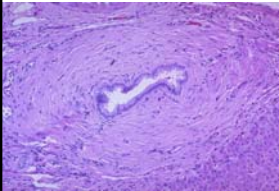


## Liver Disease in IBD




Eaton et al Gastroenterology. 2013 Sep;145(3):521-36.

**Saul J. Karpen, M.D., Ph.D.**  
*Raymond F. Schinazi Distinguished Biomedical Chair  
 Professor of Pediatrics  
 Emory University School of Medicine*



NASPGHAN October 12, 2013    No disclosures



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## Liver Disease in IBD

# 2 cases

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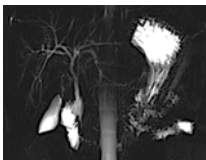
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### 6 ½ yo F bloody stools → Crohn colitis

**Other labs:**  
 ANA NEG  
 α-SMA + (46)  
 pANCA ++



**Liver Bx**

	Presentation 6 ½ y	Referral	7 y
Age:	6 ½ y		7 y
ALT:	92	105	113
AST:	110	201	179
GGT:	-	437	564
T Bili:	0.3	0.5	0.6
ALB:	3.5	4.0	4.3
Plat:	379	275	327

● Balsalazide → Metronidazole

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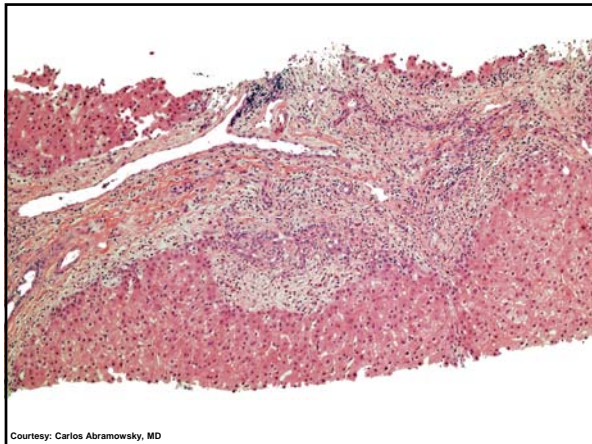
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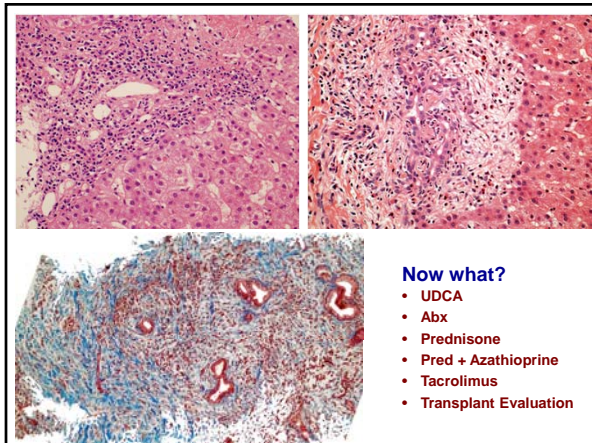
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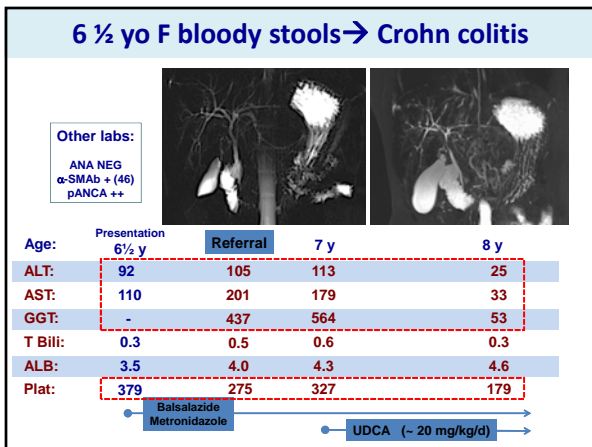
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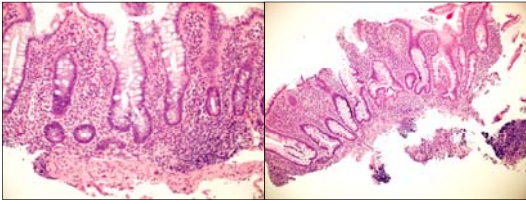
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11 year old boy with bloody stools



