Therapies for Pediatric PSC

Cara Mack, MD

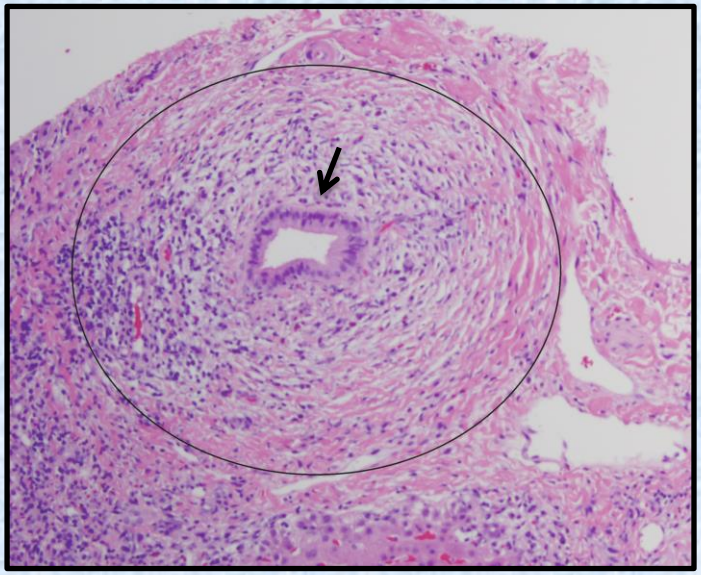
Associate Professor of Pediatrics

Director of Pediatric GI, Hepatology & Nutrition Fellowship Training Program

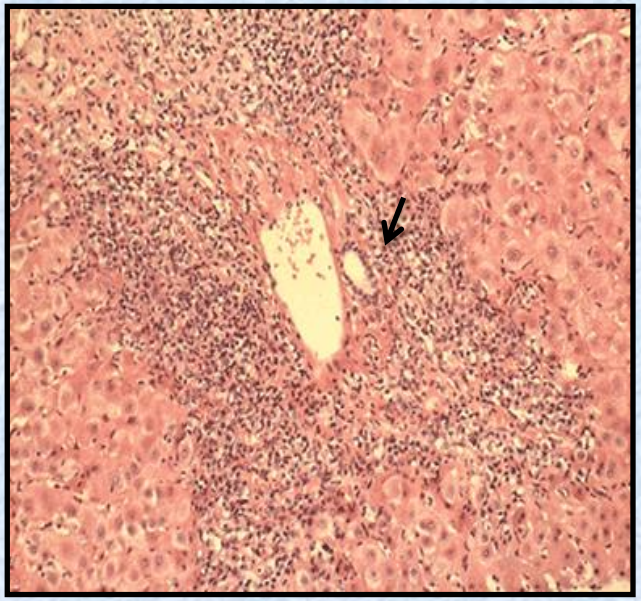
Children's Hospital CO

Pediatric PSC: How it Differs from Adults

↙ =bile duct



PSC: liver bile duct branch



Autoimmune hepatitis

- More inflammation
- Higher number of patients with “overlap” with autoimmune hepatitis (~30% of kids)
- Less scarring and less cirrhosis

Understanding treatment trials

- **Pilot study**- a small scale study (~20-30 pts):

  1. to determine how easy the medicine is to take for the patient population (feasibility)
  2. to determine the side effects of the medicine for the specific patient population (tolerability)
  3. to determine trends in improvement in the patient's disease (efficacy)
  4. to predict the appropriate number of patients needed and improve upon the study design prior to performance of a full-scale research project

Understanding treatment trials

- **Randomized Control Trial (RCT):**

  1. "gold standard" of clinical trials
  2. large number (~100) of patients tested (usually includes many centers to achieve goal)
  3. random assignment of receiving test drug or placebo (i.e. sugar tablet)
  4. determine if treatment improves multiple parameters of the disease (i.e. improvement in laboratory values, decreased bile duct strictures by MRI, decreased rate of transplant)

