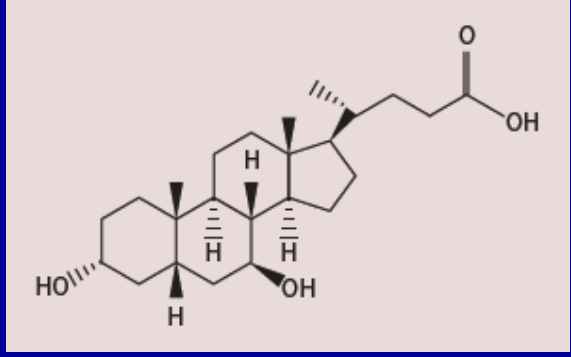


Urso does not benefit PSC

Marion Peters

UCSF 2011

Why treat PSC?

- Chronic cholestatic progressive liver disease
- Associated with
  - Inflammation and fibrosis of bile ducts
  - Biliary obstruction
  - Stone formation
  - Infection
  - Cholangiocarcinoma

Effects of Urso

- 1970's Gall stone dissolution
  - Solubilizes cholesterol from GS surface
- Converts supersaturated bile to unsaturated bile
  - Enhances transport capacity of bile for cholesterol
- Promotes liquid crystal metaphase of phospholipids and cholesterol
  - Aids dissolution even if bile is supersaturated
- ?decrease biliary pain if mild??

Bachrach Dig Dis Sci 1982; Corrigan J Pharm Sci 1980; Tomida Hepatology 1999;

Effects of Urso

- UDCA in PBC beneficial
  - stimulates biliary secretion of bile acids
  - Stimulates transporter proteins (post transl)
- In cholestatic liver diseases hydrophobic bile acids accumulate in hepatocytes
  - Cell damage, apoptosis and necrosis
- Urso cytoprotective (hydrophilic)
- ? anti-apoptotic in vitro studies
- ? Immunomodulatory activate GR, anti IFN-γ
- ? Chemopreventative colon cancer

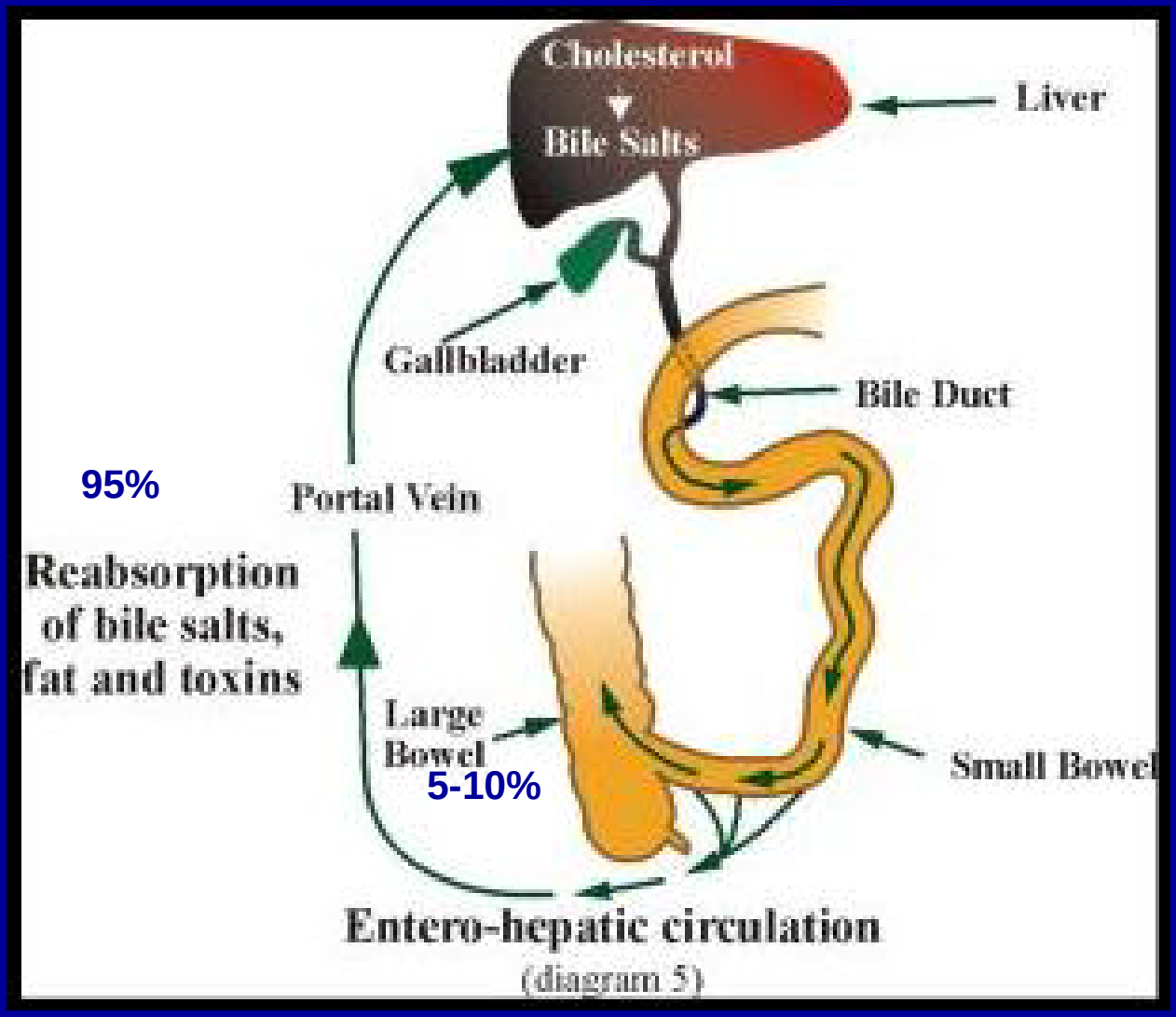
Jazrawi Gastro 1994; Marschall Gastro 2005; Rodrigues Mol Med 1998; Tanaka J Immunol 1996; Martinez Nutr Cancer 1998; Tung Ann Int Med 2001; Pardi Gastro 2003