Dx: UC

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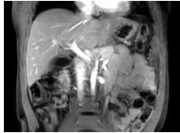
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11 yo M bloody stools → Dx UC

Age: 11 y



Other labs:  
ANA NEG  
α-SMA NEG

Liver Bx

ALT:	109
AST:	56
GGT:	153
T Bill:	<0.1
ALB:	3.6
Plat:	490

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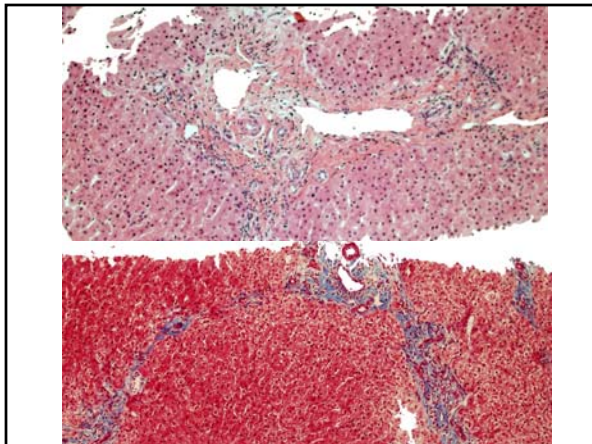
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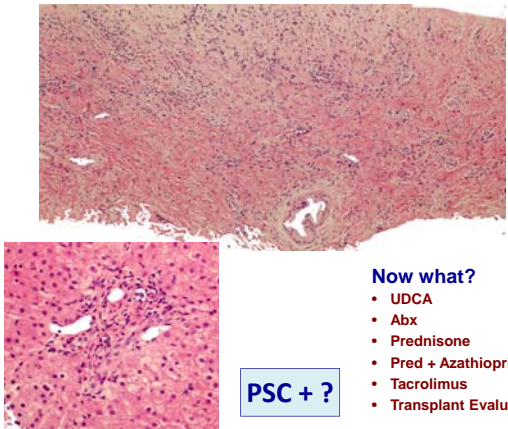
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**Now what?**

- UDCA
- Abx
- Prednisone
- Pred + Azathioprine
- Tacrolimus
- Transplant Evaluation

**PSC + ?**

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**Serial MRE's & Labs reveal rapid progression**

Age: 11 y      14½ y      15 y



ALT:	109	90	98
AST:	56	85	111
GGT:	153	115	63
T Billi:	<0.1	0.9	1.4
ALB:	3.6	Hgb 3.6 2.6	2.1
Plat:	490	56	46

• Asacol / Pred ? / Asacol / Pred / 6MP / Infliximab q 8w / Ascites, Variceal bleed, Transplant List  
 • UDCA (~ 10-13 mg/kg/d)

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**Liver Disease in IBD**

**Q: Why liver disease & Why are they so different?**

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## 1947: 1<sup>st</sup> report of Cirrhosis in a child with UC

### HEPATIC CIRRHOSIS AS A COMPLICATION OF CHRONIC ULCERATIVE COLITIS \*

By HENRY J. TUMEN, A.B., M.D., F.A.C.P., J. FREDERICK MONAGHAN, A.B., M.D., and EMIL JOBB, M.D., *Philadelphia, Pennsylvania*

#### CASE REPORTS

*Case 1.* M. C. S. Female. Age 14.

This patient was first admitted to the Graduate Hospital in April 1939. Diarrhea had begun one year prior to this. A diagnosis of amebic dysentery had been made, although the basis for this diagnosis is unknown. Seven months before this admission, pain had developed in the right upper abdomen. Because this was thought to be due to possible amebic abscess, laparotomy was performed. Empyema of the gall-bladder was discovered and the liver was found to be small and cirrhotic.

*Comment.* This 14 year old patient had been found to have hepatic cirrhosis a few months after the onset of the symptoms of chronic ulcerative colitis. During the subsequent course of her illness, she developed splenomegaly, jaundice, enlargement of the liver, and evidence of liver dysfunction.

