Pruritus Treatment

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Clinical case

**HPI:** 54 y.o. female presents with several weeks of increased itching, mostly at night. + dry eyes. She denies change in laundry detergent, travel, bug bites, or new medications.

**PMH:** Type 2 DM, hypertension

**FHX:** non-contributory

**SHX:** married, 2 children, no tobacco or alcohol use

**Laboratory testing:** AST 62 U/L, ALT 85 U/L, ALP 350 U/L, total bilirubin 1.2 mg/dL, and albumin 3.6 g/dL.

What do you do now?
Outline

• Define pruritus
• Differential diagnosis
• Understand the pathophysiology
• Evaluation
• Treatment
What is pruritus

Noun (Latin);

Severe itching of the skin, as a symptom of various ailments
<table>
<thead>
<tr>
<th></th>
<th>Autoimmune</th>
<th>Malignancy</th>
<th>Metabolic and endocrine</th>
<th>Neurologic</th>
<th>Other</th>
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<tbody>
<tr>
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<td>Dermatitis herpetiformis</td>
<td>Leukemia</td>
<td>Carcinoid syndrome</td>
<td>Cerebral abscess</td>
<td>Drug ingestion</td>
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<td>Dermatomyositis</td>
<td>Lymphoma</td>
<td>Chronic renal disease</td>
<td>Cerebral tumor</td>
<td>Eating disorders with rapid</td>
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<td>Linear immunoglobulin A disease</td>
<td>Multiple myeloma</td>
<td>Diabetes mellitus</td>
<td>Multiple sclerosis</td>
<td>weight loss</td>
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<td>Sjögren syndrome</td>
<td>Solid tumors with paraneoplastic syndrome</td>
<td>Hyper/hypothyroidism</td>
<td>Stroke</td>
<td>Neuropsychiatric disorders</td>
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<td><strong>Hematologic</strong></td>
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<td>Pregnancy</td>
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<td>Iron deficiency anemia</td>
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<td>Mastocytosis</td>
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<td>Plasma cell dyscrasias</td>
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<td>Polycythemia vera</td>
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<td><strong>Hepatobiliary</strong></td>
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<td>Biliary cirrhosis</td>
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<td>Chronic pancreatitis with obstruction of biliary tracts</td>
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<td>Drug-induced cholestasis</td>
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<td>Hepatitis, particularly hepatitis C</td>
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<td>Sclerosing cholangitis</td>
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<td><strong>Infectious disease</strong></td>
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<td>AIDS</td>
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<td>Infectious hepatitis</td>
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<td>Parasitic disease (giardiasis, onchocerciasis, schistosomiasis, ascariasis)</td>
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<td>Prion disease</td>
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Table 3. Systemic Etiologies for Pruritus
Enterohepatic circulation

1. Secreted bile salts consist of 95% old, recycled bile salts and 5% newly synthesized bile salts.

2. 95% of bile salts are reabsorbed by the small intestine.

3. Reabsorbed bile salts are recycled by enterohepatic circulation.

4. 5% of bile salts are lost in feces.
Liver Diseases (and the test for their dx)

- Biliary obstruction (US -> CT, MRCP)
  - Gallstones
  - Pancreatic mass (benign, malignant)
  - Liver mass (HCC, metastatic CA)
- Primary biliary cholangitis (AMA)
- Primary sclerosing cholangitis (MRCP)
- Autoimmune (IGG4), overlap syndromes (ANA, ASMA)
- Other (history, liver biopsy)
  - Sarcoid
  - Alcohol
  - HCV
  - Amyloid
  - Infection
  - Infiltrative
  - Medications
Pruritus in Cholestasis

Brain

Unmyelinated nerve endings

Spinal Cord

Endogenous Opioids
Mu (+) Kappa (-)

Steroid Metabolites

Bile Acids

Histamine

Increased pruritic response

Liver

Skin

Lysophosphatidylcholine

Lysophosphatidylcholine

Lysophosphatidic Acid (LPA)

ATX

Autotaxin

Brain

TGR5 receptor

Figura 4. Las vías del dolor y las intervenciones que pueden modular la actividad en cada punto.
Treatments for pruritus
Ursodeoxycholic Acid (UDCA)

• Normally makes up about 3% of bile salts
• Recommended dose: 13-15 mg/kg/d increases bile salt pool to about 30-40%
• Most common side effects: diarrhea (2-9%), mild HA, RUQ pain, thinning hair
• Used more to treat the underlying disease (PBC) than to treat pruritus
• May cause “paradoxical itching”
Antihistamines

