Pruritus: The itch that drives cholestatic patients wild!

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Financial Disclosures

In the past 12 months, I have the financial relationships with the following:

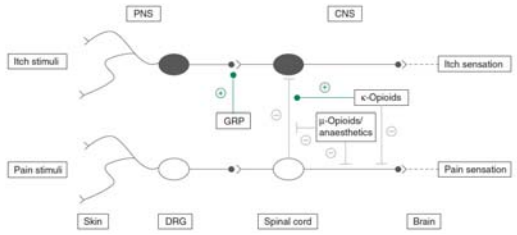
- Equity interest in Asklepion Pharma,LLC.
- Funding: NCATS, NIDDK, NICHD, and CFF
- Consultant to Nordmark

None of these relationships will be discussed in the presentation

Complications of Cholestasis

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

Pathophyiology of Cholestatic Pruritus



Potential agents responsible for cholestatic pruritus

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

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

Pruritogens- Bile Acids

- Pros
  - ↑ SBA with itching
  - Feeding BS ↑
  - Intradermal BS ↑
  - Anion exchange resins↓
  - Nasobiliary drainage ↓
  - Exlusion 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

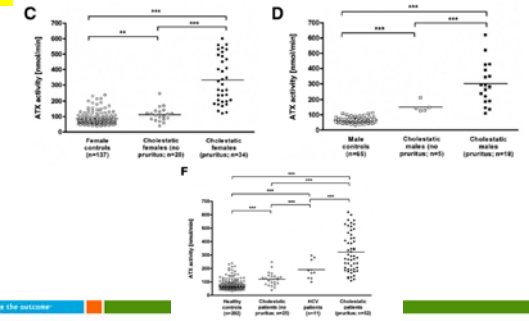
Pruritogens-Histamine/Serotonin

- 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-HT_3 antagonist, ondansetron
  - Does not seem to be direct itch mediator

Pruritogens-lysophosphatic acid

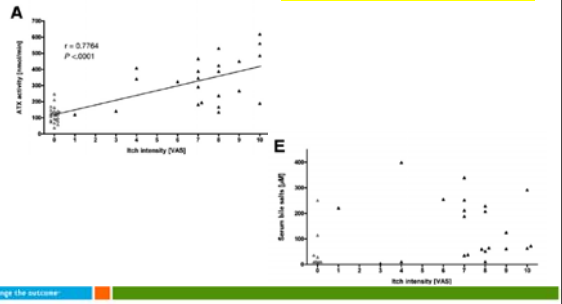
- Pros
  - ↑ Serum LPA only in cholestasis with itch
  - Intradermal injection→ itching
  - ATX activity increased in cholestasis with itch
  - NB drainage in PBC→ ↓ ATX and itch
- Cons
  - Unclear relation between serum/ intracellular levels

Autotaxin in Cholestasis



Kremer et al Gastroent 2010; 139:1008-1018

Itch v. ATX and SBA



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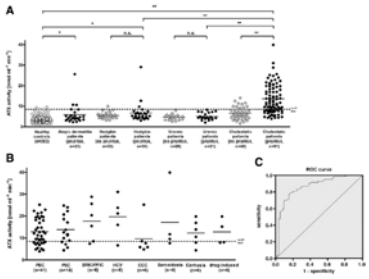
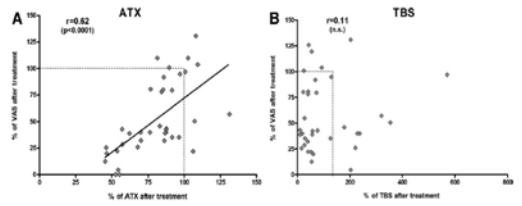
ATX Specificity



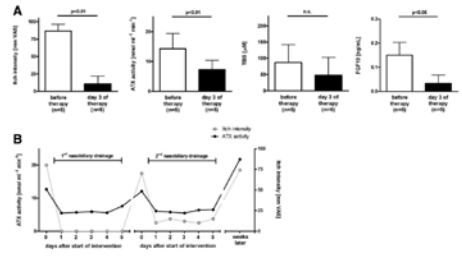
Kremer et al. Hepatol 2012;56:1391-1400

ATX Response to Treatment



Kremer et al. Hepatol 2012;56:1391-1400

Effect of Nasobiliary Drainage on ATX



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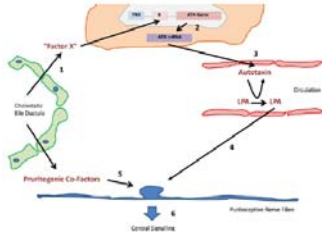
Model of Cholestatic Pruritus

