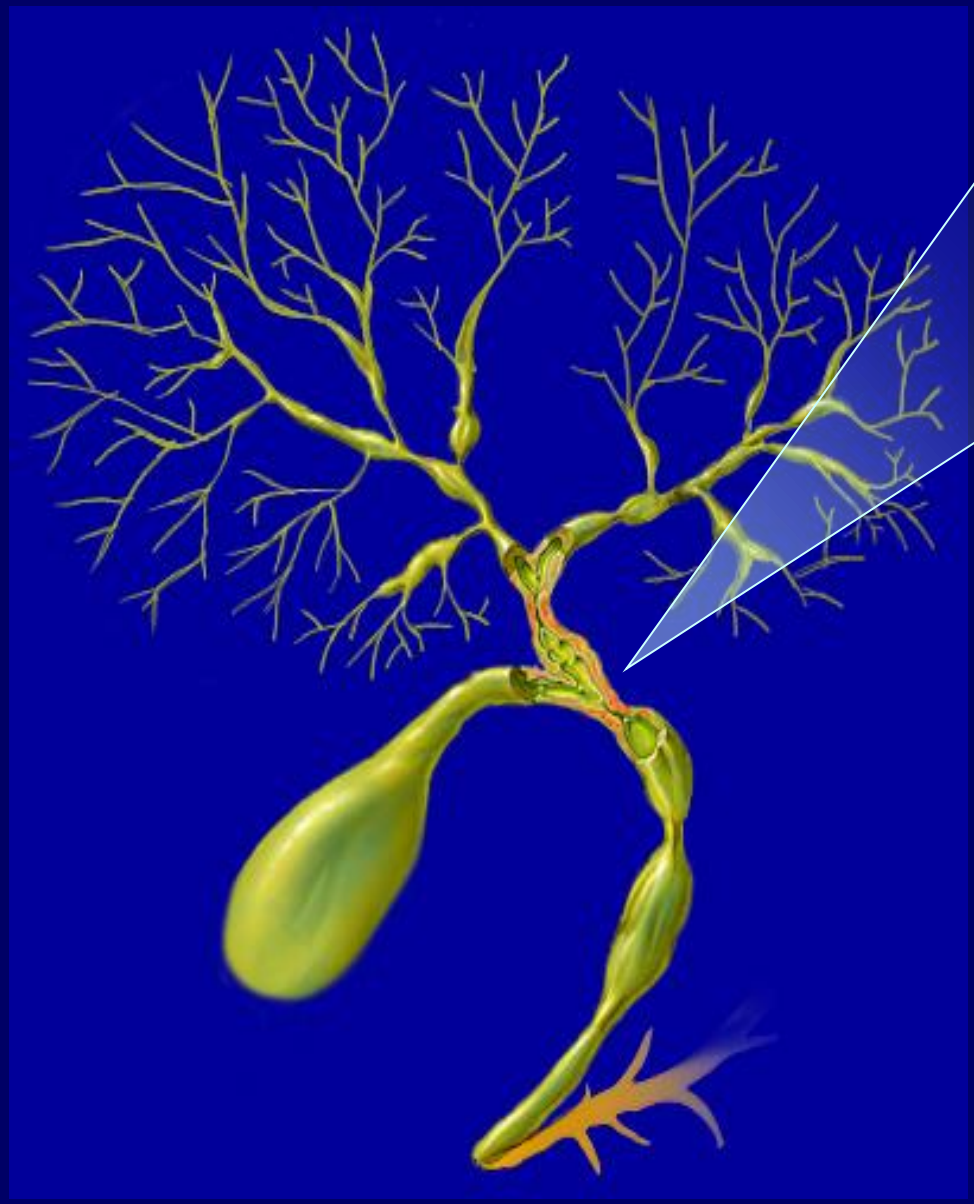
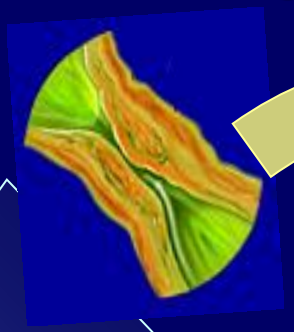
# Current Perspectives in the Treatment of PSC

