GHAPP
Gastroenterology & Hepatology
Advanced Practice Providers

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Jointly provided by the Annenberg Center for Health Sciences at Eisenhower and Gastroenterology and Hepatology Advanced Practice Providers.
PSC Management including Vancomycin

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Disclosures

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Disclosures

Vicki Shah PA-C, MMS

Advisory Board: AbbVie, Clinical Area- HCV
Research Support:  Gilead, Clinical Area-HCV
PSC Overview

- Cholestatic autoimmune biliary inflammatory disease causing inflammation and fibrosis of bile ducts
- 50%-75% having IBD, most commonly UC
- Causes multifocal bile duct strictures
- Cirrhosis, Liver transplantation, cholangiocarcinoma
- 10x increased risk of colon cancer with PSC/IBD
- No medical therapies improve disease course or slow progression

## Bile Duct Diseases

<table>
<thead>
<tr>
<th></th>
<th>PBC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Females (9:1)</td>
<td>Males (5:1)</td>
</tr>
<tr>
<td>Bile ducts</td>
<td>Interlobular Obliterative</td>
<td>Intra and extrahepatic Stricturing</td>
</tr>
<tr>
<td>ERCP</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>AMA</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>IBD association</td>
<td>-</td>
<td>UC&gt;&gt;&gt;&gt;&gt;Crohns</td>
</tr>
<tr>
<td>Cholangiocarcinoma Risk</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>
High Dose Ursodiol for PSC

Overall Endpoints: High Dose Ursodiol for PSC

Kaplan-Meier Survival Curve of 198 PSC Patients Enrolled in a 5 year UDCA Trial

Kaplan-Meier Analysis of Endpoint Free Survival Regardless of Treatment with UDCA

Kaplan-Meier Analysis of Endpoint Free Survival in all PSC Patients with UDCA Treatment

High-Dose Urso in UC & PSC

Eaton J, Silveira MG, Pardi DS, et al. High-dose ursodeoxycholic acid is associated with the development of colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. Am J Gastroenterol 2011;106(9):1638-45
UDCA and Risk of Advanced Colorectal Neoplasia in Patients with PSC - IBD

Gut Microbiota and PSC

- PSC associated with altered gut microbiota
- Overrepresentation:
  - *Enterococcus*, *Escherichia*, *Fusobacterium*, *Lactobacillus*, *Veillonella*, *Blautia*, *Lachnospiraceae*, *Barnesiellaceae*, *Megasphaera* genera, *Actinobacteria*, *Proteobacteria*, *Streptococcus* and *Rothia*
- Reduction:
  - *Clostridiales II*, *Prevotella*, *Roseburia*, and *Bacteroides*

Tetracycline

- Previous study 1959 with improvement of LFTs
- Long-term study report 1965
  - no clinical benefit
  - No histological changes
  - No changes in liver function tests

Rifaximin

• 16 patients in 12-week, open-label pilot study
• 550 mg rifaximin twice daily
• No significant changes in ALK, serum bilirubin and GGT at the end of the 12 weeks.
• No significant changes for fatigue impact scale, chronic liver disease questionnaire or the short form health survey

Metronidazole & UDCA

- Compared metronidazole alone vs UDCA with metronidazole
- Improved ALK, histology scores and Mayo risk scores.
- Neither progression nor improvement was noted for liver histology/ERCP changes.
- Long-term studies using a higher dose of ursodeoxycholic acid combined with metronidazole in larger populations are needed

Metronidazole & UDCA

Vancomycin & Metronidazole

- Randomized into four groups for 12 weeks
  - vancomycin (125 mg 4 times a day, n = 8 or 250 mg 4 times a day, n = 9)
  - metronidazole (250 mg 3 times a day, n = 9 or 500 mg 3 times a day, n = 9)
- Decrease in ALK in the high dose vancomycin
- Normalization in ALK in and low-dose vancomycin
- Mayo PSC risk score, total bilirubin, and CRP decreased in low-dose vancomycin
- Why was low-dose vancomycin more effective than higher dose vancomycin?

