GHAPP

Gastroenterology & Hepatology
Advanced Practice Providers

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PSC Management including Vancomycin

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Disclosures

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Disclosures

Vicki Shah PA-C, MMS

Advisory Board: AbbVie, Clinical Area- HCV

Research Support: Gilead, Clinical Area-HCV

PSC Overview

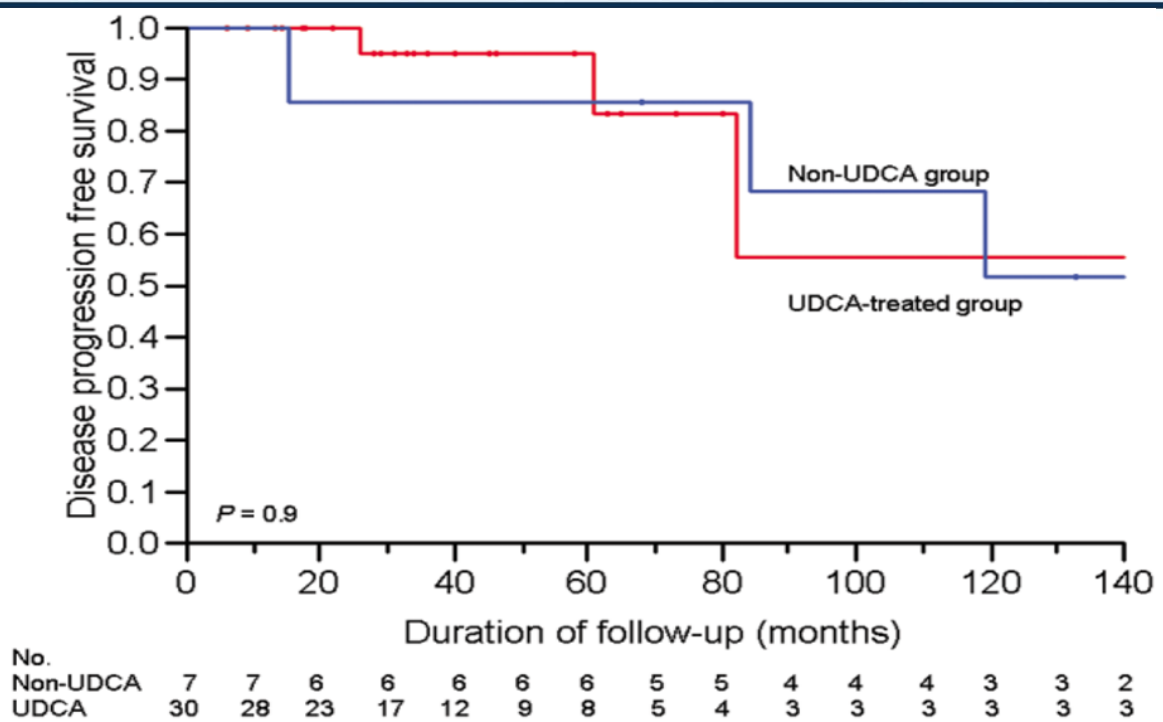
- Cholestatic autoimmune biliary inflammatory disease causing inflammation and fibrosis of bile ducts
- 50%-75% having IBD, most commonly UC
- Causes multifocal bile duct strictures
- Cirrhosis, Liver transplantation, cholangiocarcinoma
- 10x increased risk of colon cancer with PSC/IBD
- No medical therapies improve disease course or slow progression

Davies YK, Cox KM, Abdullah BA, Safta 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; 47: 61- 67.