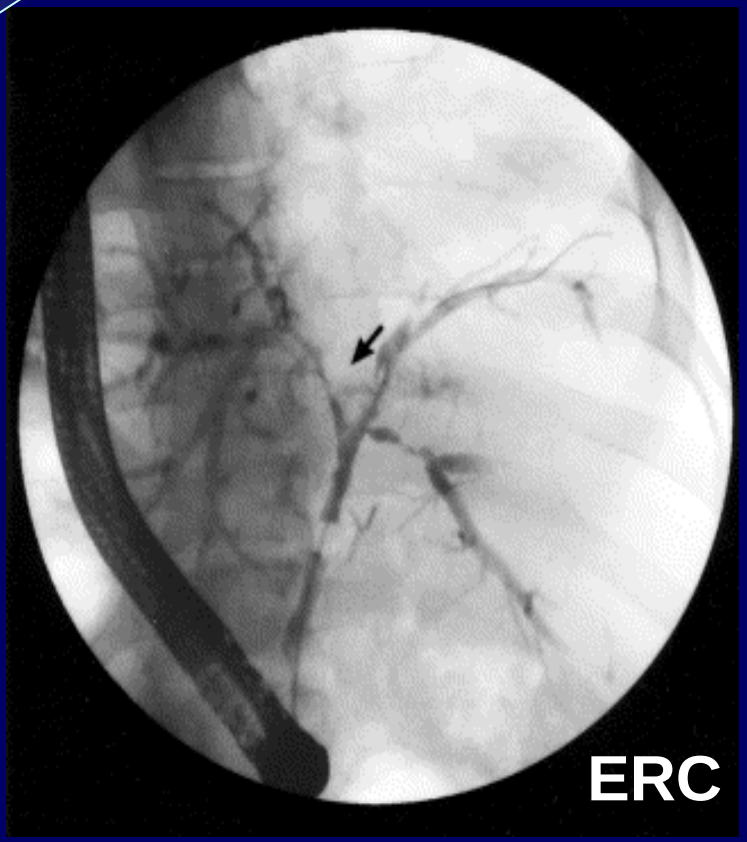
# Defining Targets for Treatment

# Pathology of Primary Sclerosing Cholangitis

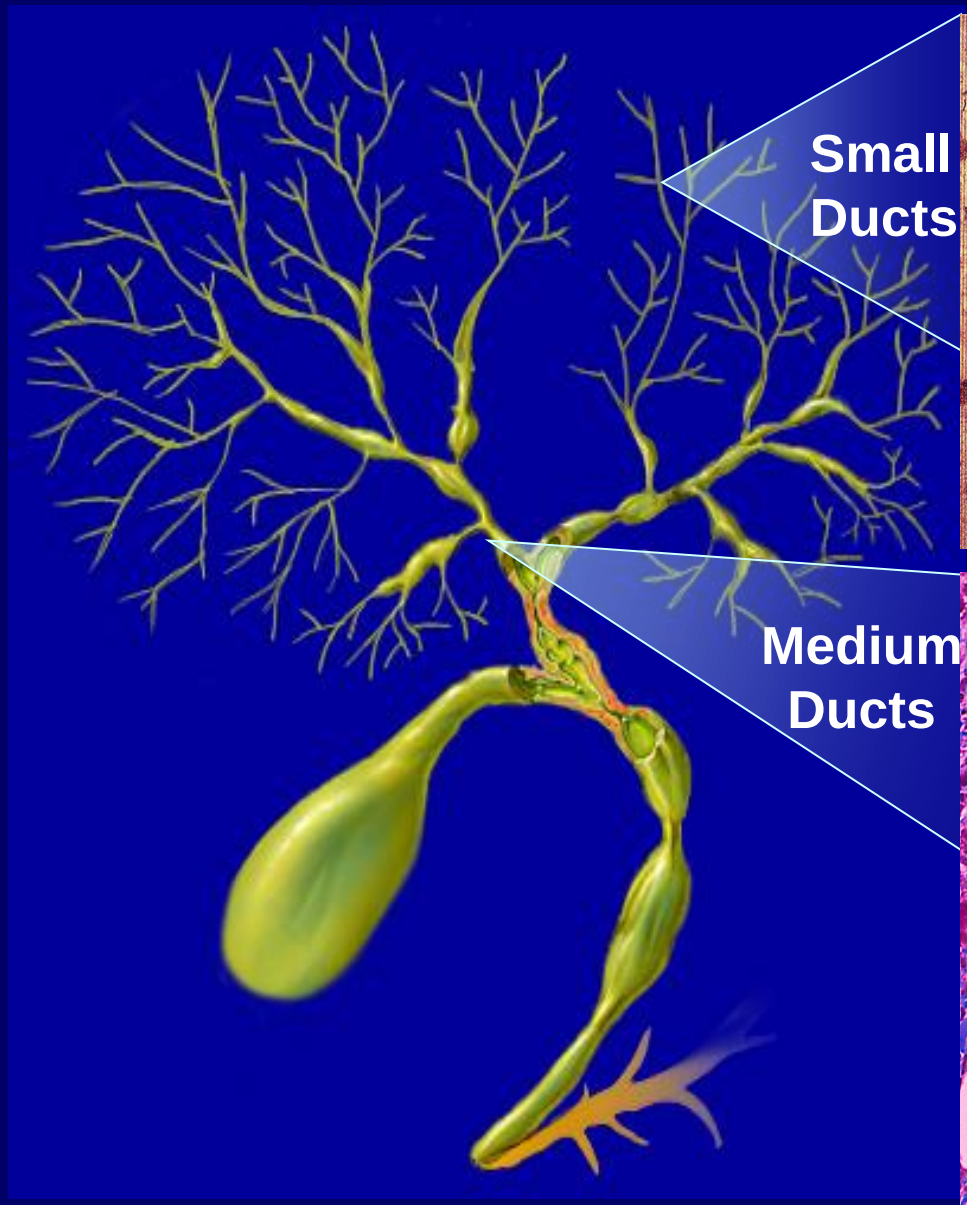
## Fibrous Obliterative Cholangitis of Medium to Large Caliber Ducts



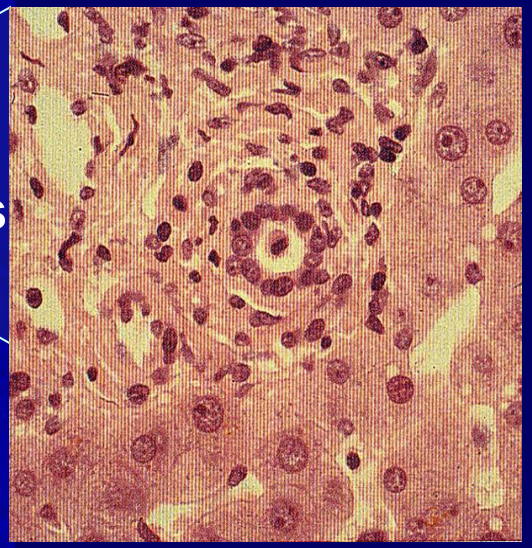




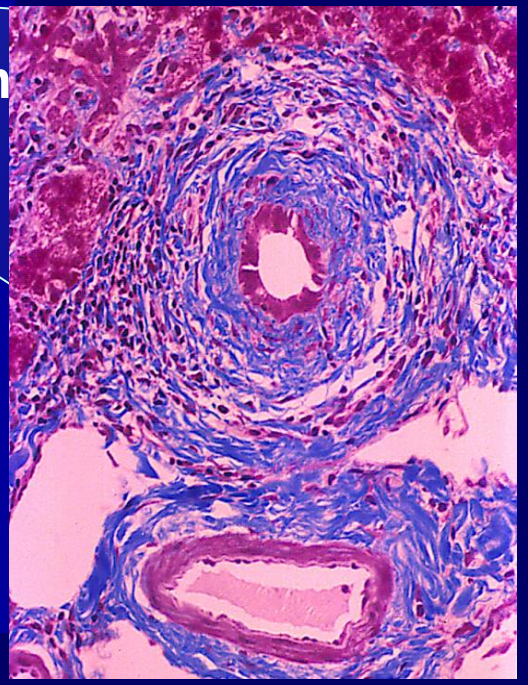
# Pathology Primary Sclerosing Cholangitis