Albumin 2.0 Hepatosplenomegaly Jaundice Emaciation

Ann Intern Med. 1947 Apr;26(4):542-53.

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## Thoughts from 1947 & 1949

A study of our patients has convinced us, on the other hand, that severe and prolonged colitis may readily produce changes in the patient which lead to the development of cirrhosis. We, therefore, believe that cirrhosis may occur occasionally as a true complication of colitis.

It is also necessary to mention the possible effect on the liver of the constant absorption of toxic material and bacteria from the bowel.

#### 1949 BMJ Editorial: Cirrhosis & Colitis

In most of the published reports the attempt to relate the cirrhosis or other hepatic lesion to the coexisting colitis is most unconvincing.

A curious and fallacious argument has been followed by both Johnson and Tumen.

TUMEN HJ, MONAGHAN JF, JOBB E. Hepatic cirrhosis as a complication of chronic ulcerative colitis. Ann Intern Med. 1947 Apr;26(4):542-53.

ANNOTATIONS. BMJ. 1949 Jan 29;1(4595):188-90.

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## Topics for 2013: 66 years later

- Incidence, prevalence, potential etiology
  - Adults vs. Children
- Recognition of clinical manifestations
  - Signs & Symptoms
  - Labs & Imaging
- Relevant clinical consequences
- Genetic, immunological, microbial contributions
- Therapies
- Future & Long-term issues

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### Topics for 2013: 66 years later

- **Incidence, prevalence, potential etiology**
  - Adults vs. Children
- **Recognition of clinical manifestations**
  - Signs & Symptoms
  - Labs & Imaging
- **Relevant clinical consequences**
- **Genetic, immunological, microbial contributions**
- **Therapies**
- **Future & Long-term issues**

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### Liver Disease in IBD – 4 Q's

- **Q1: How can I identify liver disease?**
  - Signs & Symptoms
  - Labs & Imaging
  - Invasive procedures (ERCP, PTC, Bx...)
- **Q2: Does the Liver “track” with the bowel?**
  - Or, If the bowel is better, is the liver better too?
- **Q3: What does liver disease mean for the child with IBD?**
- **Q4: Where does the field need to go?**
  - Etiologies
  - Treatments

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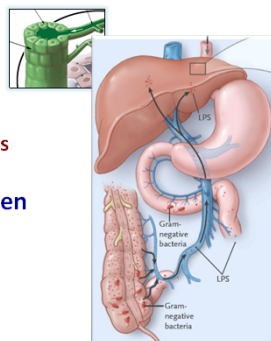
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### Why is the Liver a target in IBD?

- **Inflammation**
  - From the gut
- **Microbial products**
  - LPS & others
  - Reprocessed molecules
- **Commonalities between cholangiocytes & enterocytes.**



Lucy NEJM 2009

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## 1947: 1<sup>st</sup> report of Cirrhosis in a child with UC

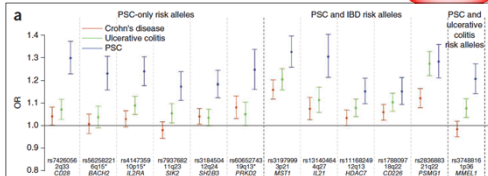
### HEPATIC CIRRHOSIS AS A COMPLICATION OF CHRONIC ULCERATIVE COLITIS\*

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It is also necessary to mention the possible effect on the liver of the constant absorption of toxic material and bacteria from the bowel

TUMEN HJ, MONAGHAN JF, JOBB E. Hepatic cirrhosis as a complication of chronic ulcerative colitis. *Ann Intern Med.* 1947;26(4):542-53.

## Etiologies & Roles for Genes & Guts



Liu JZ, ... , Karlsten TH. Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis. *Nat Genet.* 2013 Jun;45(6):670-5.