Bile Duct Diseases

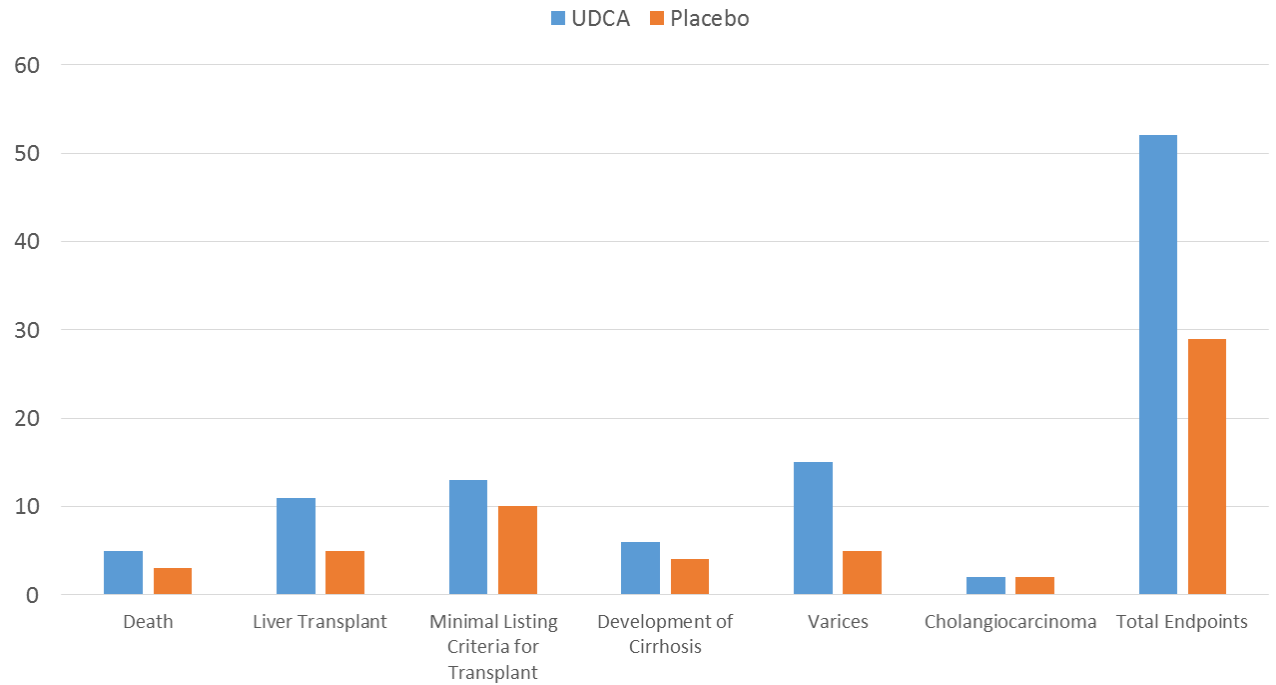
	PBC	PSC
Population	Females (9:1)	Males (5:1)
Bile ducts	Interlobular Obliterative	Intra and extrahepatic Stricturing
ERCP	Normal	Abnormal
AMA	+	-
IBD association	-	UC>>>>Crohns
Cholangiocarcinoma Risk	-	+++

Small-duct PSC Treated vs. Untreated



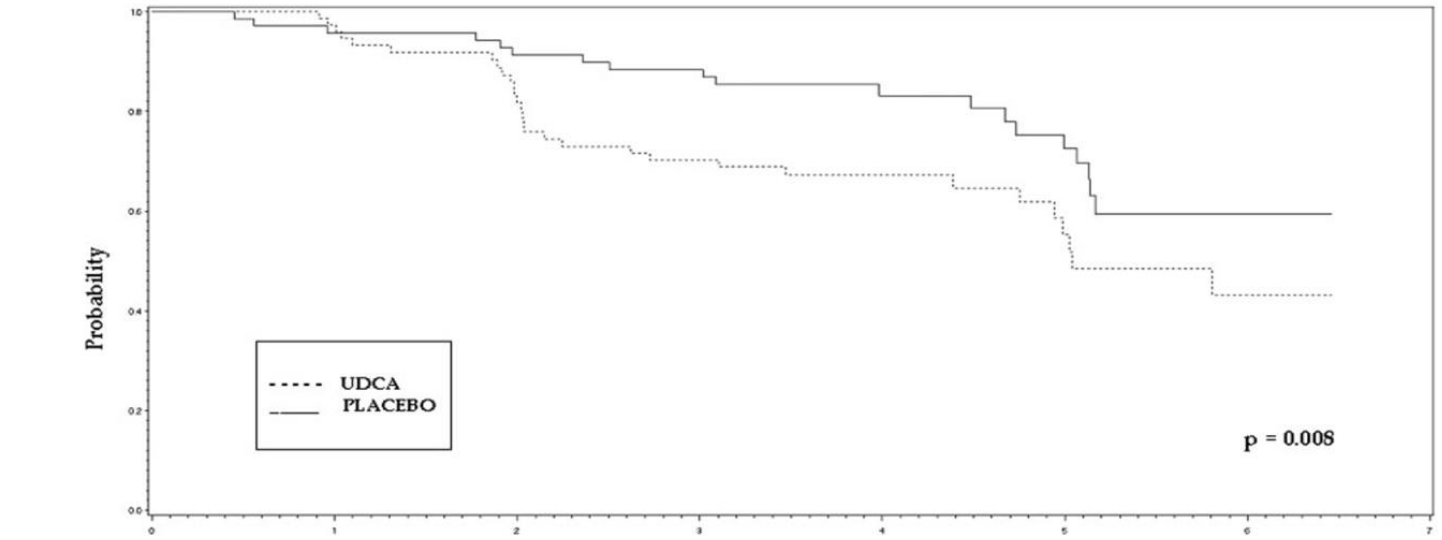
Charatcharoenwithhaya P, Angulo P, Enders FB et al. Impact of inflammatory bowel disease and ursodeoxycholic acid therapy on small-duct primary sclerosing cholangitis. Hepatology 2008;47(1):133-42