Small Ducts

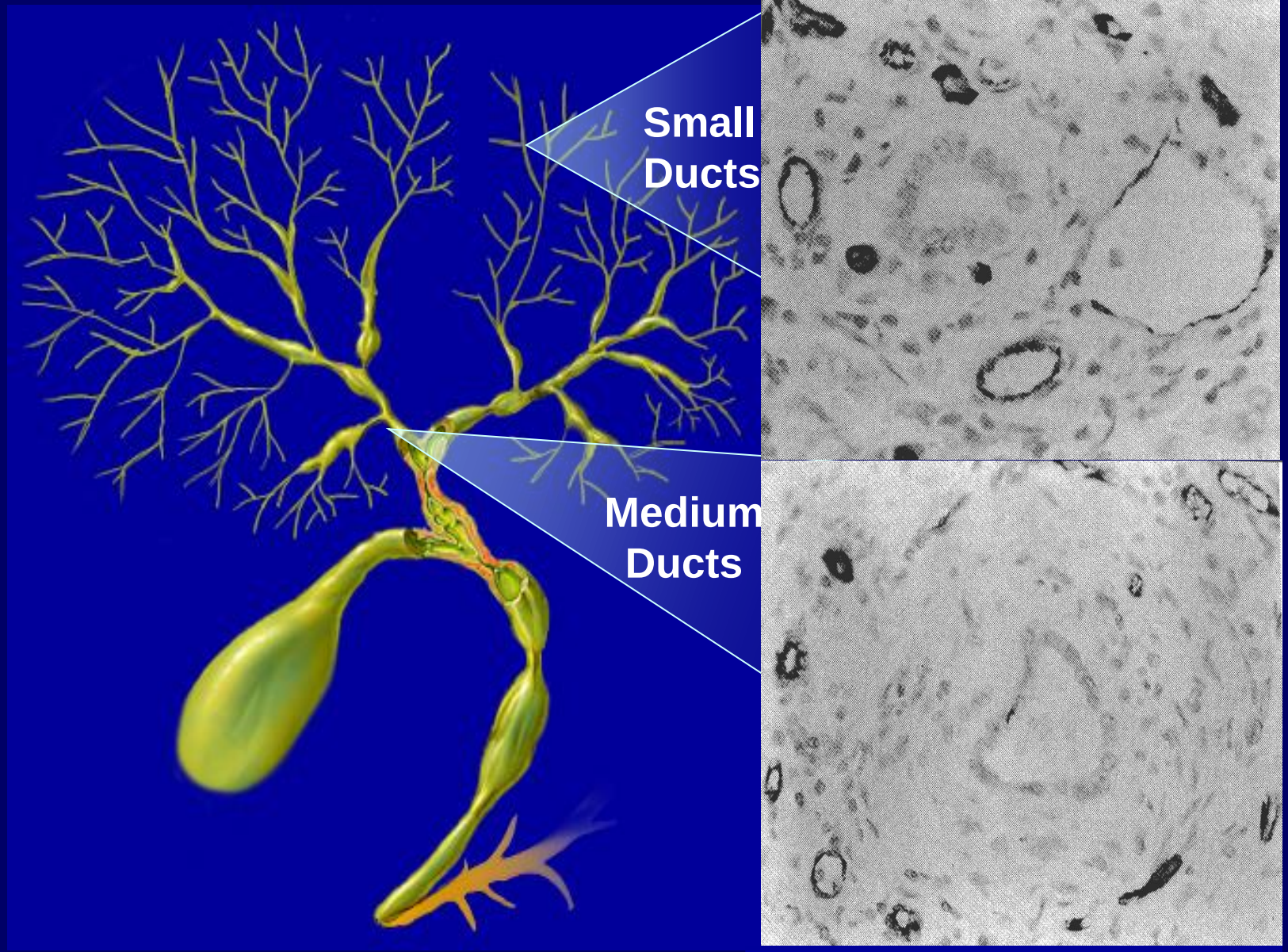


Medium Ducts



# Pathology of Primary Sclerosing Cholangitis

## Displacement of Peribiliary Capillary Plexi



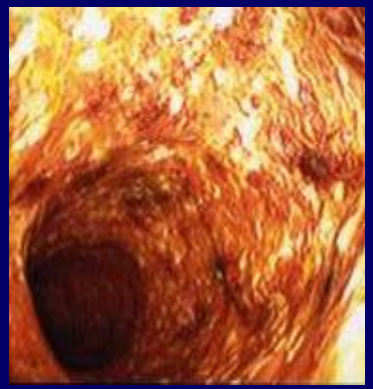

Washington K, et al: Hum Pathol 1997; 28: 791-5; Matsunaga Y, et al: Pathol International 1999; 49: 869-73

# Pathogenesis of Primary Sclerosing Cholangitis

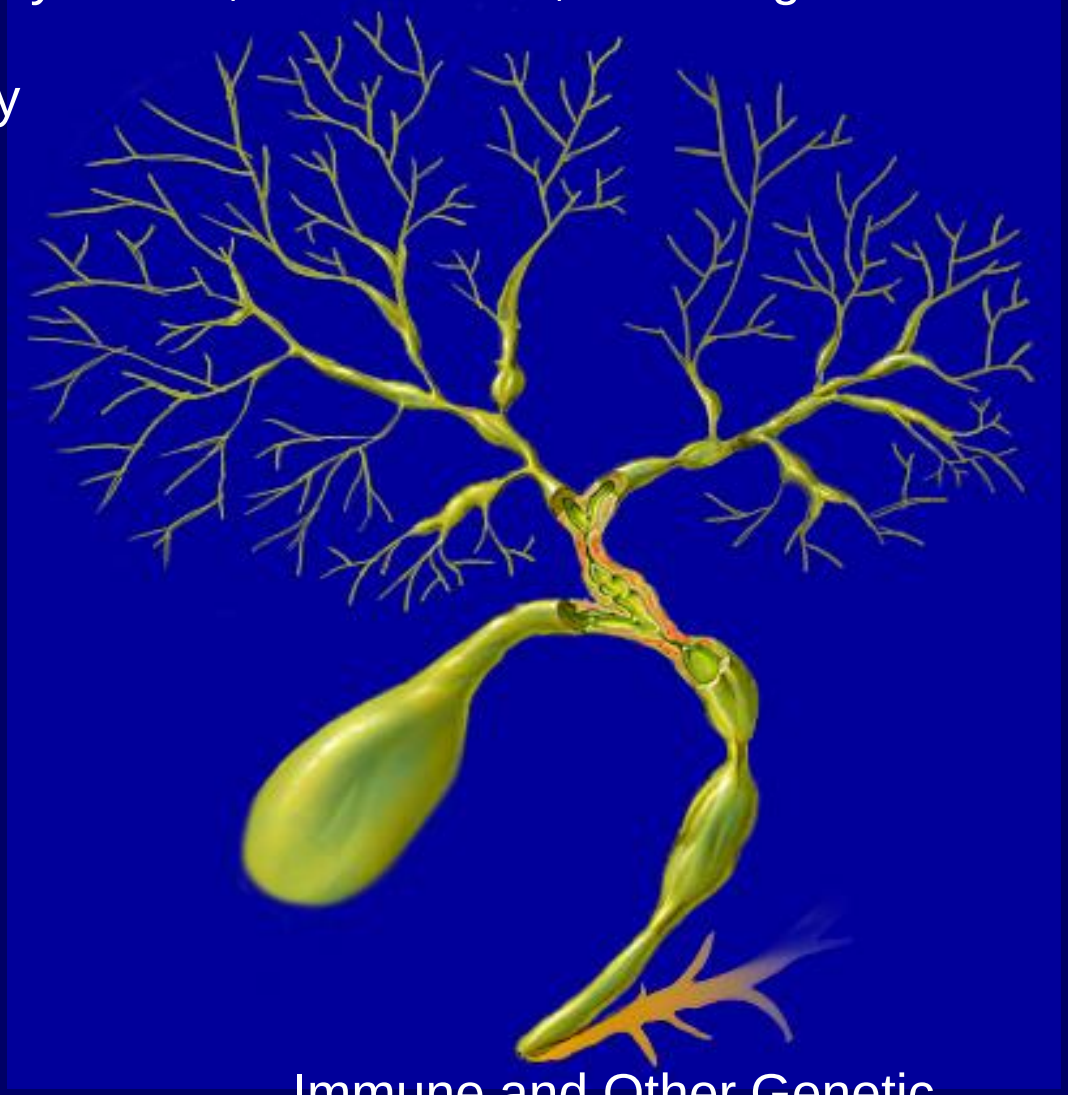
Cytokines, Chemokines, Fibrosing Inflammation

