Testing in AIH

- Genotype v. Activity testing
- Does not always predict side effects
  - Most pts w/toxicity $\Rightarrow$ normal TPMT activity
- Consider pretx testing
  - 0.3% w/absent TPMT activity
- Cytopenia & cirrhosis
  - More predictive of AZA toxicity

Czaja AJ. The management of AH beyond consensus guidelines. AP&T 2013;38:343-64.
Second Line Treatments

- Mycophenylate mofetil (MMF)
  - 750-1000 BID
  - GI side effects
- Tacrolimus
  - 3-5 mg BID
  - Side effects → CKD, HTN, DM
- Infliximab
  - 5 mg/kg 2-8 weeks
  - Infections, Infusion RXs
- Rituximab
  - 2x1000 mg infusions Day 1 and 15
  - Infections, infusion RXs

6-Mercaptopurine (6-MP)

- AZA is the prodrug of 6-MP
- Use as a second-line if intolerance of AZA?
- 2015 study
  - 15/20 6-MP successful
  - 2 pts with insufficient response to AZA → no response to 6-MP

Treatment of overlap syndromes

• No evidence based guidelines
• Steroids + Ursodeoxycholic acid 13-15 mg/kg daily

Pearls of AIH Treatment

• If patient obese, consider weight based azathioprine dosing (1-2 mg/kg) rather than flat dose 50 mg/day
• Consider budesinide if steroid maintenance required & pt at risk of side effects
Pregnancy and AIH

• High risk but possible
• Pregnancy=maternal immunosuppression
  – ↓ meds during pregnancy
• AZA ok
• Prednisone monotherapy most frequently used (avoid budesonide monotherapy)
• Post partum flares


Remission in AIH

• Before attempting, remission must be documented
• Once in remission, attempt at withdrawal ok
• 15% relapse by 6 months, 79-86% by 3 yrs
• After initial relapse → do not attempt to withdrawal again
Alcoholic liver disease

- 50% of U.S. adults drink
- 70% EtOH used by 10% population
- 11% men & 4% women alcoholics
- 15-30% alcoholics → cirrhosis
- All patients with alcoholic liver disease are not alcoholics
  – intermittent binge drinking

Kulig C. Alcoholic liver disease, alcoholism, and alcohol withdrawal syndrome. GI/Liver Secrets 2015.

Philippe Mathurin, Ramon Bataller

Trends in the management and burden of alcoholic liver disease


http://dx.doi.org/10.1016/j.jhep.2015.03.006
Spectrum of alcoholic liver disease (ALD)

- Fatty Liver (macrovesicular)
- Microvesicular steatosis (alcoholic foamy degeneration)
- Alcohol hepatitis
- Alcohol cirrhosis

Alcoholic liver disease treatment

- Abstinence
- Abstinence
- Abstinence
- Nutrition
- Substance use disorder program
- Vitamin supplements (folate & B12)
## Nutrition in alcoholic liver disease

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A, D, E, K</td>
<td>Check levels before replacement</td>
<td></td>
</tr>
<tr>
<td>Vitamin B1 (thiamine)</td>
<td>100 mg/d</td>
<td>(give with glucose initially to prevent Wernicke encephalopathy)</td>
</tr>
<tr>
<td>Vitamin B2 (riboflavin)</td>
<td>1.7 mg/d</td>
<td>Only replace if documented deficiency</td>
</tr>
<tr>
<td>Vitamin B6 (pyridoxine)</td>
<td>2 mg/d</td>
<td>Sufficient dose in MVI, neuropathy</td>
</tr>
<tr>
<td>Folate</td>
<td>400 mcg/d</td>
<td>Sufficient dose in MVI, macrocytic anemia, malabsorption</td>
</tr>
<tr>
<td>Vitamin B12 (cobalamin)</td>
<td>50 mcg/d</td>
<td>Rare unless chronic pancreatitis also</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>60 mg/d</td>
<td>Sufficient dose in MVI</td>
</tr>
<tr>
<td>Magnesium</td>
<td>100-400 mg/d</td>
<td>May need IV replacement</td>
</tr>
<tr>
<td>Calcium</td>
<td>Variable</td>
<td>Adjust for albumin</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Variable</td>
<td>May need IV replacement</td>
</tr>
<tr>
<td>Iron</td>
<td>Variable</td>
<td>Rule out GI blood loss</td>
</tr>
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</table>

