Cholestatic Autoimmune Hepatitis and Overlap Syndromes

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Basic Principles

• AIH “hepatitic” not “cholestatic”

• Cholestatic phenotypes exist and constitute “overlap syndromes”

• Clinical descriptions rather than valid pathological entities

• Importance: variable response to Rx

Czaja AJ: J Hepatol 44:251, 2006
Boberg KM et al: J Hepatol 54:374, 2011
Basic Principles

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Boberg KM et al: J Hepatol 54:374, 2011

Porous Diagnostic Boundaries

Common Non-specific Shared features

ANA
Alk Phos
Gamma globulin

CUC
Cholangitis
Interface hepatitis

AIH
hepatitis

PBC

PSC

Rare

2 case reports

**Pathogenic Considerations**

**Hypothesis**
- Variant or atypical classical disease
- Transition stage
- Concurrent diseases
- Separate entity

**Support**
- AIH features not disease-specific
- PBC or PSC ↔ AIH
- Possible but unlikely
- Different outcomes

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**Pervading Concept**

Predominant disease determines the nature and behavior

- AIH + PBC ≠ PBC + AIH
- AIH + PSC ≠ PSC + AIH

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Boberg KM et al: J Hepatol 54:374, 2011
Diagnostic Criteria for Overlaps

**AIH and PBC**
- AIH features
- AMA positive
- Bile duct injury or loss

**AIH and PSC**
- AIH features
- AMA negative
- Abnl cholangiogram

**Diagnostic caveat**
- AIH scoring systems should not be used

Boberg KM et al: J Hepatol 54:374, 2011
## Diagnostic Instruments

<table>
<thead>
<tr>
<th>Diagnostic Instruments</th>
<th>Performance</th>
</tr>
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<tbody>
<tr>
<td>Original scoring system</td>
<td>Sensitivity, 50-62%</td>
</tr>
<tr>
<td>Simplified scoring system</td>
<td>Sensitivity, 54%</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Independent predictor</td>
</tr>
<tr>
<td>Clinical judgment</td>
<td>Gold standard</td>
</tr>
</tbody>
</table>

Papamichalis PA et al: J Autoimmune Dis 4:3, 2007  
Gatselis NK et al: Dig Liver Dis 42:807, 2010  

AEG 2013  
ACG Postgraduate Course • October 12-13, 2013
### Frequencies of Overlap Syndromes

<table>
<thead>
<tr>
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<th>AIH Predominant</th>
<th>PBC Predominant</th>
<th>PSC Predominant</th>
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<tr>
<td>+PBC</td>
<td>7-13%</td>
<td>+AIH 3-12%</td>
<td>+AIH 6-17%</td>
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<td>+PSC</td>
<td>6-11%</td>
<td>+PSC ±0%</td>
<td>+PBC ±0%</td>
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Gheorghe L et al: Eur J Gastroenterol Hepatol 16:585, 2004  
Boberg KM et al: J Hepatol 54:374, 2011  
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“Paris Criteria” for AIH/PBC

**AIH Components (2 of 3)**
- ALT≥5-fold ULN
- IgG≥2-fold ULN or SMA
- Interface hepatitis

**PBC Components (2 of 3)**
- Alk phos≥2-fold ULN or GGT≥5-fold ULN
- AMA
- Florid duct lesions

Sensitivity, 92%; Specificity, 97%
Endorsed by EASL

EASL Clinical Practice Guidelines: J Hepatol 51:237, 2009
Kuiper EM et al: Clin Gastroenterol Hepatol 8:530, 2010
Steroids in AIH-Predominant Overlap with PBC (Alk Phos <2-fold ULN)

<table>
<thead>
<tr>
<th>Steroid response</th>
<th>Classical AIH (%)</th>
<th>AIH/PBC AP&lt;2-ULN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>86</td>
<td>81</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Partial response</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>


UCDA in PBC-Predominant Overlap

Ursodeoxycholic acid treatment, 2 yrs

- Improved (%)
- PBC + UDCA
- PBC/AIH +UDCA

**UDCA in PBC Overlap with Strong Features of AIH**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>PBC + AIH (%)</th>
<th>PBC Only (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varices</td>
<td>50</td>
<td>23</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GI Bleeding</td>
<td>35</td>
<td>15</td>
<td>0.03</td>
</tr>
<tr>
<td>Ascites</td>
<td>42</td>
<td>15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Death or LT</td>
<td>38</td>
<td>19</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>


**Steroid and UDCA Rx for Overlap by “Paris Criteria”**

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Final</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alk phos (IU/L)</td>
<td>140</td>
<td>95*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>132</td>
<td>32*</td>
<td>0.02</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>52</td>
<td>31*</td>
<td>0.02</td>
</tr>
<tr>
<td>Fibrosis worse</td>
<td>0/6**</td>
<td></td>
<td>0.04</td>
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Combined therapy endorsed by EASL
Not strongly evidenced-based

EASL Clinical Practice Guidelines: J Hepatol 51:237, 2009
# Budesonide with Azathioprine and UDCA in AIH/PBC Overlap

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Hepatic Fibrosis</th>
<th>Rx Duration</th>
<th>Response</th>
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<tbody>
<tr>
<td>AIH/PBC ++</td>
<td>6 weeks</td>
<td>FAILURE</td>
<td></td>
</tr>
<tr>
<td>AIH/PBC +</td>
<td>19 months</td>
<td>RESPONSE</td>
<td></td>
</tr>
<tr>
<td>AIH/PBC +</td>
<td>3 months</td>
<td>FAILURE</td>
<td></td>
</tr>
<tr>
<td>AIH/PBC +</td>
<td>1 week</td>
<td>FAILURE</td>
<td>ALLERGY</td>
</tr>
</tbody>
</table>

Results of Corticosteroid Therapy in AIH/PSC Overlap

- Remission
- Treatment failure
- Death or transplant


Treatment Options for AIH/PSC

<table>
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<th>Treatment Options</th>
<th>Response (%)</th>
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<tr>
<td>Mycophenolate mofetil</td>
<td>0</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>2 patients</td>
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<tr>
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<td>20-100</td>
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<td>Steroids + Low dose UDCA</td>
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Combined Rx endorsed by EASL and AASLD
Not evidence-based

EASL Practice Guidelines: J Hepatol 51:237, 2009
AASLD Practice Guidelines: Hepatology 51:660, 2010

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**Subclassifications**

- **Autoimmune hepatitis**
  - PBC
    - AMA
    - Alk Phos > 2-ULN or GGT > 5-ULN
    - Bile duct injury
  - Cholestatic Syndrome
    - AMA-negative
    - Normal cholangiogram
    - Bile duct injury/loss
  - PSC
    - AMA-negative
    - Abnormal cholangiography

AMA-negative PBC
Small duct PSC


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Steroids in AIH Overlap Syndrome with Undefined Cholestatic Nature

- AIH + Undefined Cholestatic Nature
- AIH + Large Duct PSC
- Classical AIH

Remission: *P=0.003
Treatment failure: **P=0.05
Death or transplant: **P=0.05

Treatment Options for AIH with Undefined Cholestasis

<table>
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<tr>
<th>Treatment Options</th>
<th>Response</th>
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<tr>
<td>Corticosteroids</td>
<td>None</td>
</tr>
<tr>
<td>Low dose UDCA</td>
<td>Variable</td>
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<tr>
<td>Steroids + Low dose UDCA</td>
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No preferred Rx and all unendorsed


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Conclusions

- Overlaps common
- Cholestatic diseases with AIH
- Affect outcome and Rx strategy
- Consider in problematic patients
- Management guidelines recommend combination Rx