Adaptive Immunity
+
Innate Immunity

Bacterial Molecules Into Portal Vein



Ulcerative or Crohn's Colitis



Immune and Other Genetic Susceptibilities

Bile Regurgitation

Abnormal Cholangiocyte Functions

Displacement Of Arterial Vessels

Atrophy of Cholangiocytes

# Types of PSC

**How many clinical types of PSC are now included in its diagnostic classification?**

1. 1
2. 2
3. 3
4. 4
5. 5
6. 6

**How many clinical types of PSC are now included in its diagnostic classification?**

1. 1
2. 2
3. 3
4. 4
5. 5
6. 6

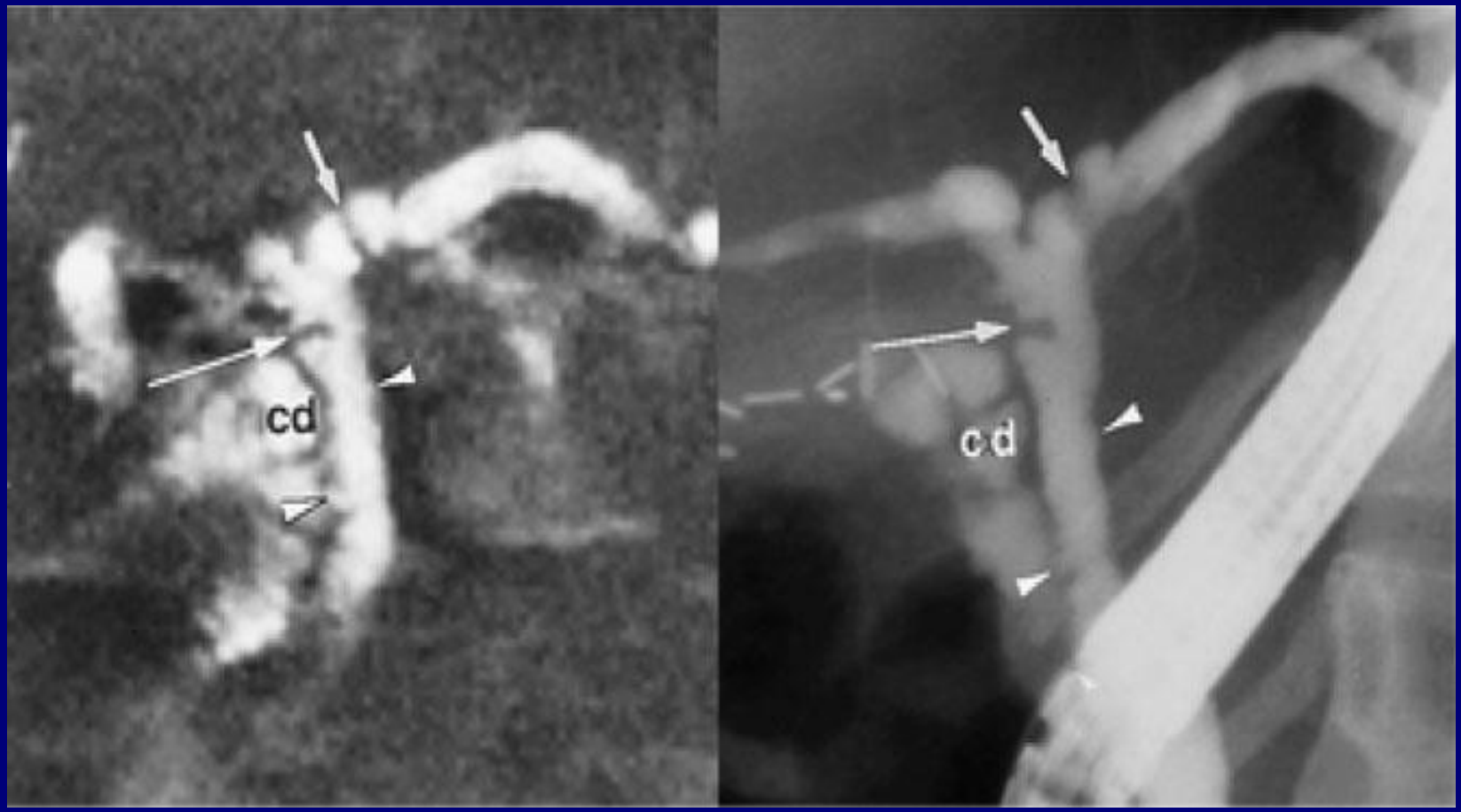
# Clinical Categories of PSC

1. Typical PSC
2. Small duct PSC
3. AIH – PSC
4. IAC – Immunoglobulin G4 – associated cholangitis

# The Cholangiography (ERCP) of PSC

1. Typical PSC:  Intra- and extra-hepatic strictures
2. Small duct PSC:  Normal
3. AIH – PSC:  same as typical PSC
4. IAC – Immunoglobulin G4 – associated cholangitis: same as typical PSC, pancreatic involvement