Historical Treatment Trials- Adults
No Definitive Efficacy

Immunomodulatory

-Methotrexate

-Prednisone

-Penicillamine

-Tacrolimus

-Cyclosporine

-Mycophenolate mofetil

-Azathioprine

-Infliximab

Antibiotics

Minocycline

Metronidazole

(Chandok et al. Can J Gastro 2012)

ClinicalTrials.gov
Current Pediatric Studies for PSC

- Efficacy of ursodeoxycholic acid in pediatric PSC (multi-centered in US)
- A Pilot Study of Xifaxan to Treat Patients With PSC (ongoing but no longer recruiting) (Mayo)
- Pilot Study of PSC and Oral Vancomycin: Antimicrobial and Immunomodulating Effects (Stanford)

Ursodeoxycholic Acid (UDCA) Therapy in Pediatric Primary Sclerosing Cholangitis: A Withdrawal/Reinstitution Trial

STOPSC Pediatric Consortium

Sponsor: FDA OOPD
Grant PI: Dennis Black, MD (Memphis)
Research co-investigator: Cara Mack, MD
Children's CO: Shikha Sundaram, MD

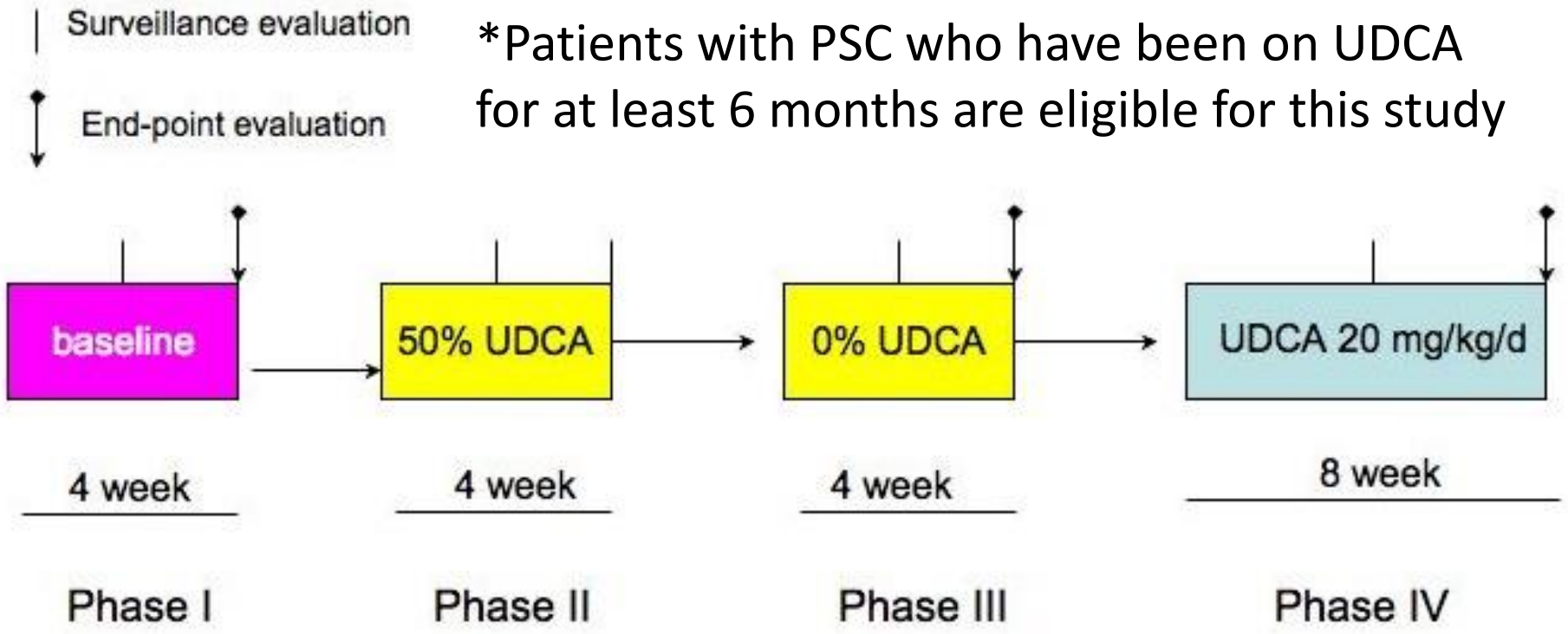
STOPSC Consortium

- Le Bonheur Children's Medical Center, Univ. of Tennessee Health Science Center, Memphis
- Mt. Sinai School of Medicine, New York
- University of California, San Francisco