High Dose Ursodiol for PSC



Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology 2009;50(3):808-14

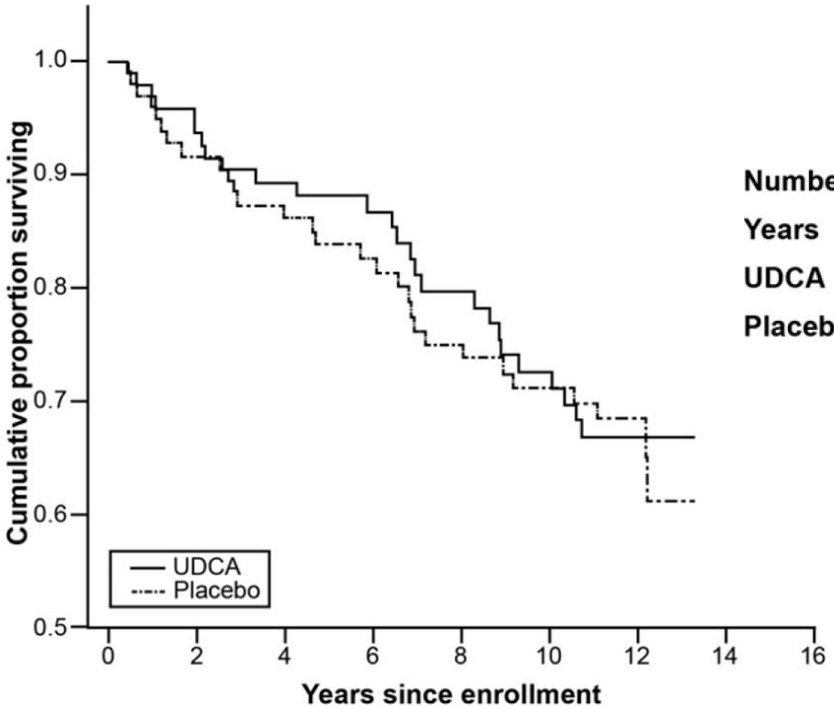
Overall Endpoints: High Dose Ursodiol for PSC



Number at Risk								
UDCA	76	73	60	51	34	18	9	0
PLACEBO	74	65	60	58	41	24	7	0

Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for treatment of primary sclerosing cholangitis. Hepatology 2009;50(3):808-14