**Vancomycin Trials**

<table>
<thead>
<tr>
<th>Clinical trial or Case report</th>
<th>Number of patients (n = x)</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabibian et al(^{52})</td>
<td>35</td>
<td>Decrease in alkaline phosphatase (both high and low vancomycin dose groups) and decrease in Mayo PSC score (low-dose vancomycin group) at the end of the 12 wk of treatment. Adverse effects: diarrhoea. 500-1000 mg per day for 3 months.</td>
</tr>
<tr>
<td>Rahimpour et al(^{61})</td>
<td>29</td>
<td>Decrease in Mayo PSC score, alkaline phosphatase, ESR, GGT, fatigue, pruritus, diarrhoea and anorexia in the oral vancomycin group after 12 weeks of treatment. 500 mg per day for 3 months.</td>
</tr>
<tr>
<td>Davies et al(^{1})</td>
<td>14</td>
<td>Clinical and laboratory (ALT, GGT and ESR) improvement after 1-2 mo of oral vancomycin. Worsening findings when it was stopped and overall improvement when resumed. Decreased clinical and laboratory improvement for patients with cirrhosis. 50 mg per kilogram per day for 54 months +/- 43 months.</td>
</tr>
<tr>
<td>Abarbanel et al(^{58})</td>
<td>14</td>
<td>GGT, ALT, WBC, MRCP findings, liver biopsy and immunological improvements noted with 12 wk of oral vancomycin. 50 mg per kilogram per day for 12 months.</td>
</tr>
<tr>
<td>Cox &amp; Cox(^{62})</td>
<td>3</td>
<td>Clinical, laboratory and pathological improvement during treatment with oral vancomycin. Not all patients improved after stopping the treatment. 375-1000 mg per day for 18 months.</td>
</tr>
<tr>
<td>Buness et al(^{59})</td>
<td>1</td>
<td>Single case, clinical, laboratory and endoscopic improvement after escalating dose of oral vancomycin until optimal dose was determined. 1500-2250 mg per day for 5.5 years.</td>
</tr>
<tr>
<td>Davies et al(^{60})</td>
<td>1</td>
<td>Single case, normalization of liver enzymes after orthotropic liver transplantation and PSC recurrence. 1500mg per day for 5 yrs.</td>
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</tbody>
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### Ongoing Clinical Trials for PSC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Design</th>
<th>N</th>
<th>Phase</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>5-ASA modulates inflammatory response</td>
<td>RCT</td>
<td>42</td>
<td>II</td>
<td>22 weeks</td>
</tr>
<tr>
<td>DUR-928</td>
<td>Endogenous sulfated oxysterol, ligand of LXRss</td>
<td>RCT</td>
<td>40</td>
<td>II</td>
<td>4 weeks + 56 days observation</td>
</tr>
<tr>
<td>Vidofludimus calcium</td>
<td>Small-molecule inhibitor of dihydroorotate dehydrogenase</td>
<td>OL</td>
<td>30</td>
<td>II</td>
<td>6 months</td>
</tr>
<tr>
<td>Umbilical cord mesenchymal stem cells</td>
<td>Stem cell therapy for immunomodulation</td>
<td>RCT</td>
<td>20</td>
<td>I/II</td>
<td>1 year</td>
</tr>
<tr>
<td>Cilofexor</td>
<td>FXR agonist</td>
<td>RCT</td>
<td>400</td>
<td>III</td>
<td>96 weeks</td>
</tr>
<tr>
<td>BTT1023</td>
<td>Anti-VAP1</td>
<td>OL</td>
<td>23</td>
<td>II</td>
<td>120 days</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Manipulation of gut microbiome</td>
<td>RCT</td>
<td>102</td>
<td>II/III</td>
<td>2 years</td>
</tr>
<tr>
<td>HTD1801</td>
<td>UDCA+berberine (antioxidant supplement)</td>
<td>RCT</td>
<td>90</td>
<td>II</td>
<td>18 weeks</td>
</tr>
<tr>
<td>NorUDCA (Europe)</td>
<td>Anticholestatic</td>
<td>RCT</td>
<td>300</td>
<td>III</td>
<td>2 years</td>
</tr>
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Q&A