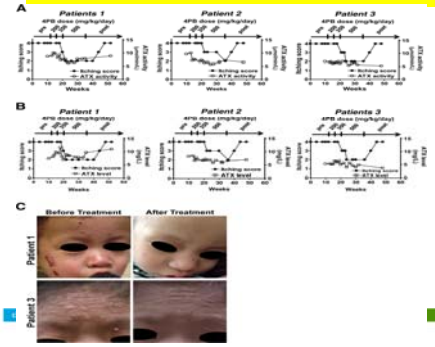


Kremer et al. Hepatol 2012;56:1391-1400

Treatment of Pruritus (itching)

- Avoid dry skin (use emolients)
- 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 2 Current therapeutic recommendations for the management of pruritus in cholestasis [2].

Approach	Drug/Therapy	Final dosage	Evidence
	Ursodeoxycholic acid (UDCA)*	10–15 mg/kg/d (po)	I/B1*
1st line	Cholestyramine	4–16 g/d (po)	II-2/B1
2nd line	Rifampicin	300–600 mg/d (po)	I/A1
3rd line	Naltrexone	50 mg/d (po)	I/B1
4th line	Sertraline	100 mg/d (po)	II-2/C2

I: randomized controlled trial, II-1:Controlled trials w/o randomization, II-2: cohort or case-control
A: High quality, strong; B:Moderate quality, strong; C: Low quality, weak
1: Strong; 2:weak

Beuers U et al. J Hepatol 2009;51:237-67.

Evidence Based Management

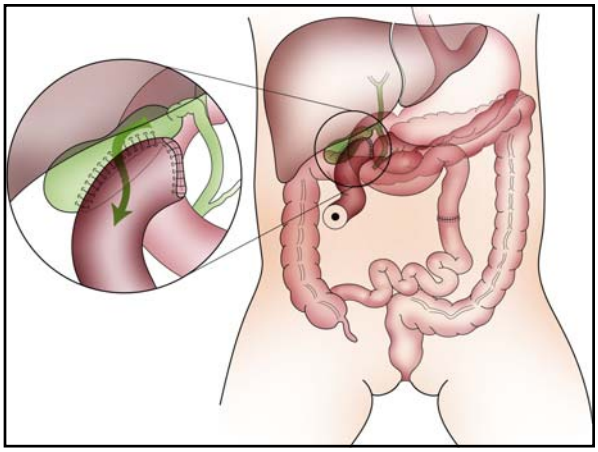
Drug/therapy	Final dose	Recommendation/evidence[1]
Efficacy proven in controlled trials		
Ursodeoxycholic acid[a]	10–15 mg/kg/d (PO)[a]	I A – II C[a]
Cholestyramine[a]	4–16 g/d (PO)[a]	I B – IIb C[a]
Rifampicin	300–600 mg/d (PO) 10 mg/kg/d (PO)[a]	I A
Naltrexone	25–50 mg/d (PO)	I A
Naloxone	0.2 µg/kg/min (IV)	I B
Serotonin reuptake inhibitors (e.g. sertraline)	75–100 mg/d (PO)	IIa B
Contradictory efficacy observed in controlled trials		
Ondansetron	4–24 mg/d (PO) 4–8 mg/d (IV)	II A
Efficacy shown in case series or case reports		
Propofol	10–15mg (IV bolus) 1 mg/kg/h (IV)	IIa B
Lidocaine	100 mg/d (IV)	IIa B
Dronabinol	15 mg/d (PO)	IIb C
Butorphanol	1–2 mg/d (intranasal)	IIb C
Phenobarbital	2–5 mg/kg/d (PO)	IIb B
Phototherapy (UVA, UVB)		IIb C
Bright light therapy reflected towards the eyes	10 000 lux 60–120 min/d	IIb C
Plasmapheresis, extracorporeal albumin dialysis (e.g. MARS), plasma separation, anion absorption, nasobiliary drainage, biliary diversion		IIa C
Liver transplantation		I C