Kaplan-Meier Survival Curve of 198 PSC Patients Enrolled in a 5 year UDCA Trial

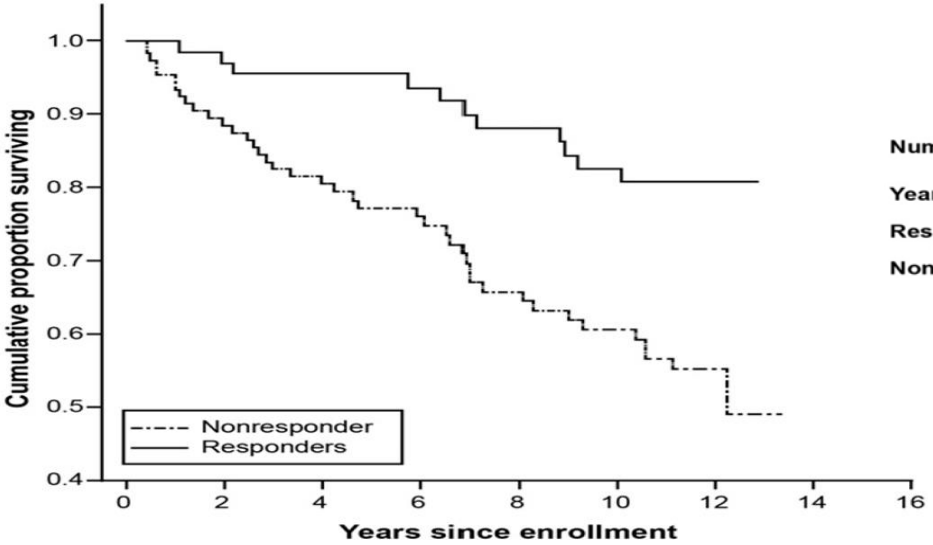


Numbers at risk

Years	0	2.5	5	7.5	10	12.5
UDCA	97	84	78	56	51	20
Placebo	101	84	72	59	56	19

Lindstrom L, Hultcrantz R, Boberg KM,, et al. Assoc. btwen reduced levels of ALK and Survival Times of Patients with PSC. Clin Gastro Hep. 2013;11(7):841-846.

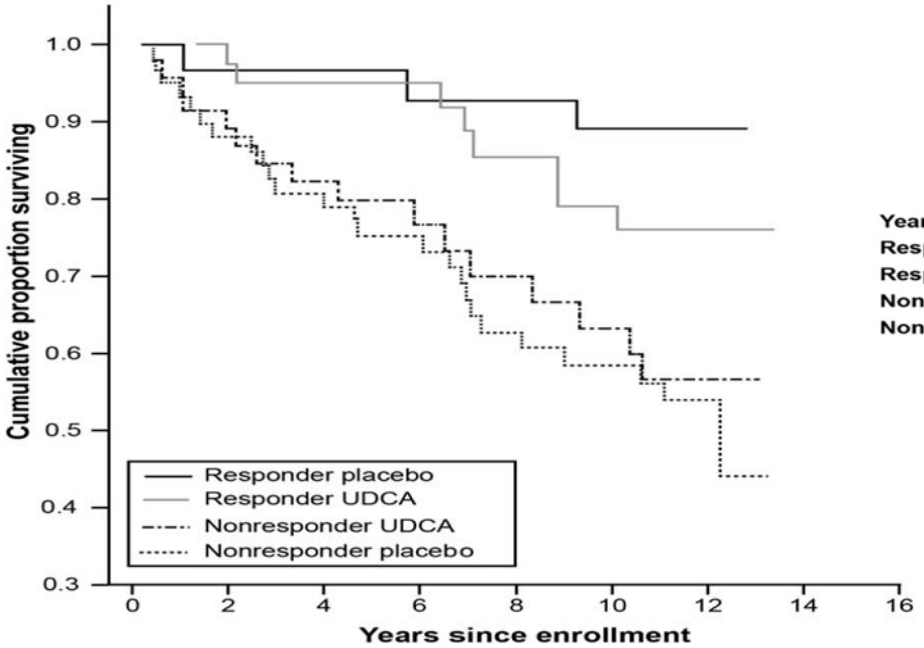
Kaplan-Meier Analysis of Endpoint Free Survival Regardless of Treatment with UDCA



Numbers at risk						
Years	0	2.5	5	7.5	10	12.5
Responders	79	72	69	56	53	17
Nonresponders	116	93	78	56	52	21

Lindstrom L, Hultcrantz R, Boberg KM,, et al. Assoc. btwen reduced levels of ALK and Survival Times of Patients with PSC. Clin Gastro Hep. 2013;11(7):841-846.

