Interface hepatitis in PBC: Prognostic marker and therapeutic target

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Key features of piecemeal necrosis

adapted from Bianchi L. et al. 1988
Grading severity of PMN

- **Minimal:**
  - Not present in all portal tracts (PT)
  - Patchy distribution

- **Moderate:**
  - Present and restricted at the periphery of at least half of the PT

- **Severe:**
  - Necrosis surrounding more than half of the circumference of the majority of PT and along fibrous septa
Prevalence of lymphocytic and biliary piecemeal necrosis

Portmann et al. Gastroenrology 1984


Biliary piecemeal necrosis
Moderate lymphocytic piecemeal necrosis
Severe lymphocytic piecemeal necrosis
Grading severity of PMN

- **Minimal:**
  - Focal alteration of the periportal plate in some portal tracts.

- **Moderate:**
  - Diffuse alteration of the periportal plate in some portal tracts
  or
  - Focal lesions around all portal tracts.

- **Severe:**
  - Diffuse alteration of the periportal plate in all portal tracts.
### Relationships between fibrosis and other elementary histological lesions

<table>
<thead>
<tr>
<th>Elementary lesions</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interlobular bile duct lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary cell necrosis</td>
<td>0.50†</td>
<td>0.58</td>
<td>0.54</td>
<td>0.33</td>
<td>NS</td>
</tr>
<tr>
<td>Paucity (prevalence)</td>
<td>0.38</td>
<td>0.54</td>
<td>0.80</td>
<td>0.83</td>
<td>0.002</td>
</tr>
<tr>
<td>Ductular proliferation</td>
<td>0</td>
<td>0.66</td>
<td>1.03</td>
<td>1.60</td>
<td>0.002</td>
</tr>
<tr>
<td>Lymphocytic piecemeal necrosis</td>
<td>0.25</td>
<td>0.71</td>
<td>1.40</td>
<td>1.30</td>
<td>0.002</td>
</tr>
<tr>
<td>Mononuclear portal and periportal inflammation</td>
<td>1.50</td>
<td>1.80</td>
<td>0.79</td>
<td>0.70</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*P values for the Jonckheere-Terpstra test
†For each lesion, the mean value in the scoring system was calculated

Degott et al. Hepatology 1999
Biochemistries according to severity of bile duct paucity and lymphocytic PMN in PBC

Poupon et al. J Hepatol 1999
FibroScan®

TM Mode

A-scan

Pressure Gauge

ID

patient

SMITH

JOHN

A12478

21/03/1973

BROWN

07/10/03

00:02:55

Median

3.9

IQR

0.7

3.6

IQR (kPa)

CS (kPa)

Information

Start

Print

Valid 10

Test 4/10
Impact of 2-year UDCA treatment on histology in PBC

Poupon et al. NEJM 1991
Effect on fibrosis

![Graph showing the effect of UDCA, Placebo, and Spontaneous course on the probability of remaining free of extensive fibrosis or cirrhosis over 10 years. The graph includes error bars and lines for each group.]
Analysis of factors assessed under UDCA therapy affecting histological stage progression

- **Univariate analysis**
  - Stage at diagnosis
  - S. bilirubin
  - S. albumin
  - Biochemical response to UDCA
  - ILBD paucity
  - L. PMN grade

- **Multivariate analysis**
  - Stage at diagnosis
  - S. bilirubin
  - L. PMN grade
Time profile of cirrhosis development

Graphs showing the incidence of cirrhosis over time from different stages.

- A: From stage I
- B: From stage II
- C: From stage III

Incidence of cirrhosis (%) vs Years
Time profile of cirrhosis development

from Stage II

A  with bilirubin ≤ 17 μM and albumin ≥ 38 g/l

B  with albumin ≥ 38 g/l and a moderate PMN

Incidence of cirrhosis (%) vs. years

Severe PMN
Moderate PMN
Mild PMN

Bilirubin > 17 μM
Bilirubin ≤ 17 μM
Pathophysiiological events in PBC

- Insult
  - Auto / alloimmune
  - Genetic
  - Virus
  - Exotoxin (bact. Ag.)
  - Bile acid

- Inflammatory response

- Resolution

- Host genetic background

- Progression

- Chronic inflammation
  - Cholestasis (i.e. retention of bile acids / toxins)

- Necrosis
- Apoptosis

- PAMPs
- Infection

- Stellate cells
- Myofibroblasts: prolif. activation

- Cholestasis
- T reg lymphocytes
- Intraimmune immunity

- Fibrosis
The inflammatory process in cholangiopathies

Schuppan et al. 1998, Fava et al. 2005
Ductal cholestasis
Mechanisms of action of UDCA