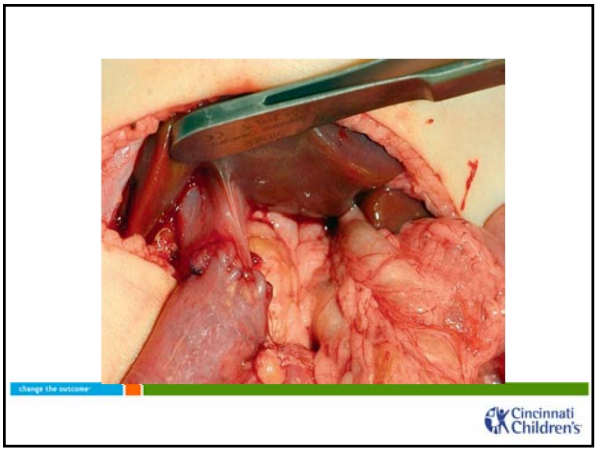
IIa:conflicting evidence (+)
III:conflicting evidence (-)
A:Multiple randomized trials
B:Single randomized trial
C:Consensus opinion

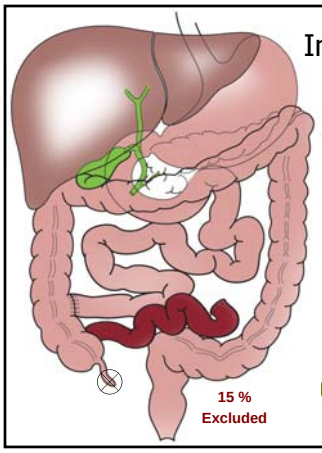
Kremer et al. Drugs 2008; 68:2163-2182

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?)

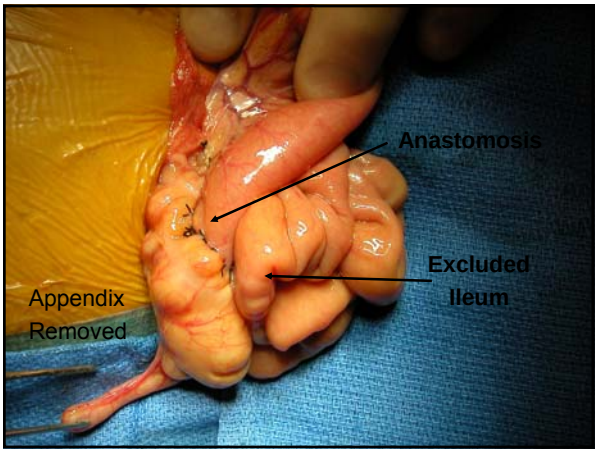




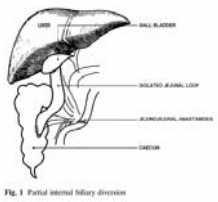


Internal Ileal Bypass

- 15 % excluded ileum
- Appendectomy
- Intussusception prevention seems necessary



Gall bladder-colonic diversion



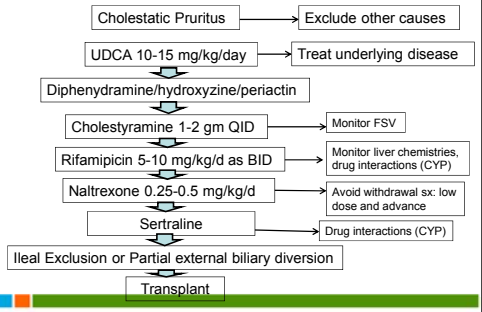
Ramachandran P et al Pediatr Surg Int 2014

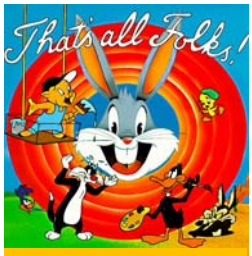
IE/PEBD in Cholestatic Pruritus

- 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





Questions:
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