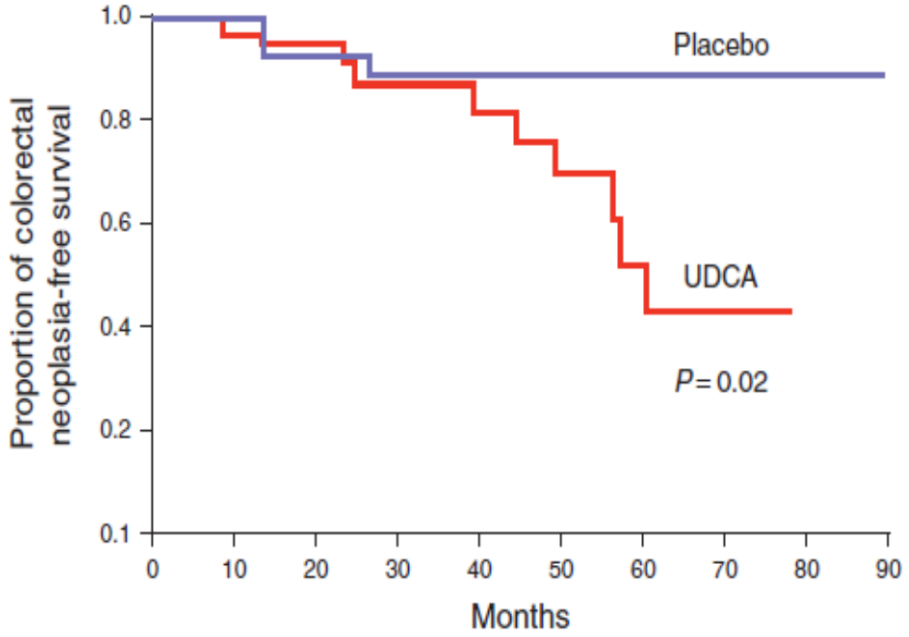
Kaplan-Meier Analysis of Endpoint Free Survival in all PSC Patients with UDCA Treatment



Years	0	2.5	5	7.5	10
Responder placebo	36	32	29	26	25
Responder UDCA	43	40	38	30	27
Nonresponder UDCA	51	41	33	25	23
Nonresponder placebo	65	51	43	33	31

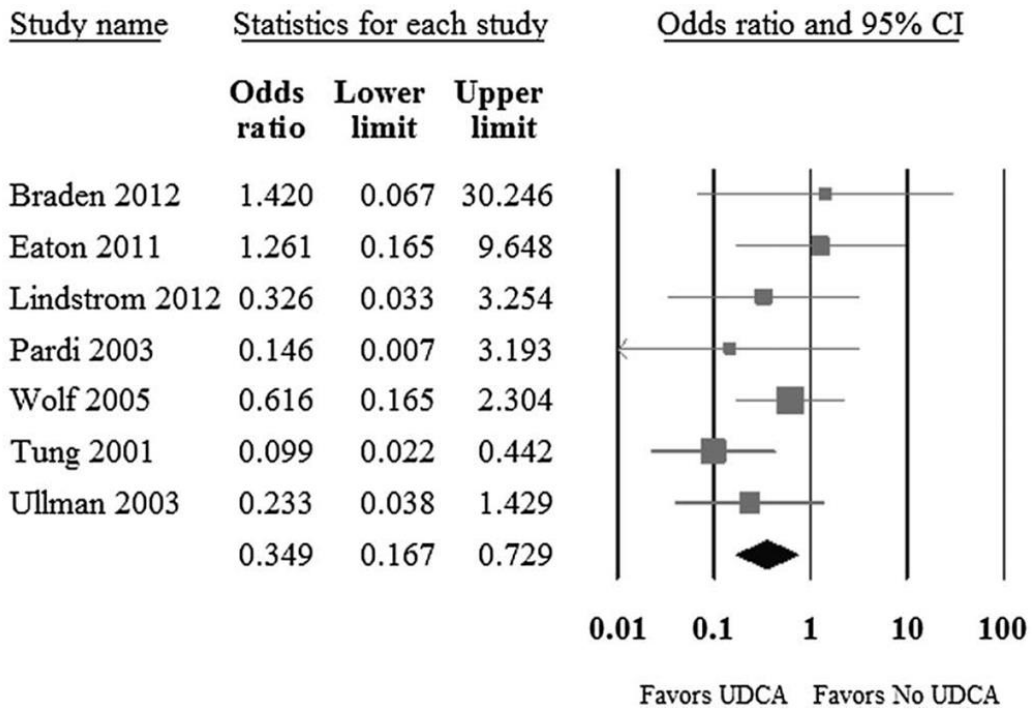
Lindstrom L, Hultcrantz R, Boberg KM,, et al. Assoc. btwen reduced levels of ALK and Survival Times of Patients with PSC. Clin Gastro Hep. 2013;11(7):841-846.