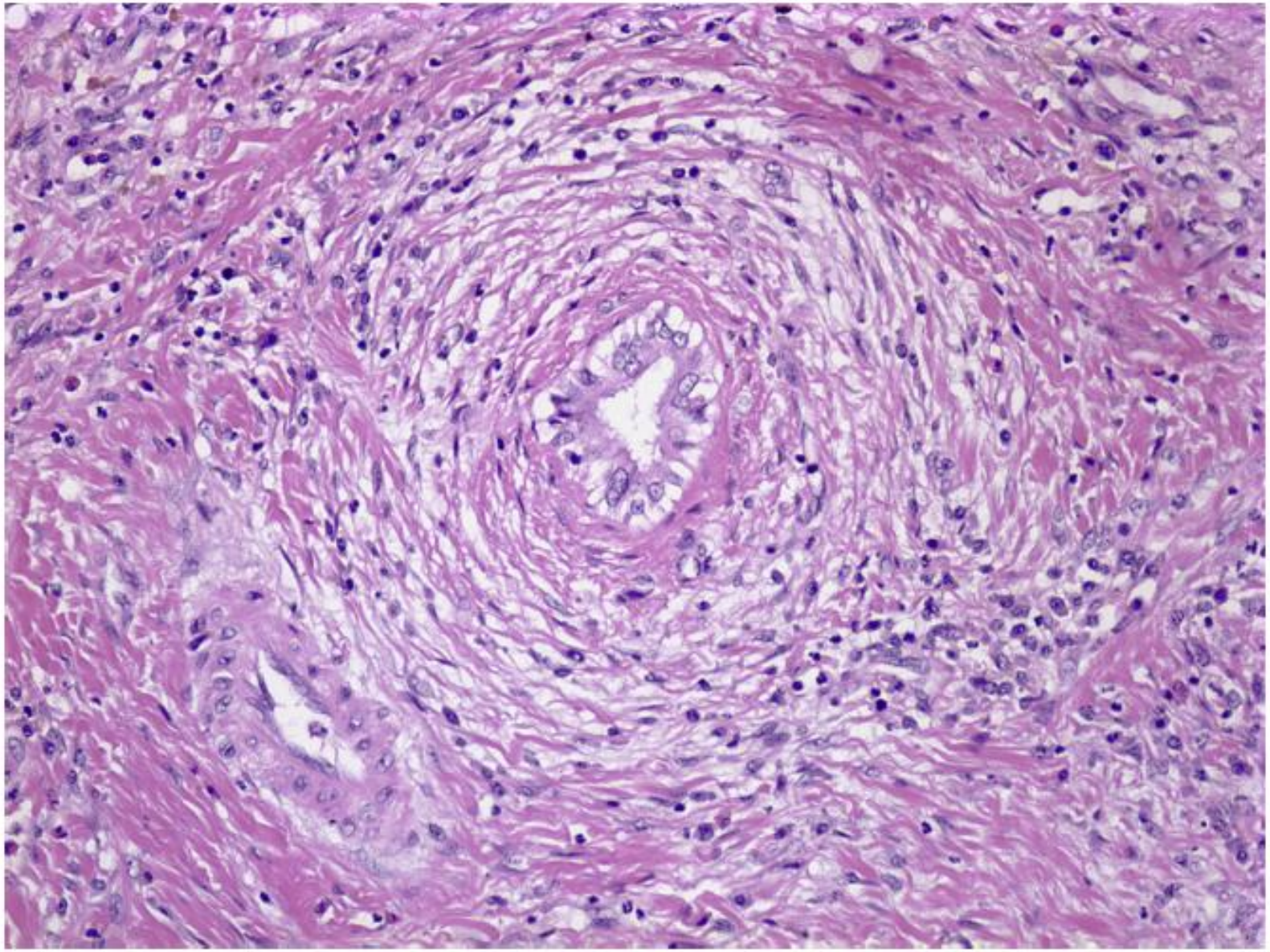
# MRCP vs ERCP

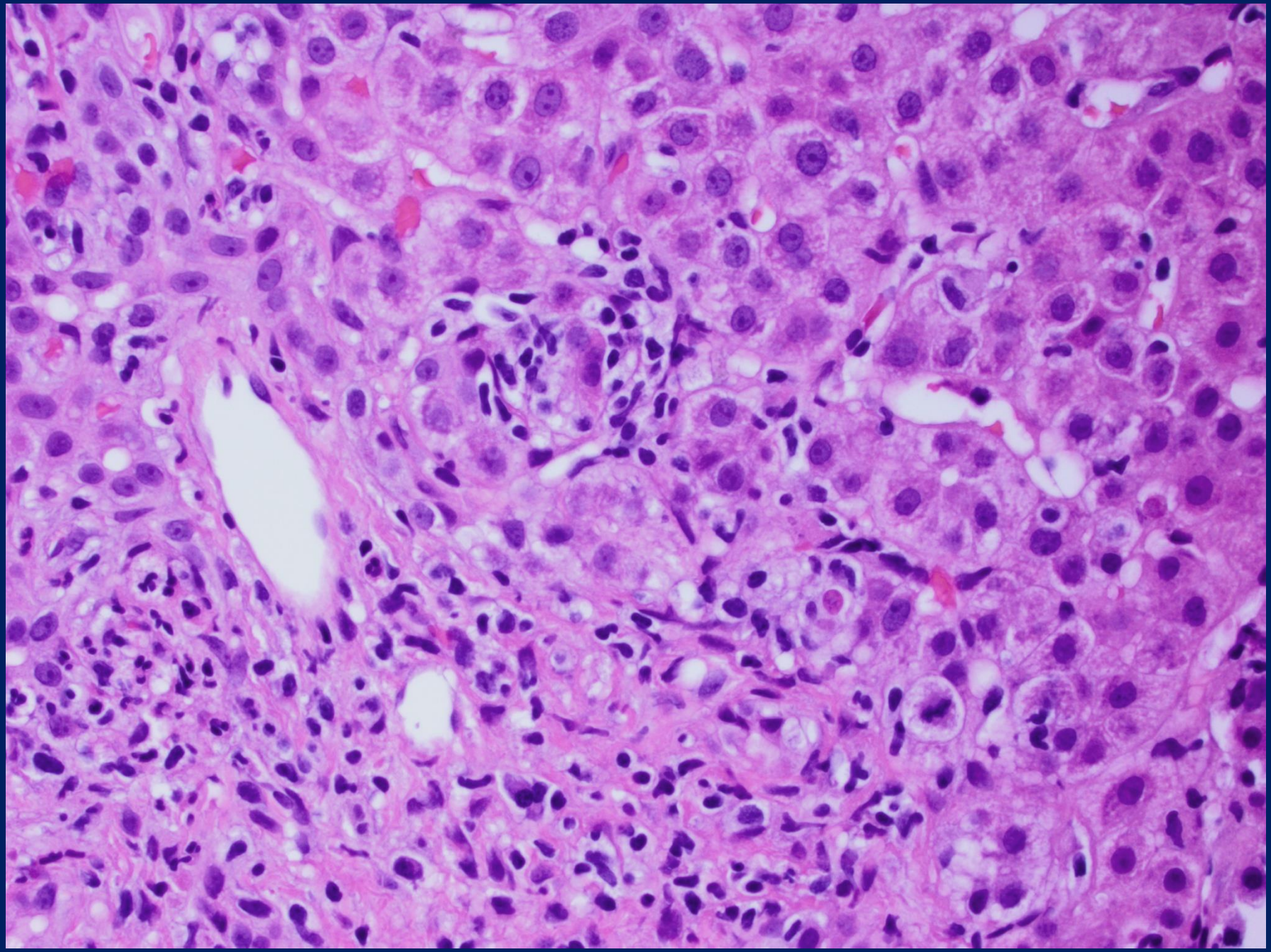



LaRusso NF, et al. NIH Workshop. Hepatology 2006;44:746-764.

# The Pathology of PSC

1. Typical PSC:  Concentric ductal fibrosis
2. Small duct PSC:  Same as typical PSC
3. AIH – PSC:  lymphoplasmacytic infiltration, interface hepatitis
4. IAC – Immunoglobulin G4 – associated cholangitis: lymphoplasmacytic infiltration with >10 IgG4-positive cells per hpf





# The Diagnosis of PSC

1. Typical PSC:  MRCP
2. Small duct PSC:  Liver Biopsy
3. AIH – PSC:  Liver Biopsy
4. IAC – Immunoglobulin G4 – associated cholangitis:  MRCP;  Liver Biopsy

# The Medical Treatment of PSC

# What medical therapies have been shown to prevent progression of typical PSC?

1. Low dose UDCA
2. High dose UDCA
3. Corticosteroids
4. Azathioprine
5. Cyclosporine, Tacrolimus
6. Methotrexate
7. Anti-TNF-α drugs

# No obvious or Consistent Clinical Benefit.

**Karlsen TH, et al. Aliment Pharmacol Ther 2014;39:282-301.**

**Table 4 |** Overview of clinical studies of non-ursodeoxycholic acid treatment in primary sclerosing cholangitis. References for studies refer to the online supplementary reference list (Data S1 for tables 1–5)

| Study | Year | Treatment | *N* (treat/ placebo) | Study duration | Lab | Histology | OLT-free survival | Outcome |
|---|---|---|---|---|---|---|---|---|
| La Russo *et al.*[75] | 1988 | Penicillamine | 70 (39/31) | 3 years | – | – | – | No effect on liver tests, histology or survival |
| Knox *et al.*[76] | 1994 | Methotrexate | 24 (12/12) | 2 years | + (ALP only) | – | – | Improved ALP. No effect on histology, cholangiography or outcome |
| Olsson *et al.*[77] | 1995 | Colchicine | 84 (44/40) | 3 years | – | – | – | No effect on liver tests, histology or survival |
| Sterling *et al.*[78] | 2004 | Mycophenolate mofetil/UDCA vs. UDCA | 25 (12/13) | 2 years | – | – | – | No effect on liver tests, histology, cholangiography or Mayo Risk Score |
| Farkkila *et al.*[79] | 2004 | Metronidazole/ UDCA | 80 (39/41) | 36 months | + | (+) | | Improved liver tests and Mayo Risk Score, but no improvement in histology or cholangiography |
| Hommes *et al.*[80] | 2008 | Infliximab | 10 (6/4) | 12 months | – | – | ND | Patient enrolment was prematurely stopped when interim analysis showed no treatment benefit. No effect on liver tests, histology |

# Current Treatment for PSC: ?UDCA?

## By Clinical Category of PSC

1. Typical PSC: ?UDCA?; Stricture management; CCA screening

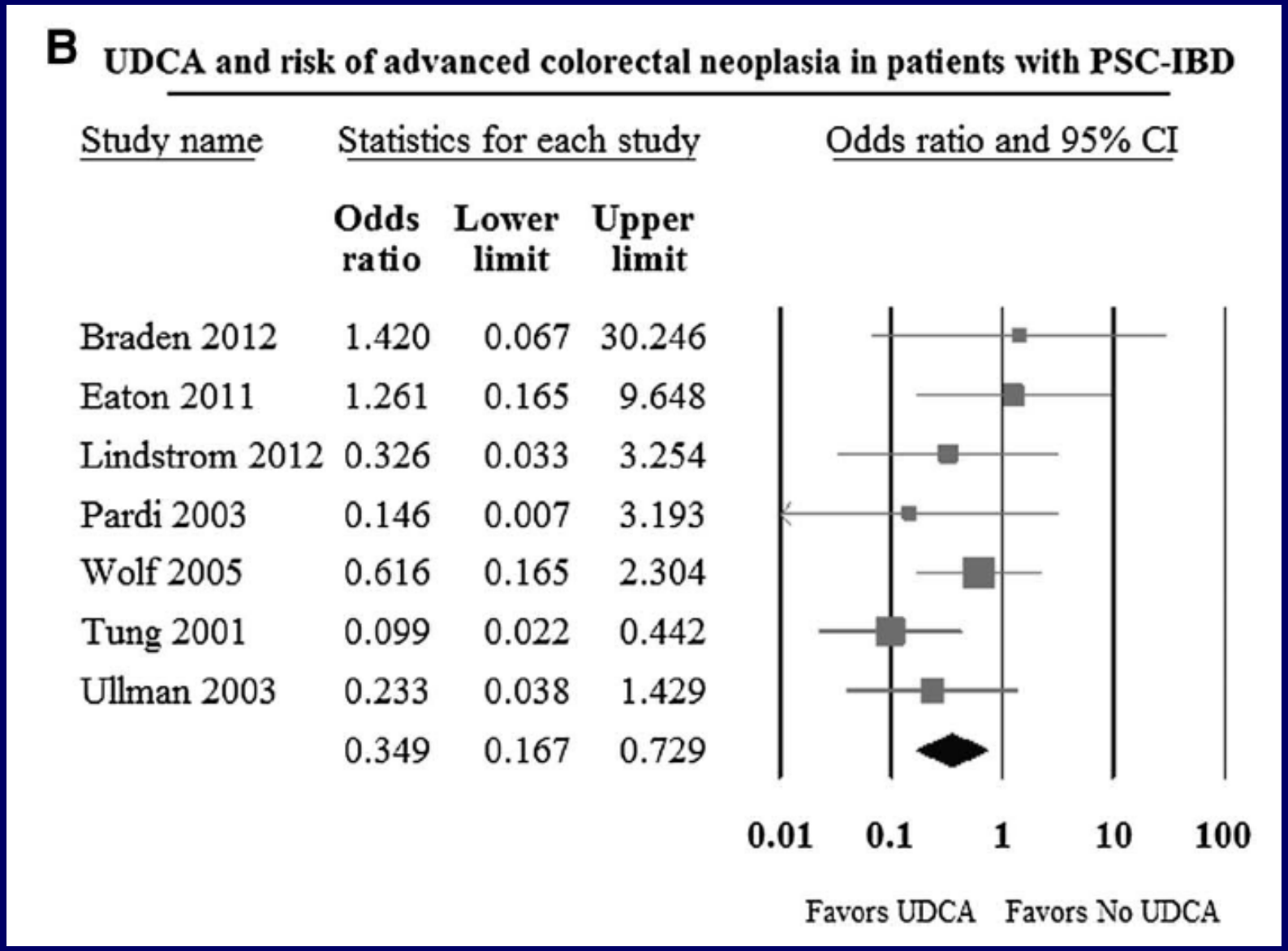
2. Small duct PSC: ?UDCA?; Rarely need Stricture management; CCA screening