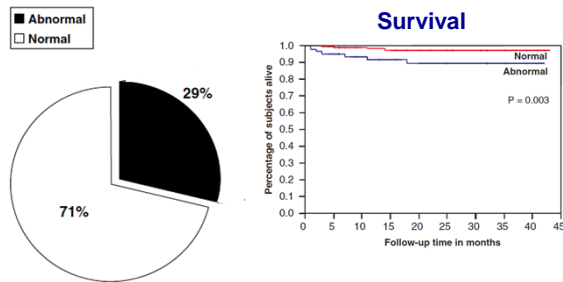
Karlsten TH, Boberg KM. Update on primary sclerosing cholangitis. *J Hepatol.* 2013 Sep;59(3):571-82.

## Adult onset PSC: Basics

- Incidence ~ 1/100,000 Prevalence ~ 10/100,000
- Median age 41 y (~ 50% asymptomatic at Dx)
  - Within 5 years ~ 22% have symptoms
    - fatigue, pruritus, jaundice, abdominal pain
- 60-80% have IBD & 4% of UC have PSC
- 6% have overlap PSC+AIH
- Symptomatic on presentation → 9y to death/LT
- IgG<sub>4</sub>+ with AI Pancreatitis
- Screening for Colon CA, Cholangio CA (1%/yr)

Eaton JE, Talwalkar JA, Lazaridis KN, Gores GJ, Lindor KD. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. *Gastroenterology.* 2013 Sep;145(3):521-36.

## Adult IBD: Abnormal LFTs → ↓Survival



Mendes FD, Levy C, Enders FB, Loftus EV, Angulo P, Lindor KD. Abnormal hepatic biochemistries in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2007 Feb;102(2):344–50.

## Prevalent autoantibodies in PSC in Adults



Trivedi PJ, Hirschfield GM. Review article: overlap syndromes and autoimmune liver disease. *Aliment Pharmacol Ther*. 2012 Sep;36(6):517–33.

## Pediatric Liver Disease in IBD: Single Center Study

- Reported Prevalence ~ 5%
- 8 years: 52 children Dx with Colitis. Ages 9-16 y
- 17 (11 M) with ↑ Liver Indices in (32%)
- 14/17 (82%) had ↑ liver labs on presentation
  - Liver Bx during Colonoscopy
  - GGT: 83-1401
  - ALT: 51-1435
  - MRCP: Abnormal in 12/17
  - All 12 with Auto-Immune “features” (10 + pANCA, 8 + αSMAb)
  - Rx with Pred +/- AZA
- 15/17 normal liver labs 3 y of f/U
- No association of severity of colitis with liver disease

Noble-Jamieson G, Heuschkel RB, Torrente F, Hadzic N, Zilbauer M. Colitis-associated sclerosing cholangitis in children: A single centre experience. *J Crohns Colitis*. 2013 Nov 1;7(10):e414–8.



## Pediatric PSC: Mt. Sinai referral series

- 12 year retrospective study
- 47 patients with PSC
- Med 12 y (2 - 20 y)
  - IBD dx 1<sup>st</sup> : 26%
  - PSC dx 1<sup>st</sup> : 15%
  - IBD + PSC dx together: 59%
- Liver Bx in 45
  - Fibrosis 1/2 16 (35%)
  - Bridging Fibrosis 25 (56%)
  - Cirrhosis 4 (9%)
  - AIH features 12 (25%)
- MRCP in 39
- ERCP Interventions in 8
  - Papillotomies, Stents

Signs and symptoms at presentation	
Hepatomegaly	19 (40%)
Abdominal pain	17 (36%)
Diarrhea	13 (28%)
Splenomegaly	11 (23%)
Fatigue	11 (23%)
Pruritus	9 (19%)
Weight loss/delayed growth	9 (19%)
Jaundice	8 (17%)
Fever	6 (13%)
Asymptomatic	9 (19%)

Test	All patients (n = 47)	
	Mean at diagnosis	Mean at 1 year into UDCA therapy
ALT	233 ± 327	62 ± 69
AST	236 ± 248	58 ± 48
ALP	640 ± 340	218 ± 131
GGT	553 ± 676	92 ± 32

Miloh T, Arnon R, Shneider B, Suchy F, Kerker N. A retrospective single-center review of primary sclerosing cholangitis in children. *Clin Gastroenterol Hepatol*. 2009 Feb;7(2):239–45.