High-Dose Urso in UC & PSC



Eaton J, Silveira MG, Pardi DS, et al. High-dose ursodeoxycholic acid is associated with the development of colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. Am J Gastroenterol 2011;106(9):1638-45

UDCA and Risk of Advanced Colorectal Neoplasia in Patients with PSC - IBD



Singh S, Khanna S, Pardi DS,, et al. Effect of UDCA on the Risk of Colorectal Neoplasia in Patients with PSC and IBD: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2013;19(8):1631-1638

Gut Microbiota and PSC

- PSC associated with altered gut microbiota
- Overrepresentation:
  - *Enterococcus, Escherichia, Fusobacterium, Lactobacillus, Veillonella, Blautia, Lachnospiraceae, Barnesiellacea, Megasphaera genera, Actinobacteria, Proteobacteria, Streptococcus and Rothia*
- Reduction:
  - *Clostridiales II, Prevotella*, *Roseburia*, and *Bacteroides*

Sabino J, Vieira-Silva S, Machiels K, et al. Primary sclerosing cholangitis is characterised by intestinal dysbiosis independent from IBD. Gut. 2016;65:1681-1689.
Kummen M, Holm K, Anmarkrud JA, et al. The gut microbial profile in patients with primary sclerosing cholangitis is distinct from patients with ulcerative colitis without biliary disease and healthy controls. Gut. 2016;66:611-619.
Quraishi MN, Sergeant M, Kay G, et al. The gut-adherent microbiota of PSC-IBD is distinct to that of IBD. Gut. 2016;66:386-388.
Ruhlemann MC, Heinsen FA, Zenouzi R, Lieb W, Franke A, Schramm C. Faecal microbiota profiles as diagnostic biomarkers in primary sclerosing cholangitis. Gut. 2016;66:753-754.
Torres J, Bao X, Goel A, et al. The features of mucosa-associated microbiota in primary sclerosing cholangitis. Aliment Pharmacol Ther. 2016;43:790-801.

Tetracycline

- Previous study 1959 with improvement of LFTs
- Long-term study report 1965
  - no clinical benefit
  - No histological changes
  - No changes in liver function tests

Rankin JG, Boden RW, Goulston SJ, Morrow W. The liver in ulcerative colitis; treatment of pericholangitis with tetracycline. Lancet. 1959;2:1110-1112
Mistilis SP, Skyring AP, Goulston SJ. Effect of long-term tetracycline therapy, steroid therapy and colectomy in pericholangitis associated with ulcerative colitis. Australas Ann Med. 1965;14:286-294.

Rifaximin

- 16 patients in 12-week, open-label pilot study
- 550 mg rifaximin twice daily
- No significant changes in ALK, serum bilirubin and GGT at the end of the 12 weeks.
- No significant changes for fatigue impact scale, chronic liver disease questionnaire or the short form health survey