- Lurie Children's Hospital, Northwestern Univ., Chicago
- Children's Hospital CO, Univ. of Colorado, Aurora
- Cincinnati Children's Hospital, Univ. of Cincinnati
- Children's Hospital of Pittsburgh, Univ. of Pittsburgh
- The Hospital for Sick Children, Univ. of Toronto

Ursodeoxycholic Acid (Ursodiol, Actigall)

- "Bear bile"
- Normally 3% of human bile acid pool
- Beneficial effects
  - Protects liver cells from damage
  - Stimulates bile flow
  - Decreases inflammation

Pediatric UDCA Withdrawal/Reinstitution Trial



Surveillance: New symptoms, labs

End-points: New symptoms, labs, research inflammatory biomarkers

Efficacy of ursodeoxycholic acid in pediatric PSC

- Currently enrolling
- Goal sample size of patients: 100
- On track to complete collection of data in next year

A Pilot Study of Xifaxan to Treat Patients With PSC

- Ongoing analysis but no longer recruiting
- PI: Dr. Talwalkar, Mayo Clinic, Rochester, MN
- Xifaxan: non-absorbed antibiotic given 2x/day for 3 months
- Goal: Determine improvement in symptoms and liver enzymes with the use of xifaxan
- Enrolled 15 adults and 5 children
- Results pending