## Adult onset PSC: Medical Treatment

- Medications without efficacy in PSC (no AIH):
  - Steroids
  - Etanercept
  - Infliximab
  - Tacrolimus
  - Cyclosporine
  - Azathioprine
  - Methotrexate

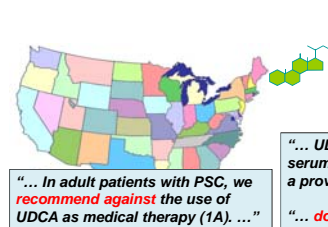
## ? UDCA

Eaton JE, Talwalkar JA, Lazaridis KN, Gores GJ, Lindor KD. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. *Gastroenterology*. 2013 Sep;145(3):521–36.

## AASLD PRACTICE GUIDELINES

### Diagnosis and Management of Primary Sclerosing Cholangitis

Roger Chapman,<sup>1</sup> Johan Frey,<sup>2</sup> Anthony Kallou,<sup>2</sup> David M. Saperstein,<sup>2</sup> Kirsten Muri Eideberg,<sup>3</sup> Benjamin Schneider,<sup>4</sup> and Gregory J. Gurov<sup>2</sup>



**"... In adult patients with *PSC*, we *recommend against* the use of *UDCA* as medical therapy (1A). ..."**

**EASL Clinical Practice Guidelines:  
Management of cholestatic liver diseases**

European Association for the Study of the Liver\*



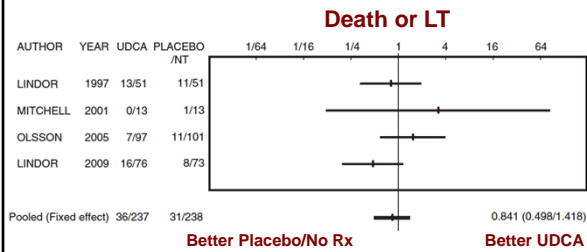
***“... UDCA (15-20 mg/kg/d) improves serum liver tests ... but does not reveal a proven benefit on survival...”***

**"... does not yet allow a specific recommendation for the general use of UDCA in PSC..."**

Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ, American Association for the Study of Liver Diseases. *Hepatology*. 2010. pp. 660–78.

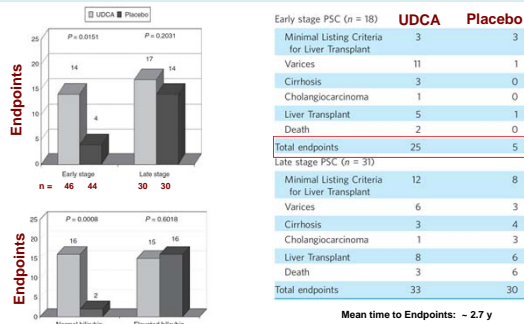
European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol*. 2009. pp. 237–67.

## Adult onset PSC: UDCA Meta-analysis



Triantos CK, Koukias NM, Nikolopoulou VN, Burroughs AK. Meta-analysis: ursodeoxycholic acid for primary sclerosing cholangitis. *Aliment Pharmacol Ther.* 2011 Oct;34(8):901-10.

## HD UDCA (28-30 mg/kg/d) → Worse Outcomes in Early PSC



Lindor KD, ... *Hepatology.* 2009 Sep;50(3):808-14.

Imam MH, ... *Alimentary Pharm. & Ther.* 2011 Sep 29;34(10):1185-92.