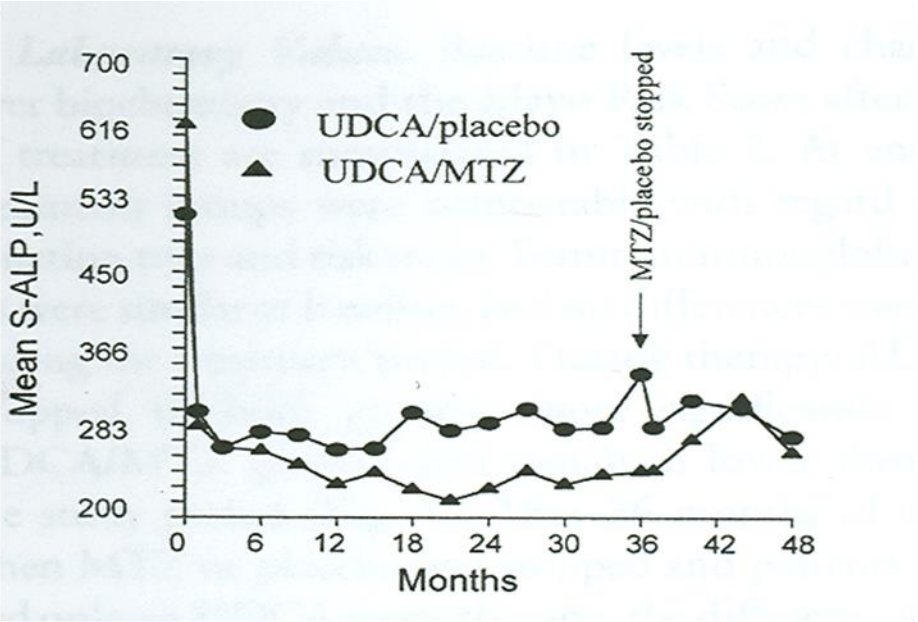
Tabibian JH, Gossard A, El-Youssef M, et al. Prospective clinical trial of rifaximin therapy for patients with primary sclerosing cholangitis. Am J Ther. 2014;24:e56-e63.

Metronidazole & UDCA

- Compared metronidazole alone vs UDCA with metronidazole
- Improved ALK, histology scores and Mayo risk scores.
- Neither progression nor improvement was noted for liver histology/ERCP changes.
- Long-term studies using a higher dose of ursodeoxycholic acid combined with metronidazole in larger populations are needed

Farkkila M, Karvonen AL, Nurmi H, et al. Metronidazole and ursodeoxycholic acid for primary sclerosing cholangitis: a randomized placebo-controlled trial. Hepatology. 2004;40:1379-1386.

Metronidazole & UDCA



Farkkila M, Karvonen A, Nurmi H, et al. Metronidazole and ursodeoxycholic acid for primary sclerosing cholangitis: A randomized placebo-controlled trial. Hepatology 2004;40(6):1379-86

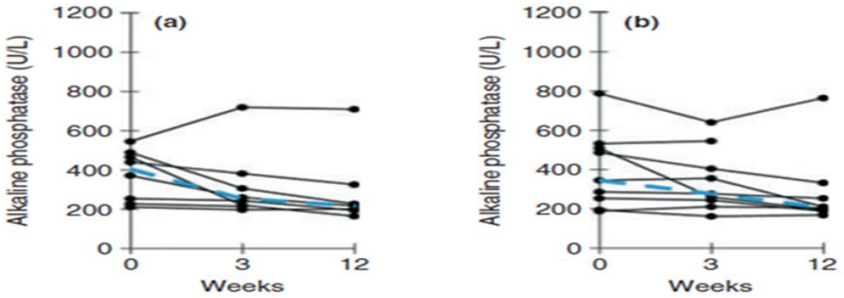
Vancomycin & Metronidazole

- Randomized into four groups for 12 weeks
  - vancomycin (125 mg 4 times a day, n = 8 or 250 mg 4 times a day, n = 9)
  - metronidazole (250 mg 3 times a day, n = 9 or 500 mg 3 times a day, n = 9)
- Decrease in ALK in the high dose vancomycin
- Normalization in ALK in and low-dose vancomycin
- Mayo PSC risk score, total bilirubin, and CRP decreased in low-dose vancomycin
- Why was low-dose vancomycin more effective than higher dose vancomycin?

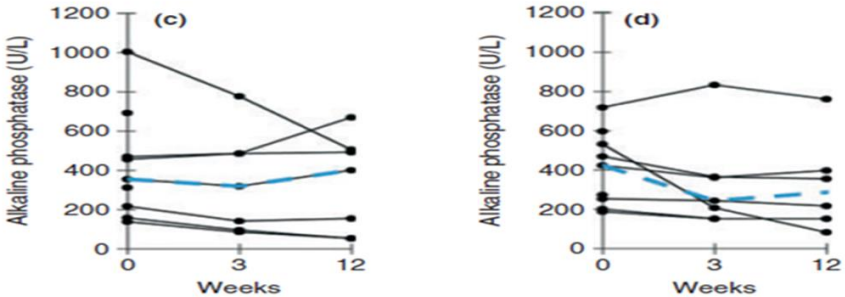
Tabibian JH, Weeding E, Jorgensen RA, et al. Randomized clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis – a pilot study. Aliment Pharmacol Ther. 2013; 37(6): 604-12.

