Itching (Pruritus) in Primary Biliary Cholangitis

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Itching in Primary Biliary Cholangitis.

- In urso trials, 60%-70% of patients had itching, 23% severe
- Not correlated with disease severity
- Not unique to PBC, but appears earlier in biliary diseases
- Localized → Generalized. Predilection for palms/soles
- No primary rash, but may have secondary skin lesions (scratches, red crusted bumps, darkening of skin, butterfly sparing.
- Worse in evenings
- Exacerbated by heat/pressure
- 74% disturbed sleep
- May cause social isolation, depression
- Intermittent, progressive, self-extinguishing

Pederson & Mayo, 2018
Dante’s Inferno: Relentless Itching in Hell

Botticelli

8th Circle of Hell
### Ways to Measure Itching

#### 5-D Itch Scale

1. **Duration:** During the last 2 weeks, how many hours a day have you been itching?
   - Less than 1hr/day
   - 1-6 hrs/day
   - 6-12 hrs/day
   - 12-18 hrs/day
   - 18-23 hrs/day
   - All day

2. **Degree:** Please rate the intensity of your itching over the past 2 weeks
   - Not present
   - Mild
   - Moderate
   - Severe
   - Unbearable

3. **Direction:** Over the past 2 weeks has your itching gotten better or worse compared to the previous month?
   - Completely resolved
   - Much better, but still present
   - Little bit better, but still present
   - Unchanged
   - Getting worse

4. **Disability:** Rate the impact of your itching on the following activities over the last 2 weeks
   - Sleep
     - Never affects sleep
     - Occasionally delays falling asleep
     - Frequently delays falling asleep
   - Delays falling asleep and occasionally wakes me up at night
   - Delays falling asleep and frequently wakes me up at night
   - Leisure/Social
     - N/A
     - Never affects this activity
     - Rarely affects this activity
     - Occasionally affects this activity
     - Frequently affects this activity
     - Always affects this activity
   - Housework/Errands
   - Work/School

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.
   - Head/Scalp
   - Face
   - Chest
   - Abdomen
   - Back
   - Buttocks
   - Thighs
   - Lower legs/Twist
   - Top of feet/Toes

### Scale

- 0: No itching
- 10: Worst possible itching

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*Image: © Original Artist*
Liver doctors are not good at addressing itch

<table>
<thead>
<tr>
<th>Specialty</th>
<th># of Notes Documenting</th>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burn</td>
<td>89/106 (84%)</td>
<td></td>
</tr>
<tr>
<td>Dermatology</td>
<td>91/92 (99%)</td>
<td></td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td><strong>48/90 (53%)</strong></td>
<td></td>
</tr>
<tr>
<td>Primary Care</td>
<td>17/24 (71%)</td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td>5/15 (33%)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>2/10 (20%)</td>
<td></td>
</tr>
<tr>
<td>Psychiatry</td>
<td>2/6 (33%)</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>4/5 (80%)</td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>4/5 (80%)</td>
<td></td>
</tr>
<tr>
<td>Gynecology</td>
<td>2/3 (67%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2/11 (18%)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>266/373 (71%)</strong></td>
<td></td>
</tr>
</tbody>
</table>
The Cause of Itch in PBC is Complex

Putative Culprits
- Histamine
- Opioids
- Bile Acids
- Sulfated Progesterones
- Prostaglandins
- Serotonin
- Acetylcholine
- IL-31
- Endocannabinoids
- Endothelins
- Endovanilloids
- Leukotrienes
- LPA/autotaxin

Paus, J Clin Invest 2006
Activation of the Limbic System during Itch in Patients with PBC

Amygdala: fear conditioning

Orbitofrontal Cortex: sensory integration, response inhibition

Anterior Cingulate: emotional responses

Posterior Insula: viscerosensory

No sensory cortex!
Don’t talk to me about having an itch you can’t scratch...
“I don’t like taking medicine”

- Loose, absorbent clothes
- Frequent use of emollients
- Avoid precipitants (narcotics)
- Trim nails
- Cool (not dry) environment/ showers/packs
- Controlled sun exposure
Ultraviolet Rays

• Inhibits release of histamine and proliferation of mastocytes
• Mobilizes bile and uremic salts from skin
• Increases [BA] in urine
• Hanid, Lancet, 1980 N=6 PBC
  • onset 1 week, duration 2 weeks
Effect of Urso on Pruritus in PBC

N=214

Better Placebo

Better UDCA

Frankfurt
Tokyo
Helsinki
Villejuf
Toronto

Gluud, Cochrane database 2006
“OK, It’s bad enough for me to take something now”

**Step 1:** Bile Acid Sequestrants
(Cholestyramine, Colestipol)

**Step 2:** Rifampin

**Step 3:** Opioid Antagonists
(Naloxone, Naltrexone)

**Step 4:** Selective Serotonin Uptake Inhibitors (Sertraline, Paroxetine)
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>4 to 16 mg daily</td>
<td>Side effects include bloating, constipation, and unpleasant taste. May affect the absorption of other medications, and should be dose 1 hour prior or 3-4 hours after other medications.</td>
</tr>
<tr>
<td>Colestipol</td>
<td>2 to 16 mg daily</td>
<td>Similar to cholestyramine.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>150 to 600 mg daily</td>
<td>Side effects include rash, fever, nausea, vomiting, and elevated liver enzymes. May affect the metabolism of other medications, such as warfarin, digitoxin, and tacrolimus.</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>25 to 50 mg daily</td>
<td>Side effects include nausea, dizziness, flushing, drowsiness, and muscles cramps. Should not be used on patients taking chronic opiates.</td>
</tr>
<tr>
<td>Sertraline</td>
<td>75 to 100 mg daily</td>
<td>Side effects include irritability, insomnia, loose stool, and decreased libido.</td>
</tr>
</tbody>
</table>
What’s New: Clinical Trials for Itching in PBC