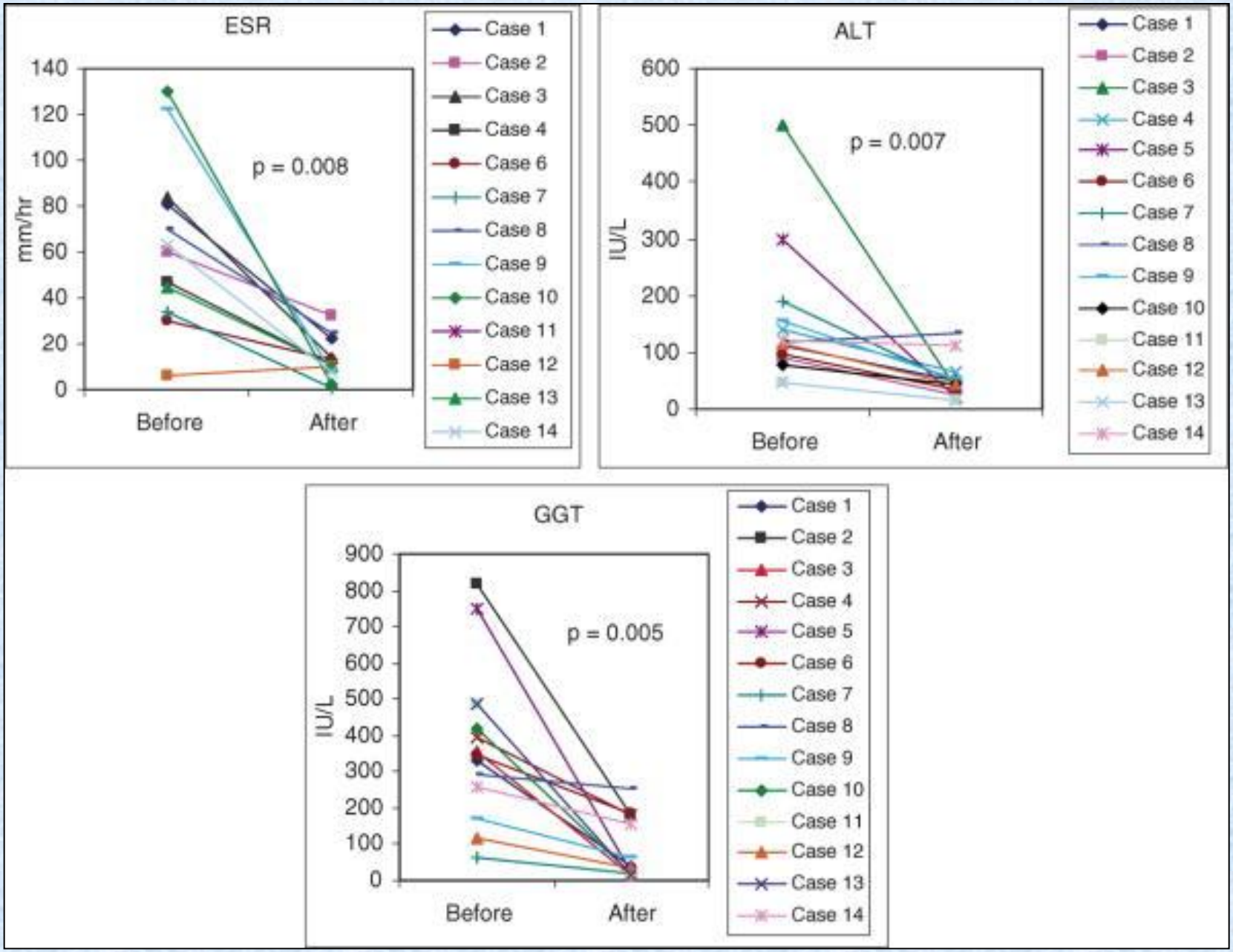
PSC Treatment With Oral Vancomycin: A Study of Its Antimicrobial and Immunomodulating Effects

- PI: Dr. Kenneth Cox, MD. Stanford University
- Study design: vancomycin 3x/day for 3 months
- Outcomes measured:
  -Blood tests (liver enzymes - ALT and GGT)
  -imaging studies (MRI, ERCP) and/or liver biopsy
  -stool microbiome (measure bacteria in colon)
- Currently enrolling