## Alcohol use disorder treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone</td>
<td>50-100 mg/day</td>
<td>Cannot use w/opioids</td>
</tr>
<tr>
<td></td>
<td>380 mg q4 wks (Depot)</td>
<td></td>
</tr>
<tr>
<td>Acamprosate</td>
<td>666 mg TID (↓ renal insufficiency)</td>
<td>Glutamate neurotransmitter Better results → European</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>250-500 mg/day</td>
<td>Ineffective in meta-analysis High rates of non-compliance</td>
</tr>
<tr>
<td>Topiramate</td>
<td>50-150 mg/day</td>
<td>Not FDA approved for EtOH Further study needed</td>
</tr>
<tr>
<td>Baclofen</td>
<td>30 mg/day</td>
<td>Mixed results in trails but overall safe</td>
</tr>
<tr>
<td>SSRI’s</td>
<td>Variable</td>
<td>Good if co-existing depression</td>
</tr>
</tbody>
</table>
Alcohol investigational treatments

• Not ready for prime time
  – Nalmefene
  – Gabapentin
  – Ondansetron
  – Combination therapy

Alcohol withdrawal treatment

• Hydration & Nutrition
• Thiamine
• Benzodiazepines
  – reduce severity of symptoms
• Seizures
  – Diazepam, phenytoin, carbamezepine
• Agitation/hallucinations
  – Haloperidol
• Tachycardia
  – B-blockers or clonidine
Alcoholic hepatitis

- Maddrey discriminant function
  - Bilirubin + 4.6 (PT-control)
  - Usual cutoffs <32, ≥32, >54
- Prednisolone, Pentoxyfylline, N-acetylcysteine (NAC)
- Liver transplant

Steroids or Pentoxyifylline (PTX) for Alcoholic Hepatitis (STOPAH) Trial

- >1000 severe alcoholic hepatitis pts
- Prednisolone, PTX, Pred+PTX, Placebo
- Modest short term ↓ mortality w/steroids
- ↑ infection w/steroids

Kaplan–Meier Curves Showing Overall Survival According to Study Group

A. Prednisolone vs. No Prednisolone

<table>
<thead>
<tr>
<th>Days since Start of Treatment</th>
<th>Prednisolone</th>
<th>No prednisolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>6</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>8</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>12</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>14</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>16</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>18</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

No. at Risk
- Prednisolone: 546
- No prednisolone: 542

B. Pentoxifylline vs. No Pentoxifylline

<table>
<thead>
<tr>
<th>Days since Start of Treatment</th>
<th>Pentoxifylline</th>
<th>No pentoxifylline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>6</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>8</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>12</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>14</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>16</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>18</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

No. at Risk
- Pentoxifylline: 546
- No pentoxifylline: 533

C. One-Year Survival in All Groups

No. at Risk
- Placebo-placebo: 272
- Prednisolone-placebo: 274
- Pentoxifylline-placebo: 271
- Prednisolone-pentoxifylline: 272

Proportion Surviving
- Placebo-placebo
- Prednisolone-placebo
- Pentoxifylline-placebo
- Prednisolone-pentoxifylline
Prednisolone with n-acetylcysteine

- 6 month survival Pred/NAC 38% versus Pred 27% (p=0.07)
- Pred/NAC group
  - ↓ Short term mortality
  - ↓ Infections

The Lille model: A tool for therapeutic strategy in pts w/severe alcoholic hepatitis treated w/ steroids

Hepatology. 45(6);1348-1354, 22 MAY 2007
Two- & 6-month overall mortality probability according to combination model (Lille model & Maddrey DF)


The Alcoholic Hepatitis Histological Score (AHHS)

**Alcoholic hepatitis summary**

- Maddrey up front to determine prednisolone
- OK to add NAC
- Little role for pentoxyfylline
- Lille score at Day#7 to determine response
- Consider liver biopsy if transplant is a consideration

**Transplant for Alcoholic Hepatitis**

- Survey of 45 centers
- 12/45 listed AH for OLT
- 45/3290 transplants for AH (1.4%)
- Good 1 year (93%) & 5 year survival (87%)
- 18% recidivism

Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls


ELAD for Severe Alcoholic Hepatitis (AASLD 2015)

- 96 ELAD, 107 SOC 40 sites globally
- No difference in overall survival
  - 52.1% v 52.3%
- Subgroup MELD<28 better OS with ELAD
  - 71% versus 57%, p=0.077
- Subgroup younger better OS with ELAD
  - 67% versus 55%, p=0.167
Alcoholic liver disease conclusions

• Wide spectrum of disease
• Alcoholic hepatitis
  – High mortality
  – ? Steroids short term
• No single treatment for detox & abstinence
  – Individualized to the patient
• Transplant for EtOH liver disease
  – Similar survival
  – Controversial without 6 months abstinence