• Often used but little clinical data
• Can use for their sedative properties to help sleep at night
  • Cyproheptatine (periactin) 4mg tid
  • Benadryl
  • Hydroxazine (less sedating)
• Can worsen sicca symptoms (dry eyes and dry mouth)
Lotions

• Aqueous cream with 1% menthol
• Oatmeal based creams
**Cholestyramine**

- Non-absorbable anion exchange resin
- Binds potential pruritogens (bile salts) in the gut
- Need to space out from other medications (2-4 hours)
- Initial dose 4g/d in the morning
- Can increase to 16g/d
- Side effects often limit its use
  - Unpleasant taste
  - Bloating
  - Constipation or diarrhea
Rifampicin

• Induces bile salt transporters
• Pregnane X receptor (PXR) agonist
  • Decrease autotaxin levels
• Start 150mg/d and titrate up to 600mg/d
• Side effects: nausea, vomiting, diarrhea, HA, fever, rash, flushing
• Rare side effects may occur in first few months require close monitoring:
  • Severe hepatitis, AKI, hemolysis

\[
\text{LPC} \quad \downarrow_{\text{ATX}} \quad \rightarrow \quad \text{LPA}
\]
Sertraline

• Selective serotonin re-uptake inhibitor (SSRI)
• Modulates nociception and perception of pruritus
• Affects the serotonergic system involved in central itch and pain signaling
• Start 25mg/d and titrate increase every week to maximum 100mg/d
• Uncommon side effects
  • Nausea, fatigue, diarrhea, dizziness, visual hallucinations
Naltrexone

- Selective $\mu$-opioid receptor antagonist
- Both central and peripheral effects
- Can cause "opioid withdrawal"
  - Abdominal pain, tachycardia, HTN, piloerection, nightmares
- Start 12.5 mg/d and titrate gradually to maximum 50 mg/d
- Requires careful monitoring
- Contraindicated if on chronic opiates, decompensated cirrhosis or severe pulmonary disease
“Experimental” therapies for pruritus

• Ultraviolet light
• Plasmapheresis
• Fibrates (PPAR agonist)
• Clinical trials
  • Bile acid transport inhibitors (apical Na-dependent)
  • Autotaxin inhibitors
  • LPA receptor blockers
Bezafibrate 400mg/d + Urso (13-15mg/kg/d) vs. Urso alone

- 50 subjects with PBC and inadequate response (ALP or ALT > 1.5 x ULN) to URSO
- 24 week placebo-controlled, double blinded Study
- 31% had complete response
- Biochemical response plateaued at 15 mo
- Itching response plateaued at 6 mo

C Corpechot et al. NEJM 2018;378:2171-2181
Pruritus

Bile duct obstruction

Present: Biliary drainage → Cholestyramine (4-16 g/d) → Rifampicin (150-300 mg) → Naltrexone (50 mg) → Sertraline (75-100 mg) → Experimental approach

Absent: Evidence level

1st line: Biliary drainage → Cholestyramine (4-16 g/d)
2nd line: Rifampicin (150-300 mg)
3rd line: Naltrexone (50 mg)
4th line: Sertraline (75-100 mg)
5th line: Experimental approach
How did I manage this patient

- Made diagnosis: US normal, + AMA, HCV-, HBV-, ANA-
  - PBC
- Started UDCA for PBC (not for itching, but seemed to help some)
- Tried lotions and antihistamines without much improvement and made dry eyes worse
- Started cholestyramine 4g/d and increased to bid separated by 2 hours from other meds
- Started sertraline 25mg at night
Pruritus

**Initial Management**
1) Rule out other systemic causes
2) Assess quality of life and institute multidisciplinary management
3) Assess severity of pruritus
4) Consider conservative measures
5) Initiate pharmacologic intervention

**Step 1**
Cholestyramine

**Step 2**
Rifampicin

**Step 3**
Opioid Antagonists*

**Step 4**
Sertraline

**Step 5**
Experimental Therapies**

**Step 6**
Consider Liver Transplantation
Conclusions

• Pruritus is a common symptom in liver disease
• The pathogenesis may vary depending on the disease
• Need to exclude obstruction, infiltrative or other system disease
• Evaluate consequences of chronic cholestasis
  • Fat malabsorption
  • Osteoporosis
• Treatment should be thoughtful and sequential