## Antibiotics → Improved Liver Indices in PSC

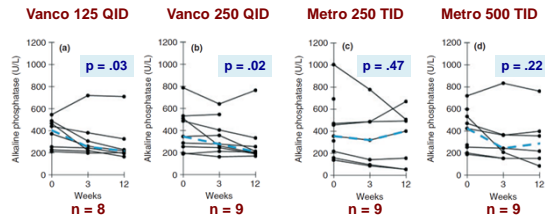
Table 1   Previously reported results of antibacterial treatment in primary sclerosing cholangitis								
Drug	Year	n	Antibiotic dose	Months of therapy	% change from baseline post-therapy			
Tetracycline <sup>32a</sup>	1959	5	500 mg/day	1-10	-45	-60	-45	-
Tetracycline <sup>36a</sup>	1965	5	500 mg/day	48 (mean)	+21	-	-	-
Sulfasalazine (+UDCA) <sup>37b</sup>	1998	2*	-	30	-79	-38	-70	-26
				45	-35	-87	-95	-94
Vancomycin <sup>38</sup>	1998	3*	375-1000 mg/day	9 (mean)	-	-	-89	-93
Sulfasalazine (+UDCA) <sup>39</sup>	2002	1	50 mg/kg/day	37	-	-	-92	-83
Metronidazole (+UDCA) <sup>40</sup>	2004	39	600-800 mg/day	36	-52.4	-41.0	-67.9	-
Sulfasalazine <sup>41</sup>	2006	1	2-4.5 g/day	24	-74	-	-	-84
Azithromycin (+UDCA) <sup>43</sup>	2007	1	500 mg/day, 3 days/week	5	-72	-31	-33	-54
Vancomycin <sup>47</sup>	2008	14*	50 mg/kg/day	54 ± 43	-	-	-78	-89
Minocycline <sup>49</sup>	2009	16	200 mg/day	12	-19.7	-2.8	-	-

3 Pediatric Studies

*Aliment Pharmacol Ther.* 2013 Mar;37(6):604-12

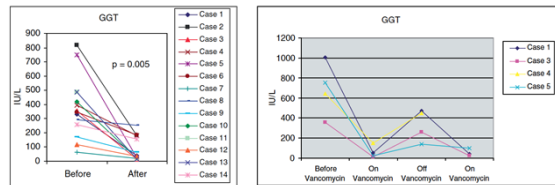
### Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis - a pilot study

J. H. Tabibian<sup>1,2</sup>, E. Weeding<sup>1,3</sup>, R. A. Jorgensen<sup>1</sup>, J. L. Petr<sup>1</sup>, J. C. Keach<sup>1</sup>, J. A. Talwalkar<sup>1</sup> & K. D. Linder<sup>1</sup>



Aliment Pharmacol Ther. 2013 Mar;37(6):604-12.

### 14 patients on po Vanco (50 mg/kg/d) → Improved Liver Indices in PSC



- 2-17 y (mean 12 y)
- 11 UC, 3 CD No AIH
- Variable Rx lengths: 5-56+ months
- Less effective in cirrhotics

Davies YK, Cox KM, Abdullah BA, Satta A, Terry AB, Cox KL. Long-term treatment of primary sclerosing cholangitis in children with oral vancomycin: an immunomodulating antibiotic. *J Pediatr Gastroenterol Nutr.* 2008 Jul;47(1):61-7.

### PSC: Clinicaltrials.gov → 41 trials (8 for children)

#### Select Pediatric Trials:

- **UDCA withdrawal:** NCT01088607: WUP PSC (Black, U Tenn)
- **Vancomycin:** NCT01802073: Microbiome (Cox, Stanford)
- **Genomics:** NCT01161992: ages 5-90 (Lazaridis, Mayo)

#### Select Adult Trials:

- **Endoscopic U/S, ERCP** (Spyglass, Narrow Band Imaging, Stents...)
- **NorUDCA** NCT01755507: Ph II double-blind Europe (Trauner, Falk)
- **Fenofibrate** NCT01142323: Pilot study ↓Alk Phos (Levy, Miami)
- **Simtuzumab** NCT01672853: Ph II anti-LoxL2 (anti-fibrotic) Gilead
- **Rifaximin** NCT01695174: Ph II (Talkwalker, Mayo)
- **UDCA + ATRA** NCT01456468: Ph I (Boyer, Yale)

October 6, 2013: search terms "sclerosing cholangitis AND children"