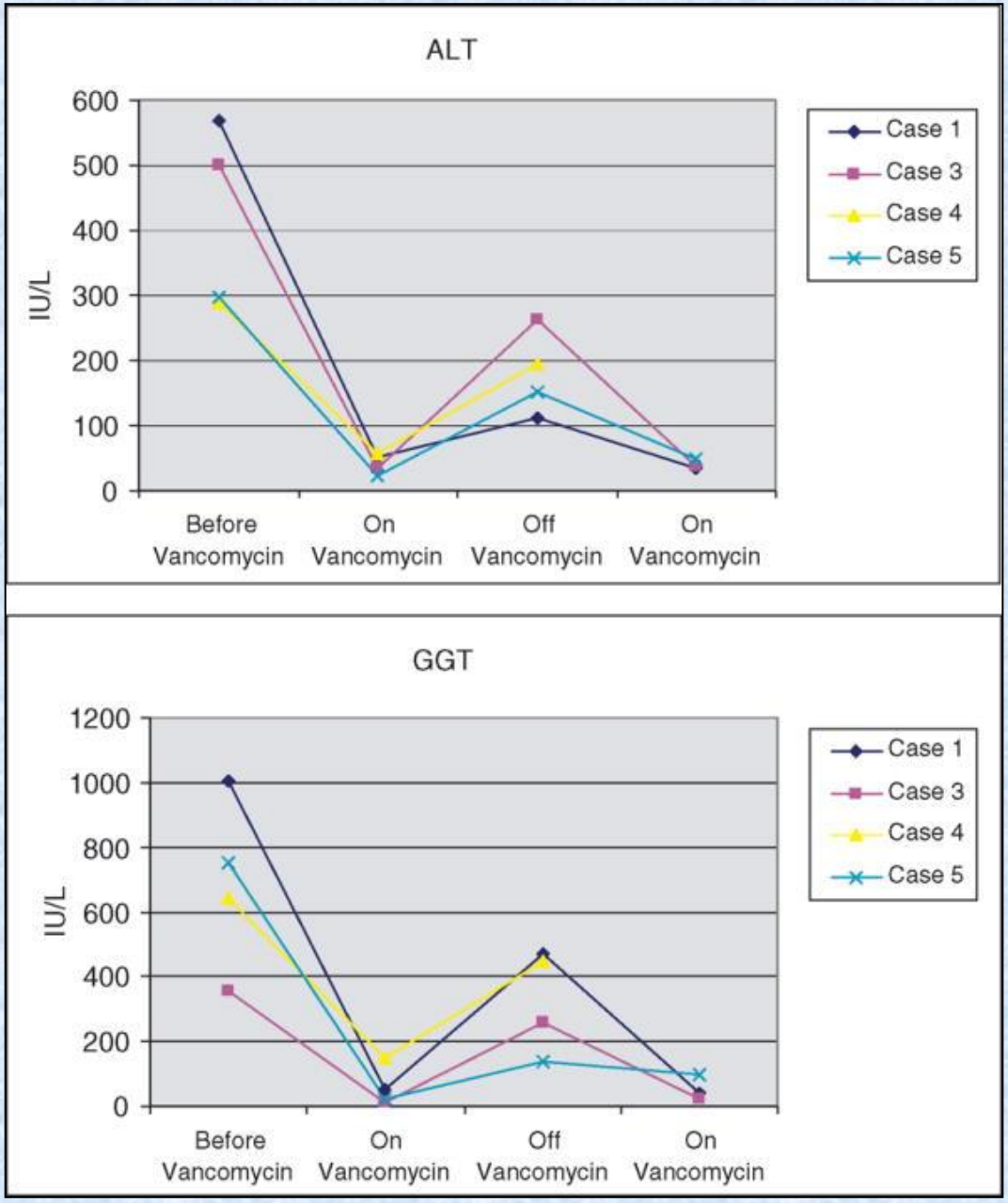
Long-term Treatment of PSC in Children with Oral Vancomycin

- 2008- Cox et al. Jrl Pediatr Gastro Nutr: previously published results from 14 children with PSC (no autoimmune hepatitis) and IBD
- All children had evidence of active colitis at the onset of treatment
- Oral vancomycin given until liver tests normalized and repeated as needed for elevated liver tests (i.e. on and off vancomycin for many years)

