Pruritus: The itch that drives cholestatic patients wild!

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Complications of Cholestasis

- Related of cholestasis
  - Growth Failure
- Nutritional
  - Growth Failure
  - Vitamin Deficiencies
  - Pancreatic insufficiency
- Bone Disease
- Pruritus
- Hypercholesterolemia
- Xanthomata

Financial Disclosures

In the past 12 months, I have the financial relationships with the following:
- Equity interest in Asklepion Pharma, LLC.
- Funding: NCATS, NIDDK, NICHD, and CFF
- Consultant to Nordmark
None of these relationships will be discussed in the presentation

Potential agents responsible for cholestatic pruritus

- Correlates with severity of cholestasis, but not serum bile acid concentrations
- Potential causes (historical)
  - Bile acids
  - Endogenous opiates
  - Histamine
  - Serotonin
  - Lysophosphatidic acid

Aretaeus of Cappadocian identified itch with jaundice in 2nd Century B.C.

Pathophysiology of Cholestatic Pruritus

Pruritogens - Bile Acids

- Pros
  - ↑ SBA with itching
  - Feeding BS ↑
  - Intradermal BS ↑
  - Anion exchange resins ↓
  - Nasobiliary drainage ↓
  - Exclusion surgery ↓
  - ↑ SBA in non cholestatic diseases with itching
- Cons
  - No correlation between SBA and itching
  - Frequency and intensity of itching does not correlate with severity of cholestasis
  - Colesevelam (more specific BA binder) ineffective
**Pruritogens-Endogenous Opioids**

- **Pros**
  - ↑ in cholestasis
  - Induce pruritus with spinal application
  - μ-opioid antagonists ↓
  - Spinally administered serum extracts induce pruritus
- **Cons**
  - No correlation between serum opioids and itch
  - Opioid levels similar in PBC with or w/o itch
  - M-opioid

**Pruritogens-Histamine/Serotonin**

- **Pros (Histamine)**
  - ↑ serum histamine in cholestasis
  - ↑↑↑ SBA lead to histamine release
- **Pros (Serotonin)**
  - Cholestasis may alter serotonin homeostasis
  - Response to Sertraline and peroxetine
- **Cons (Histamine)**
  - Antihistamines largely ineffective
- **Cons (Serotonin)**
  - Conflicting response to 5-HT3 antagonist, ondansetron
  - Does not seem to be direct itch mediator

**Pruritogens-lysophosphatic acid**

- **Pros**
  - ↑ Serum LPA only in cholestasis with itch
  - Intradermal injection → itching
  - ATX activity increased in cholestasis with itch
  - NB drainage in PBC → ↓ ATX and itch
- **Cons**
  - Unclear relation between serum/intracellular levels

**Autotaxin in Cholestasis**

**Itch v. ATX and SBA**

**ATX Specificity**
**ATX Response to Treatment**

**Effect of Nasobiliary Drainage on ATX**

**Model of Cholestatic Pruritus**

**Treatment of Pruritus (itching)**
- Avoid dry skin (use emollients)
- Ursodeoxycholic acid (URSO, Actigall)
- Antihistamines
- Rifampin
- Anionic resin binders (cholestyramine, colestipol, colesevelam)
- Other drugs (sertraline, ondansetron, phenobarbital)
- UVB
- Plasmapheresis
- MARS
- Biliary diversion
  - Partial external diversion
  - Ileal exclusion
- Potential future agents
  - ASBT inhibitor
  - 4-PB

**4-PB Effect on Pruritus**

**Evidenced based management**

<table>
<thead>
<tr>
<th>Drug/Treatment</th>
<th>Dose</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ursodeoxycholic acid</td>
<td>10-15mg/kg/day</td>
<td>A</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600-1000mg/day</td>
<td>B</td>
</tr>
<tr>
<td>Halofenate</td>
<td>330mg/day</td>
<td>B</td>
</tr>
<tr>
<td>Smaller</td>
<td>10mg/kg/day</td>
<td>B</td>
</tr>
</tbody>
</table>

A: randomized controlled trial; B: controlled trial non-randomized; C: cohort or case-control

1: high quality, strong; 2: intermediate quality, strong; 3: low quality, weak
1: strong; 2: weak
**Evidence Based Management**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td>Partial biliary diversion (PEBD)</td>
<td>A: Multiple randomized trials</td>
</tr>
<tr>
<td>Ileal Exclusion (IE)</td>
<td>B: Single randomized trial</td>
</tr>
<tr>
<td>Gall bladder to Colon anastomosis</td>
<td>C: Consensus opinion</td>
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<tr>
<td>Small case series reports of ALGS, PFIC 1, 2</td>
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</tbody>
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**Surgical Interventions**

- Partial external biliary diversion (PEBD)
- Ileal Exclusion (IE)
- Gall bladder to Colon anastomosis
- Small case series reports of ALGS, PFIC 1, 2 from multiple centers
  - PEBD > IE, no comparison to GB-C
  - Most reports indicate improvement or freedom from itching in 75% (reporting bias?)

- Partial ileal bypass
- Excluded ileum
- Appendectomy
- Intussusception prevention seems necessary

- Partial ileal bypass
  - 15% excluded ileum
  - Appendectomy
  - Intussusception prevention seems necessary
Gall bladder-colonic diversion

IE/PEBD in Cholestatic Pruritus
- 57 children (20 ALGS, 16 PFIC1, 15 PFIC 2, 6 low gGT cholestasis
- Age at surgery: ALGS: 65±65 mos, PFIC 28±37 mos
- 39 (15 ALGS, 12 PFIC 1, 10 PFIC 2, 2 low gGT) had PEBD
  - 54% of ALGS less severe or no pruritus at 24 mos
  - PFIC 1 and 2 significantly less pruritic (p<0.001)
  - Complications: 4 electrolyte imbalance, 2 obstruction, 1 ischemia, 6 stoma prolapse/revision
- 11 (4 ALGS, 2 PFIC1, 3 PFIC 2, 2 low gGT) had IE
  - Non-significant trend in improvement of pruritus
  - Complications: 2 electrolyte imbalance
- 7 GB colon diversion
  - 3/6 with less post pruritus at 24 months
  - 2 electrolyte imbalance, 1 obstruction, 1 ischemia

Wang KS et al. AASLD 2014

Treatment Algorithm-JEH

Cholestatic Pruritus
- UDCA 10-15 mg/kg/day
- Diphendramine/hydroxyzine/periaclin
- Cholestyramine 1-2 gm QID
- Rifampin 5-10 mg/kg/d as BID
- Naltrexone 0.25-0.5 mg/kg/d
- Sertraline
- Ileal Exclusion or Partial external biliary diversion
- Transplant

Exclude other causes
Treat underlying disease
Monitor FSV
Monitor liver chemistries, drug interactions (CYP)
Avoid withdrawal tox: low dose and advance

Questions:
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