Effects of Urso

- Chemopreventative colon cancer
  - Decreased prevalence of neoplasia after median 50 and 42 months urso
  - 39% reduction in recurrence of adenomas with high-grade dysplasia
  - No difference in total adenoma recurrence
    - How long??/

Tung Ann Int Med 2001; Pardi Gastro 2003; Alberts J Natl Cancer inst 2005

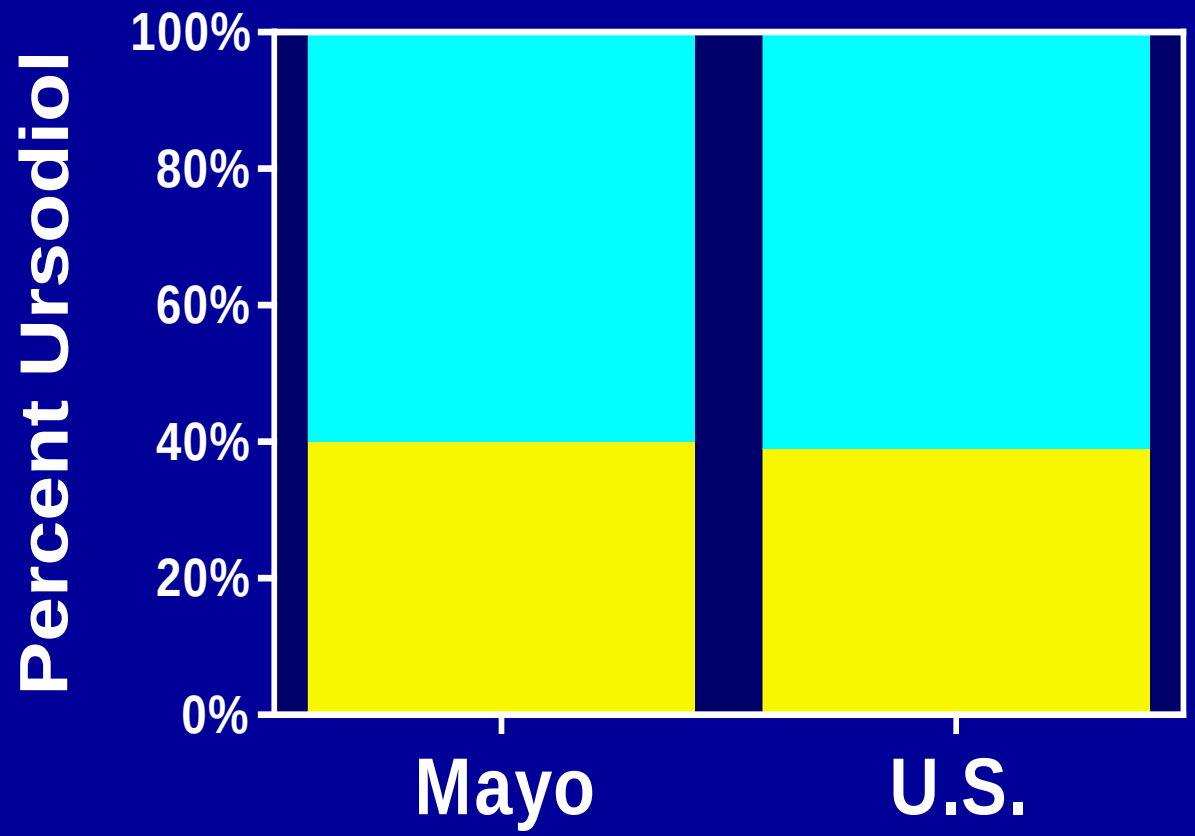
Entero-hepatic circulation



1º bile acids
CDCA
cholic acid
2º bile acids
DCA
LCA

Urso 3%

URSODIOL ENRICHMENT



Lindor; Combes

Trials of urso for PSC

Inconclusive benefit	YES	NO
• Symptoms	2/9	7/9
• LFT's	11/12	1/12
• Histology	3/7	4/7
• Outcome	2/5	3/5

- Doses 10-30 mg/Kg

Table 1 | Trials of UDCA in PSC

Reference	Type of study	No. of patients	Dose of UDCA	Duration (months)	Outcomes
Chazouillères *et al.*[44]	Prospective	15	750–1250 mg	6	Improved liver function and symptoms
O'Brien *et al.*[45]	Open-label	12	10 mg/kg	30	Improved liver function and symptoms
Beuers *et al.*[43]	Double-blind, placebo-controlled	6	13–15 mg/kg	12	Improved liver function and histology. No effect on symptoms
Lo *et al.*[175]	Double-blind placebo controlled	23	10 mg/kg	24	Improved liver function. No effect on symptoms or histology
Stiehl *et al.*[176]	Double-blind, placebo-controlled	20	750 mg	12–48	Improved liver function and histology. No effect on symptoms