# WUP PSC

Withdrawal of Ursodeoxycholic Acid in Pediatric Primary Sclerosing Cholangitis

- “Ursodeoxycholic Acid Therapy in Pediatric Primary Sclerosing Cholangitis: A Pilot Withdrawal/Reinstitution Trial”
- R01 FD003709
- Sponsored by the FDA Office of Orphan Product Development
- Study PI's
  - Dennis Black, PI
  - Ben Schneider, Co-PI
- Participating Centers
  - Univ. of Pittsburgh
  - UCSF
  - Children's Hospital Colorado
  - Cincinnati Children's Hospital
  - Mount Sinai
  - Phoenix Children's Hospital
  - Emory University
  - CHOP
  - Univ. of Tennessee, Memphis
  - Lurie Child. Hospital, Chicago
- More information
  - [dblack@uthsc.edu](mailto:dblack@uthsc.edu)
- ClinicalTrials.gov
  - NCT01088607

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## Summary: Liver Disease in IBD – 4 Q's

- **Q1: How can I identify liver disease?**
  - Look for it at presentation of IBD, mainly colitis.
  - Labs (↑GGT + ) & Imaging (MRCP)
  - Invasive procedures for obstruction (ERCP, PTC)
  - Biopsy for those with AIH features, or not sure.
- **Q2: Does the Liver “track” with the bowel?**
  - No → PSC is often linked to quiescence of colitis.
- **Q3: What does liver disease mean for the child with IBD?**
  - Potential for ↑complications or transplant.
  - UDCA & Abx treatments require better studies.
- **Q4: Where does the field need to go?**
  - Etiologies: Genes, Microbes, Immune cells, Diet
  - Treatments: Antibiotics, Anti-fibrotics, FXR Agon., NorUDCA
  - Longitudinal studies of children with IBD




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## Liver Disease in IBD – Unmet needs

- True Incidence, prevalence data
- Roles for Clinical Best Practices
- UDCA, Vancomycin, Nor-UDCA, FXR agonists ...
- True etiologic gut-liver connections
  - Genomics (e.g. TGR5, Immune pathways)
  - Microbial products and prokaryotic derived metabolites
- Transplant Evals & Post-Transplant care
- Future & Long-term issues

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## American Journal of Diseases of Children

VOLUME 59 MARCH 1940 NUMBER 3  
COPYRIGHT, 1940, BY THE AMERICAN MEDICAL ASSOCIATION

### LIFE HISTORIES OF NINETY-FIVE CHILDREN WITH CHRONIC ULCERATIVE COLITIS

A STATISTICAL STUDY BASED ON COMPARISON WITH A WHOLE GROUP OF EIGHT HUNDRED AND SEVENTY-ONE PATIENTS

RAYMOND J. JACKMAN, M.D.

J. ARNOLD BARGEN, M.D.

AND  
HENRY F. HELMHOLZ, M.D.

ROCHESTER, MINN.

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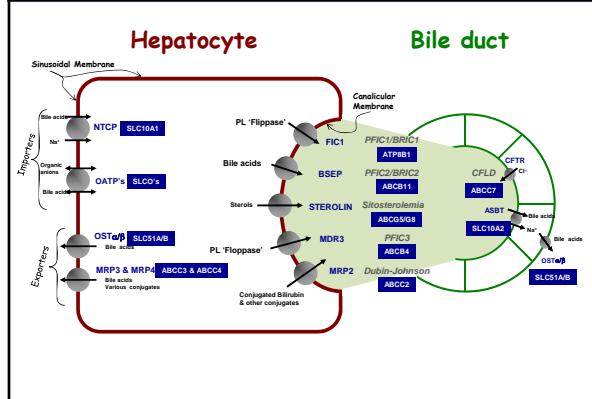
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## Bile Formation & Adaptation 2013




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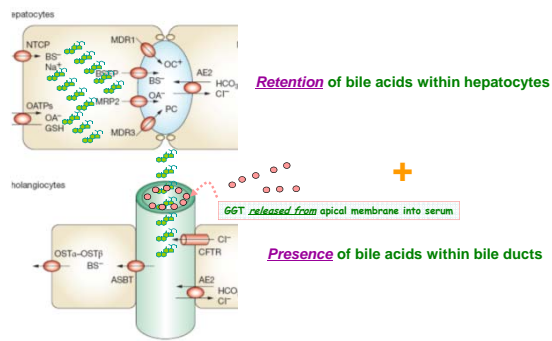
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## Mechanism of high GGT cholestasis



Geier. *Nature Clin GI & Hep* 2006