1. The Effect of Bezafibrate on Cholestatic Itch - Netherlands

2. GLIMMER-Dose Response Study of GSK2330672 for the Treatment of Pruritus in Patients With Primary Biliary Cholangitis
66 sites in US and Europe. (Texas sites are San Antonio, Dallas)
Bezafibrate Improves Cholestasis, Symptoms, and Fibrosis in PBC Suboptimal Ursodiol Responders

Median % Change from Baseline to Month 24

<table>
<thead>
<tr>
<th></th>
<th>Bezafibrate N=50</th>
<th>Placebo N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>-50</td>
<td>-20</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>-80</td>
<td>-60</td>
</tr>
<tr>
<td>Itch Score</td>
<td>-70</td>
<td>-50</td>
</tr>
<tr>
<td>Liver Stiffness</td>
<td>-70</td>
<td>-50</td>
</tr>
</tbody>
</table>

*p < 0.01
***p < 0.0001

Corpechot et al J Hepatology 2017
Improvement in Itch with Bile Acid Uptake Inhibitor

1-10 scale

PBC-40 Itch

5-D Itch
Itching with Obeticholic Acid (OCA)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=73)</th>
<th>Titration OCA (n=70)</th>
<th>OCA 10 mg (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients reporting at least 1 treatment-emergent adverse event (TEAE) Pruritus Event, n (%)</td>
<td>28 (38)</td>
<td>39 (56)</td>
<td>51 (70)</td>
</tr>
<tr>
<td>Discontinuations due to Pruritus, n(%)</td>
<td>0</td>
<td>1 (1)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Pruritus Events by Maximum Severity, n (%)</td>
<td>16 (22)</td>
<td>11 (16)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>7 (10)</td>
<td>15 (21)</td>
<td>19 (26)</td>
</tr>
<tr>
<td>Severe</td>
<td>5 (7)</td>
<td>13 (19)</td>
<td>17 (23)</td>
</tr>
</tbody>
</table>

Placebo (n=73) – Titration OCA (n=70) – OCA 10 mg (n=73)

Mean (SD) VAS Score

Time (Months)
When Medications Fail...

MARS (Molecular Adsorbents Recirculating System)/Plasmapheresis

Nasobiliary Drainage

Liver Transplantation
- Maralixibat 10 mg: -25.63 *
- Maralixibat 20 mg: -27.34*
- Placebo: - 23.36*
Bile Acid Binding Resins

- Extensive clinical experience since 1966
- Excellent safety profile
- Poor tolerability

N=5

Pruritus Score
% of Baseline

Resin    Placebo

3 g TID X 4 wk

N=5

36%

75%

Datta & Sherlock, Gastroenterology 1966

Cholestatic pruritus
N=27

Placebo X 1 mo

Cholestyramine
10 g/d        6.6 g/d       3.3 g/d
X1 mo          X1mo       X4-30mo

No response
15%

Complete Relief
67%

Partial Relief
18%
## Rifampicin

<table>
<thead>
<tr>
<th>Source</th>
<th>Dose</th>
<th>N=</th>
<th>Prefer Rifampin</th>
<th>Prefer Placebo</th>
<th>No Preference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghent, 1988</td>
<td>300-450 mg/d</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>0.04</td>
</tr>
<tr>
<td>Woolf, 1990</td>
<td>300mg/d</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Cynamon, 1990</td>
<td>10 mg/kg</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0.06</td>
</tr>
<tr>
<td>Podesta, 1991</td>
<td>600 mg/d</td>
<td>14</td>
<td>12</td>
<td>0</td>
<td>2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bachs, 1989</td>
<td>10 mg/kg</td>
<td>17</td>
<td>15</td>
<td>2</td>
<td>0</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>55</strong></td>
<td><strong>42</strong></td>
<td><strong>5</strong></td>
<td><strong>10</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rare severe hepatotoxicity
Rifampicin is more Effective than Phenobarbitol

Bachs, Lancet 1989

N=22
Opioid Receptor Blockers

• Naltrexone 50 mg/d (12.5 mg 150 mg BID)
• 38%-93% response

• Side effects:
  • early: dizziness, headache, fatigue, nausea, abdominal pain, hypertension, clammy
  • late: chronic pain
• > 50% withdrawal
• 6%-36% breakthrough
Pruritus Score

Sertraline
Placebo

P<0.001

Mayo, Hepatology in press
MARS
Molecular Adsorbents Recirculating System

N=26 case reports
No controlled trials
In BRIC, PBC, HCV, DILI, biliary strictures, rejection
6-16 hrs/day X 1-10 days
Partial or complete relief in 25/26
Lasts few days to 18 months.