De Maria *et al.*[177]	Double-blind placebo controlled	59	600 mg	24	No improvement in liver function
Lindor[47]	Double-blind, placebo-controlled	105	13–15 mg/kg	34	Improved liver function. No effect on histology and symptoms

Van Hoogstraten *et al.*[178]	Double-blind	48	10 mg/kg	24	Improved liver function. No effect on symptoms
Mitchell *et al.*[49]	Double-blind, placebo-controlled	26	20–25 mg/kg	24	Improved liver function, histology and cholangiography. No effect on symptoms. No survival benefit
Harnois *et al.*[179]	Open label	30	25–30 mg/kg	12	Improved liver function and survival compared with Mayo risk score
Okolicsanyi *et al.*[180]	Open-label, placebo-controlled	86	8–13 mg/kg	120	Improved liver function and symptoms. No effect on histology
Olsson *et al.*[50]	Multi-centre randomised Double-blind, placebo-controlled	219	17–23 mg/kg	60	Improved liver function. Nonsignificant trend towards increased survival. No effect on symptoms
Cullen *et al.*[51]	Pilot dose range study	30	10 mg/kg 20 mg/kg 30 mg/kg	24	Improved projected survival with low and standard dose. Significantly improved projected survival with high dose
Lindor *et al.*[48]	Multi-centre Double-blind, placebo-controlled	150	28–30 mg/kg	60	Improved liver function. No improvement in symptoms or histology. Discontinued early (6 years): significantly risk of death, need for liver transplant or development of varicies