3. AIH – PSC: ?UDCA?; Stricture management; Corticosteroids/Azathioprine for AIH component

4. IAC – Immunoglobulin G4 – associated cholangitis: ?UDCA?; Stricture management; Corticosteroids/Azathioprine

# Ursodeoxycholate
# Standard Doses (15 mg/kg/d)

# UDCA may reduce risk for Colon Cancer in PSC



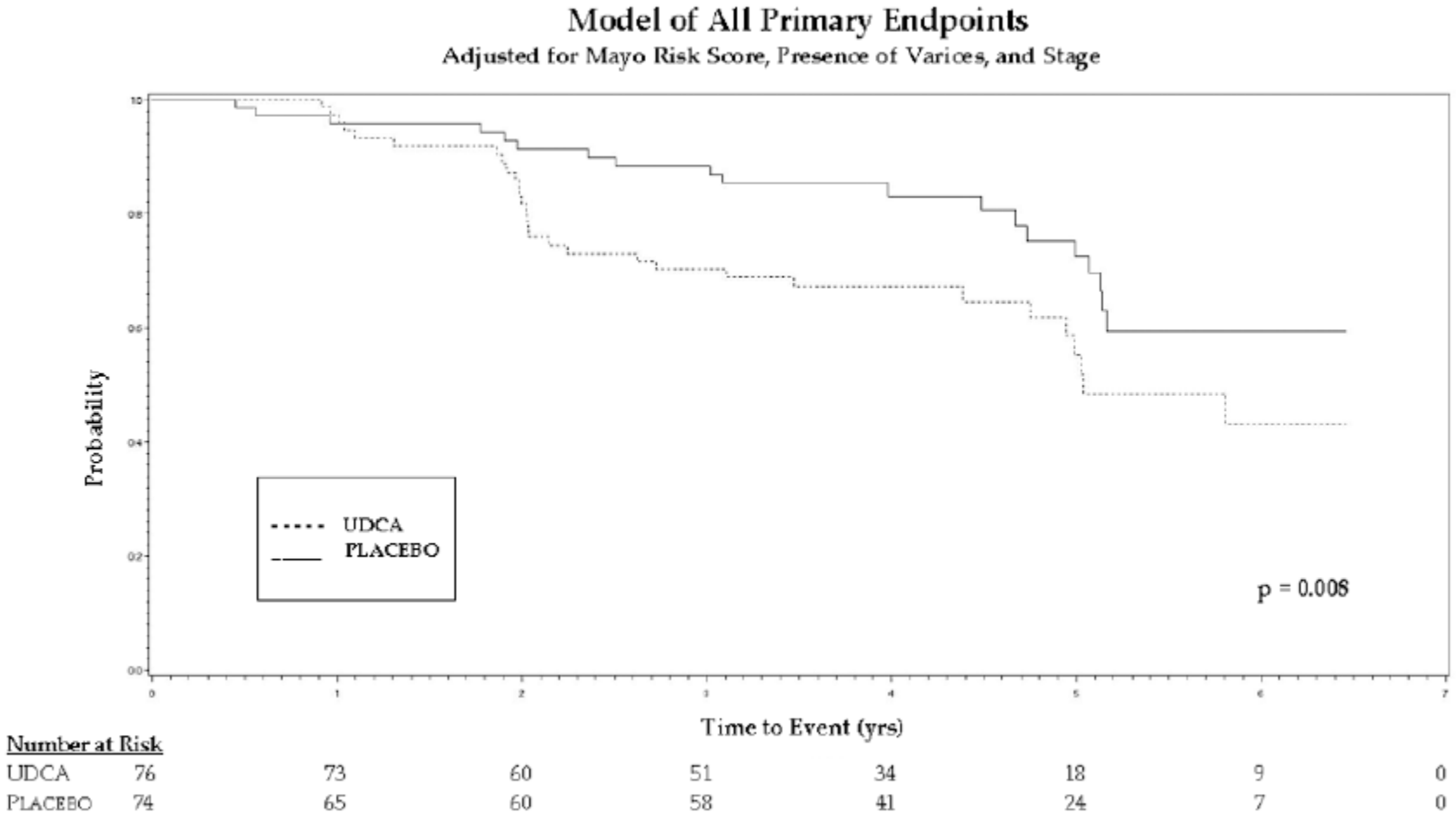

Singh S, et al. Inflamm Bowel Dis 2013;19:1631-1638.

**Table 3 |** Overview of clinical studies of treatment with ursodeoxycholic acid in primary sclerosing cholangitis (PSC). References for studies refer to the online supplementary reference list (Data S1 for tables 1–5)

| Study | Year | Dose (mg/kg bw/day) | *N* (treat/control) | Study duration | Lab | Histology | CCA | OLT-free survival | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| O'Brien *et al.*[49] | 1991 | 10 | 12* | 2.5 years | + | ND | ND | ND | Improvement of liver tests in treatment periods and worsening in nontreatment periods |
| Beuers *et al.*[50] | 1992 | 13–15 | 14 (6/8) | 1 year | + | + | ND | ND | Significant improvement in liver biochemistry |
| Stiehl *et al.*[51] | 1994 | 750/day† | 20 (10/10) | 3 months | + | ND | ND | ND | Significant improvement in liver tests |
| De Maria *et al.*[52*] | 1996 | 300 b.d.† | 40 (20/20) | 2 years | | | | | No effect on liver tests or cholangiography |
| Lindor *et al.*[53] | 1997 | 13–15 | 102 (51/51) | 2.2 years | + | – | ND | – | No significant effect on primary end-points (death, OLT, histology, lab) |
| Mitchell *et al.*[54] | 2001 | 20 | 26 (13/13) | 2 years | + | + | ND | ND | UDCA group had improved liver test results, histology and cholangiography |
| Harnois *et al.*[55] | 2001 | 25–30 | 30‡ | 1 year | + | | ND | ND | Improved Mayo Risk Score for UDCA vs. placebo and for high-dose vs. low-dose UDCA<br>Improved liver test results |
| Olsson *et al.*[56] | 2005 | 17–23 | 198 (97/101) | 5 years | (+) | ND | – | – | No effect on death, OLT, CCA or liver tests |
| Lindor *et al.*[57] | 2009 | 28–30 | 149 (76/73) | 6 years | + | | ND | – | Terminated at 6 years as worse outcome in treatment group for death or OLT<br>Improved liver tests in UDCA group |