Vancomycin & Metronidazole

Vancomycin
High and Low Doses



Metronidazole
High and Low Doses



Tabibian JH, Weeding E, Jorgensen RA, et al. Randomized clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis – a pilot study. Aliment Pharmacol Ther. 2013; 37(6): 604-12.

Vancomycin Trials

Clinical trial or Case report	Number of patients (n = x)	Summary of findings
Tabibian et al[52]	35	*Adults*. Decrease in alkaline phosphatase (both high and low vancomycin dose groups) and decrease in Mayo PSC score (low-dose vancomycin group) at the end of the 12 wk of treatment. Adverse effects: diarrhoea. 500-1000 mg per day for 3 months.
Rahimpour et al[61]	29	*Adults*. Decrease in Mayo PSC score, alkaline phosphatase, ESR, GGT, fatigue, pruritus, diarrhoea and anorexia in the oral vancomycin group after 12 weeks of treatment. 500 mg per day for 3 months.
Davies et al[1]	14	*Pediatrics*. Clinical and laboratory (ALT, GGT and ESR) improvement after 1-2 mo of oral vancomycin. Worsening findings when it was stopped and overall improvement when resumed. Decreased clinical and laboratory improvement for patients with cirrhosis. 50 mg per kilogram per day for 54 months +/− 43 months.
Abarbanel et al[58]	14	*Pediatrics*. GGT, ALT, WBC, MRCP findings, liver biopsy and immunological improvements noted with 12 wk of oral vancomycin. 50 mg per kilogram per day for 12 months.
Cox & Cox[62]	3	*Pediatrics*. Clinical, laboratory and pathological improvement during treatment with oral vancomycin. Not all patients improved after stopping the treatment. 375-1000 mg per day for 18 months.
Buness et al[59]	1	*Pediatrics*. Single case, clinical, laboratory and endoscopic improvement after escalating dose of oral vancomycin until optimal dose was determined. 1500-2250 mg per day for 5.5 years.
Davies et al[60]	1	*Pediatrics*. Single case, normalization of liver enzymes after orthotropic liver transplantation and PSC recurrence. 1500mg per day for 5 yrs.

Damman, JL, Rodriguez, EA, Ali, AH, et al. Review article: the evidence that vancomycin is a therapeutic option for primary sclerosing cholangitis. *Aliment Pharmacol Ther*. 2018; 47: 886– 895.

Ongoing Clinical Trials for PSC

Drug	Mechanism of Action	Design	N	Phase	Duration
Sulfasalazine	5-ASA modulates inflammatory response	RCT	42	II	22 weeks
DUR-928	Endogenous sulfated oxysterol, ligand of LXRs	RCT	40	II	4 weeks + 56 days observation
Vidofludimus calcium	Small-molecule inhibitor of dihydroorotate dehydrogenase	OL	30	II	6 months
Umbilical cord mesenchymal stem cells	Stem cell therapy for immunomodulation	RCT	20	I/II	1 year
Cilofexor	FXR agonist	RCT	400	III	96 weeks
BTT1023	Anti-VAP1	OL	23	II	120 days
Vancomycin	Manipulation of gut microbiome	RCT	102	II/III	2 years
HTD1801	UDCA+berberine (antioxidant supplement)	RCT	90	II	18 weeks
*Nor*UDCA (Europe)	Anticholestatic	RCT	300	III	2 years

Vesterhus M, Karlsen TH. Emerging therapies in primary sclerosing cholangitis: pathophysiological basis and clinical opportunities. J Gastroenterol. 2020;55(6):588-614. doi:10.1007/s00535-020-01681-z

Santiago P, Levy C. Novel Therapies for Managing Cholestasis. Clin Liver Dis (Hoboken). 2020;15(3):95-99. Published 2020 Apr 4. doi:10.1002/cld.886

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Q&A