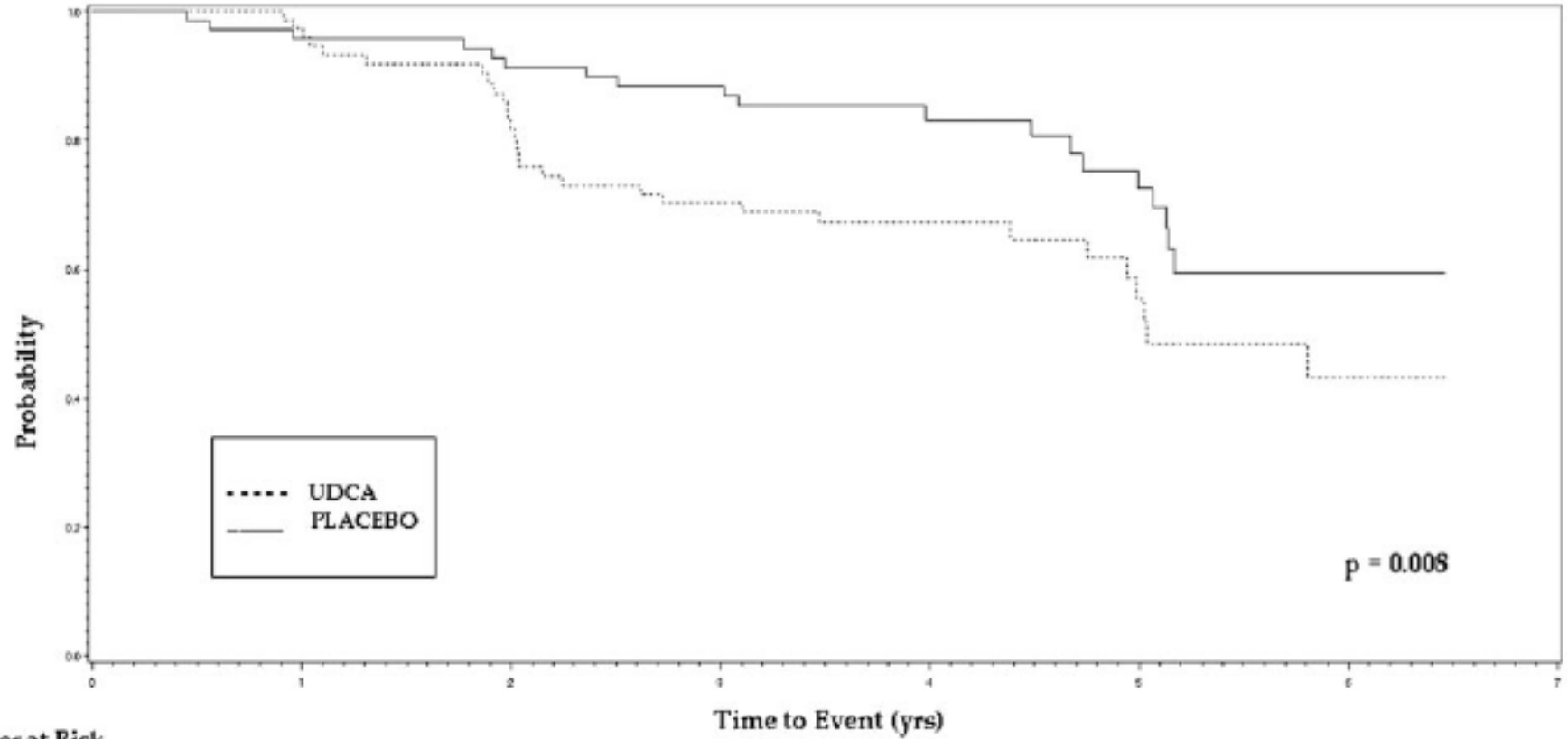
High dose Urso for PBC

- UDCA (n=76) placebo (n=74) groups: randomized, double-blind controlled trial of high-dose UDCA (28–30 mg/kg/day) for 5 y
- Similar in gender, age, duration of disease, inflammation, liver histology and Mayo risk score.
- DSMB stopped at 75% enrollment (31 (21%) reached 5 y)
- During therapy, AST and AP levels decreased more in the UDCA than the placebo group ($p<0.01$)
- Not associated with decreased endpoints: development of cirrhosis, varices, cholangiocarcinoma, liver transplantation or death
- 30 patients in the UDCA group (39%) versus 19 patients in the placebo group (26%) had reached one of the pre-established clinical endpoints.
- The risk of a primary endpoint was 2.3 times greater for patients on UDCA than for those on placebo ($p<0.01$)
- Risk 2.1 times greater for death, transplantation, or minimal listing criteria ($p=0.038$).
- Serious adverse events were more common in the UDCA than placebo group (63% vs 37%: $p<0.01$).

Lindor et al Hepatology 2009

Model of All Primary Endpoints

Adjusted for Mayo Risk Score, Presence of Varices, and Stage



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

Conclusion

- Long-term high-dose UDCA therapy is associated with
  - improvement in serum liver tests in PSC
  - but does not improve survival
  - is associated with higher rates of serious adverse events.

- “Any dose” urso improves LFT’s but little else
  - No effect on symptoms, histology or survival