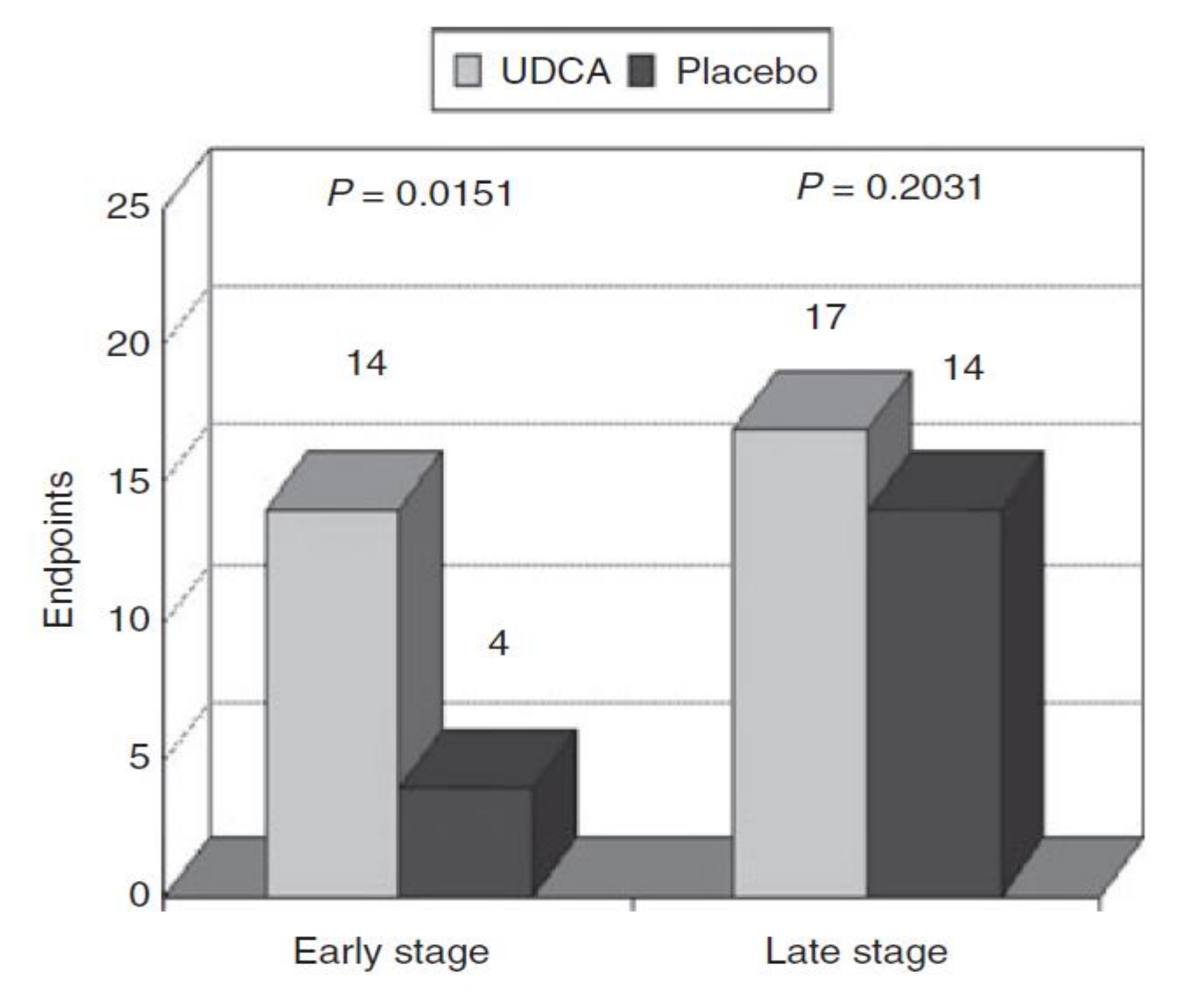
# Ursodeoxycholate
# High Doses (28 to 30 mg/kg/d)