- Antiinflammatory
- Cytoprotection
- Immunomodulation
- Choleresis
- Signalling pathways
- Mitochondrial integrity

UDCA
Mechanisms of action of UDCA

UDCA

- Ductal cholestasis
- Canalicular cholestasis
- Intestinal BA conservation

Cholestasis
Mechanisms of action of UDCA

- Cholestasis
- HLA
- PAMPs
- IFNγ, PLA2
- Cellular stress
- IFNγ
- PPARα/γ
- PL secretion

Immune activation
Apoptosis
Necrosis
Fibrogenesis
## Therapeutic targets in inflammatory cholangiopathies

<table>
<thead>
<tr>
<th>Cholestasis</th>
<th>Immune activation</th>
<th>Fibrogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Procholestatic cytokines</td>
<td>1. T cell activation and proliferation</td>
<td>1. Profibrogenic cytokines</td>
</tr>
<tr>
<td>2. Ductal secretion</td>
<td>2. Effector cell trafficking</td>
<td>2. Fibrogenic signal transduction</td>
</tr>
<tr>
<td>4. Liver cell protection</td>
<td>4. CD40 activation</td>
<td>4. Vasoactive mediators antagonist</td>
</tr>
</tbody>
</table>
Emerging targeted therapies

1. Immune activation blockers

2. Ductal choleresis inducers

3. Nucleoreceptor modulators
UDCA / Budesonide for PBC

Leuschner et al. Gastroenterology 1999
UDCA / Budesonide for PBC

Leuschner et al. Gastroenterology 1999
Emerging targeted therapies

1. Immune activation blockers
2. Ductal choleresis inducers
3. Nucleoreceptor modulators
norUDCA

UDCA
norUDCA - UDCA in mdr2 KO mice
Emerging targeted therapies

1. Immune activation blockers

2. Ductal choleresis inducers

3. Nucleoreceptor modulators
Biliary function of the liver

Diagram showing the biliary function of the liver with various molecules and receptors involved in the process:
- Common bile salts
- Lecithin
- Bilirubin/glutathione
- Organic cations
- Cholesterol
- Endotoxin

Receptors and proteins involved:
- FXR
- LXR
- PPAR
- PXR
- CAR
- RXR
- BSEP
- MDR3
- MRP2
- MDR1
- ABCG5/8
Bile acid transport and adaptative response to cholestasis
# Nuclear receptors and their inducers

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<th>Targets</th>
<th>FXR</th>
<th>PXR</th>
<th>LXR</th>
<th>PPAR</th>
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<th>RIF</th>
<th>Oxysterols</th>
<th>Fatty acids</th>
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<tr>
<td>CDCA</td>
<td></td>
<td></td>
<td></td>
<td>Eicosanoids</td>
</tr>
<tr>
<td>GW4064</td>
<td></td>
<td>Statin</td>
<td></td>
<td>Fibrates</td>
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<td>6ECDCa</td>
<td></td>
<td></td>
<td></td>
<td>Statin</td>
</tr>
<tr>
<td>Fexaramine</td>
<td></td>
<td>Troglitazone</td>
<td></td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LCA</td>
<td></td>
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Fatty acids: Eicosanoids, Fibrates, Statin, Thiazolidinediones
Effects of RIFA and UDCA on hepatobiliary transport systems and metabolizing enzymes

Marschall et al. Gastroenterology 2005
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### Inducers

- CDCA
- GW4064
- 6ECDCA
- Fexaramine
- RIF
- Statin
- Dexa
- Troglitazone
- LCA
- Oxysterols
- Fatty acids
- Eicosanoids
- Fibrates
- Statin
- Thiazolidinediones
Protection against ANIT-induced necrosis by GW4064

Protection against ANIT-induced hepatotoxicity by GW4064
Sensitivity, specificity and predictive values of AST activity for the diagnosis of moderate to severe LPM

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<tr>
<th>Cutoff value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Likelihood ratio</th>
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<tr>
<td>1.6</td>
<td>0.33</td>
<td>0.84</td>
<td>0.67</td>
<td>0.56</td>
<td>2.1</td>
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<tr>
<td>1.8</td>
<td>0.29</td>
<td>0.87</td>
<td>0.68</td>
<td>0.55</td>
<td>2.1</td>
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<tr>
<td>2.0</td>
<td>0.22</td>
<td>0.90</td>
<td>0.69</td>
<td>0.54</td>
<td>2.3</td>
</tr>
<tr>
<td>2.5</td>
<td>0.13</td>
<td>0.95</td>
<td>0.71</td>
<td>0.52</td>
<td>2.5</td>
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Corpechot et al. Liver Int 2004