Treatment of PSC with Oral Vancomycin



Long-term Treatment of PSC with Oral Vancomycin

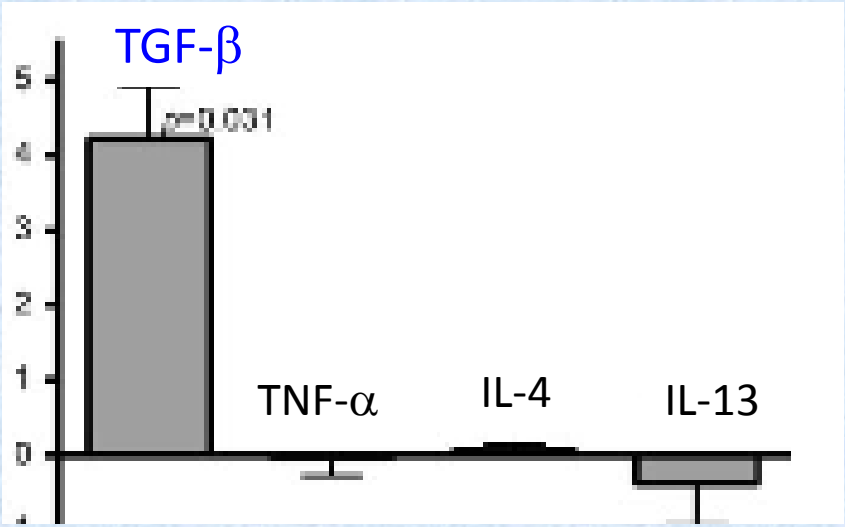


Immunomodulatory Effect of Vancomycin in Pediatric IBD and PSC

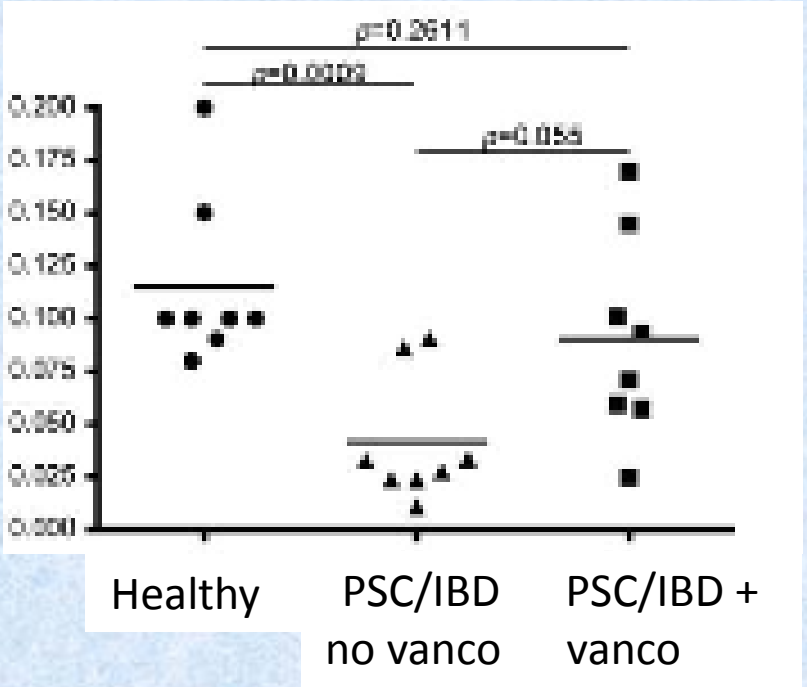
- 2013 Cox et al. Jrl Clin Immunol: second study on 14 children with PSC and IBD (again all had clinical colitis at onset of treatment)
- Groups of patients studied:
  -9 children received oral vancomycin for 1 year
  -5 children with PSC/IBD did NOT receive vancomycin
  -6 healthy children were controls
- Children had colonoscopies and liver biopsies before and after vancomycin treatment

Immunomodulatory Effect of Vancomycin in Pediatric IBD and PSC

Change in TGF-β level after vancomycin



Regulatory T cells



Follow up liver biopsies in vancomycin recipients also showed decreased inflammation

So why shouldn't every child with PSC go ahead and use vancomycin?

- Previous studies: all PILOT studies (need RCT)
  -very unique population (active colitis at time of PSC treatment)- therefore unclear how well it would work if IBD was in remission
  -no control for other medications that were given that could have explained the improvement in liver tests
- Side effects of oral vancomycin:
  -potential set up for creating highly resistant colonic bacteria that could be harmful
  -allergic reaction
  -risk of altering kidney function with long term use
  -hearing loss

Potential Future Trials in Pediatrics

- Randomized, placebo controlled trial of the use of vancomycin for pediatric PSC
- Efficacy of LUM001, an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients With Primary Sclerosing Cholangitis (to treat the itching)
- Norursodeoxycholic Acid in the Treatment of Primary Sclerosing Cholangitis (NUC-3)

Pediatric Liver Disease Research

The goals of research are to ultimately protect and improve the health and well-being of children

We couldn't do it without you!