# Endpoints: Death, Liver Transplantation, Meeting Minimal Listing Criteria, Varices, CCA, Progress to Cirrhosis



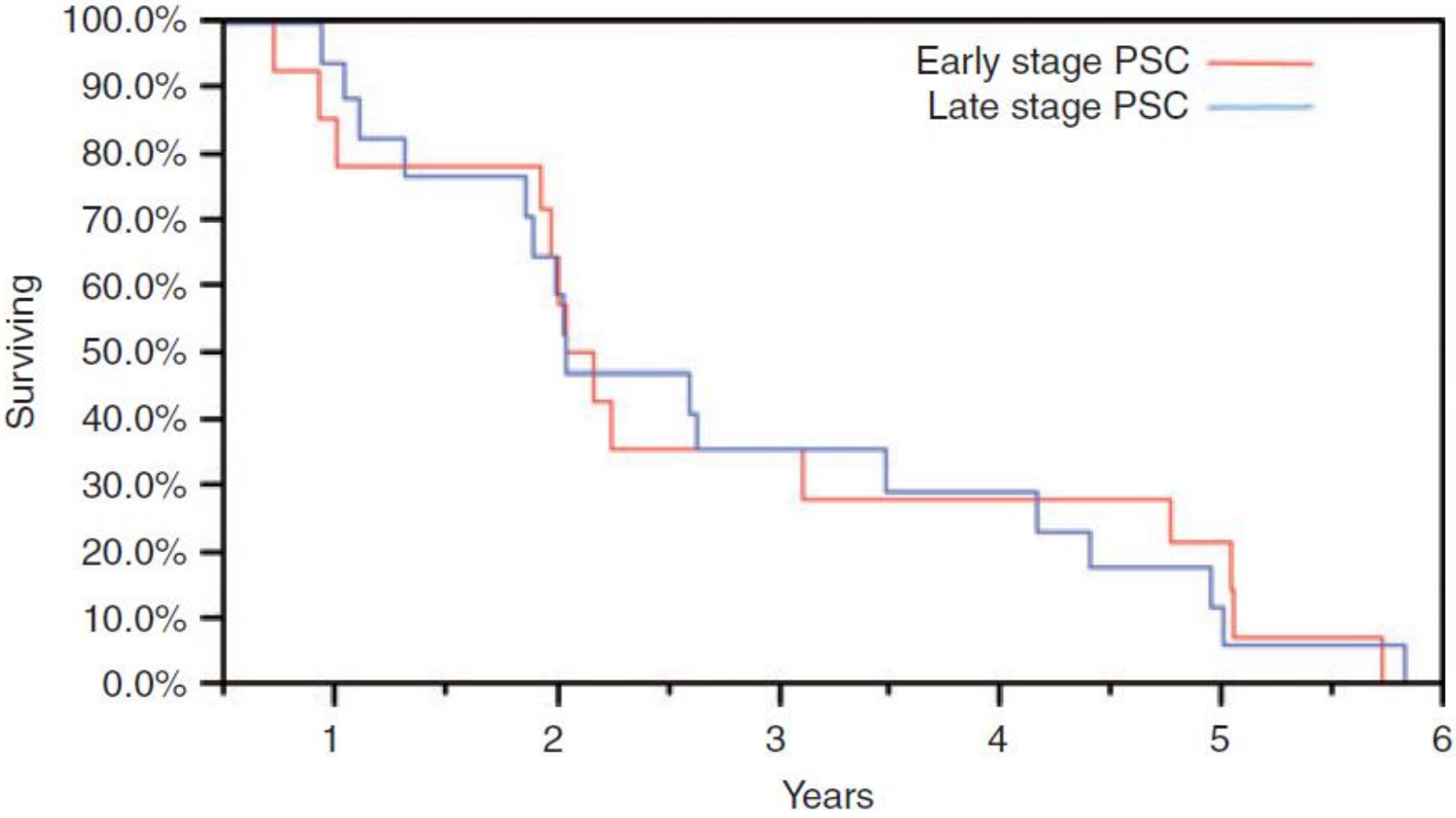

Lindor KD, et al. Hepatology 2009;50:808-814

# High Dose UDCA Increases Risk for Complications?



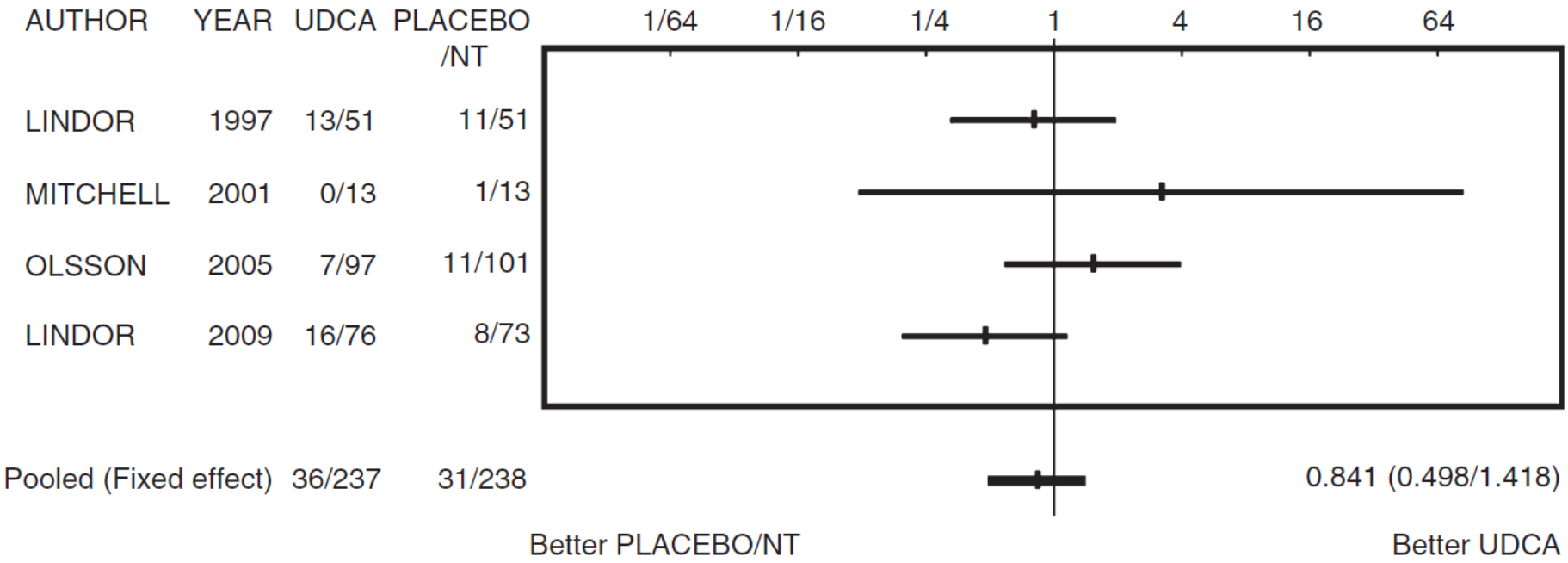

Imam MH, et al. Aliment Pharmacol Ther 2011;34:1185-1192.

# High Dose UDCA Increases Mortality in Early PSC?




Imam MH, et al. Aliment Pharmacol Ther 2011;34:1185-1192.

# Risk for Death or Liver Transplantation




Triantos CK, et al. Aliment Pharmacol Ther 2011;34:901-910

# UDCA, What's the Verdict? Friend or Foe?

1. Certainly UDCA does not benefit all patients
2. Low or normal Alkaline Phosphatase is associated with better prognosis
3. Trial of UDCA, 15 mg/kd/d, in divided doses – check Alk Phos over 3 – 6 months
4. Responders (nl Alk Phos, or >50% reduction in Alk Phos) – stay on UDCA

# Emerging Treatments

# What are the novel emerging treatments?

1. Vancomycin, microbiota therapy
2. Tumor Necrosis Factor (TNF-α) antagonists
3. Interleukin blockade
4. α-Integrin antagonists
5. FXR Agonists
6. Anti-fibrotic drugs

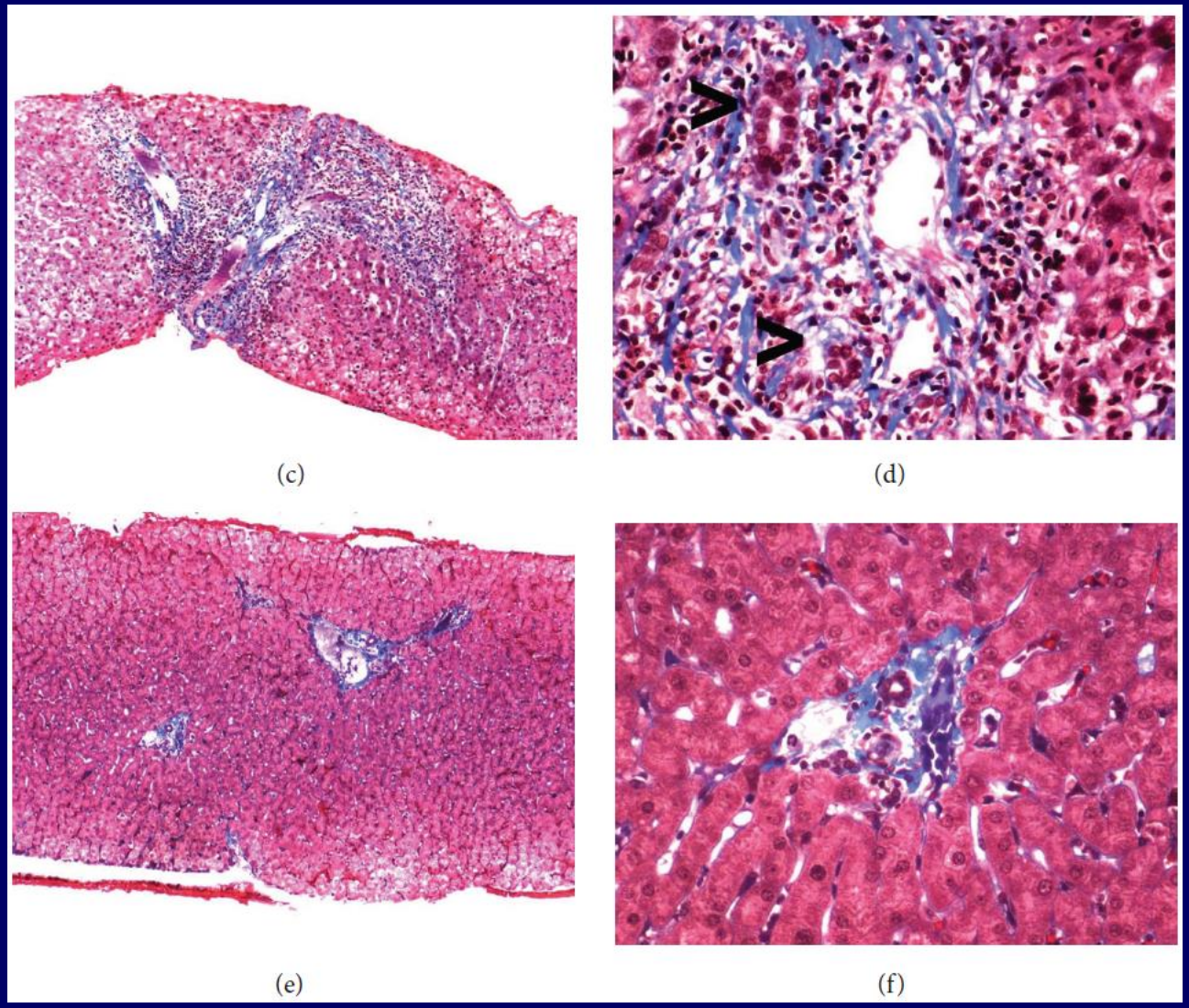
# Oral Vancomycin

# Case Report Suggesting Benefit of Vancomycin

## 15 yo with PSC recurrence after liver transplantation

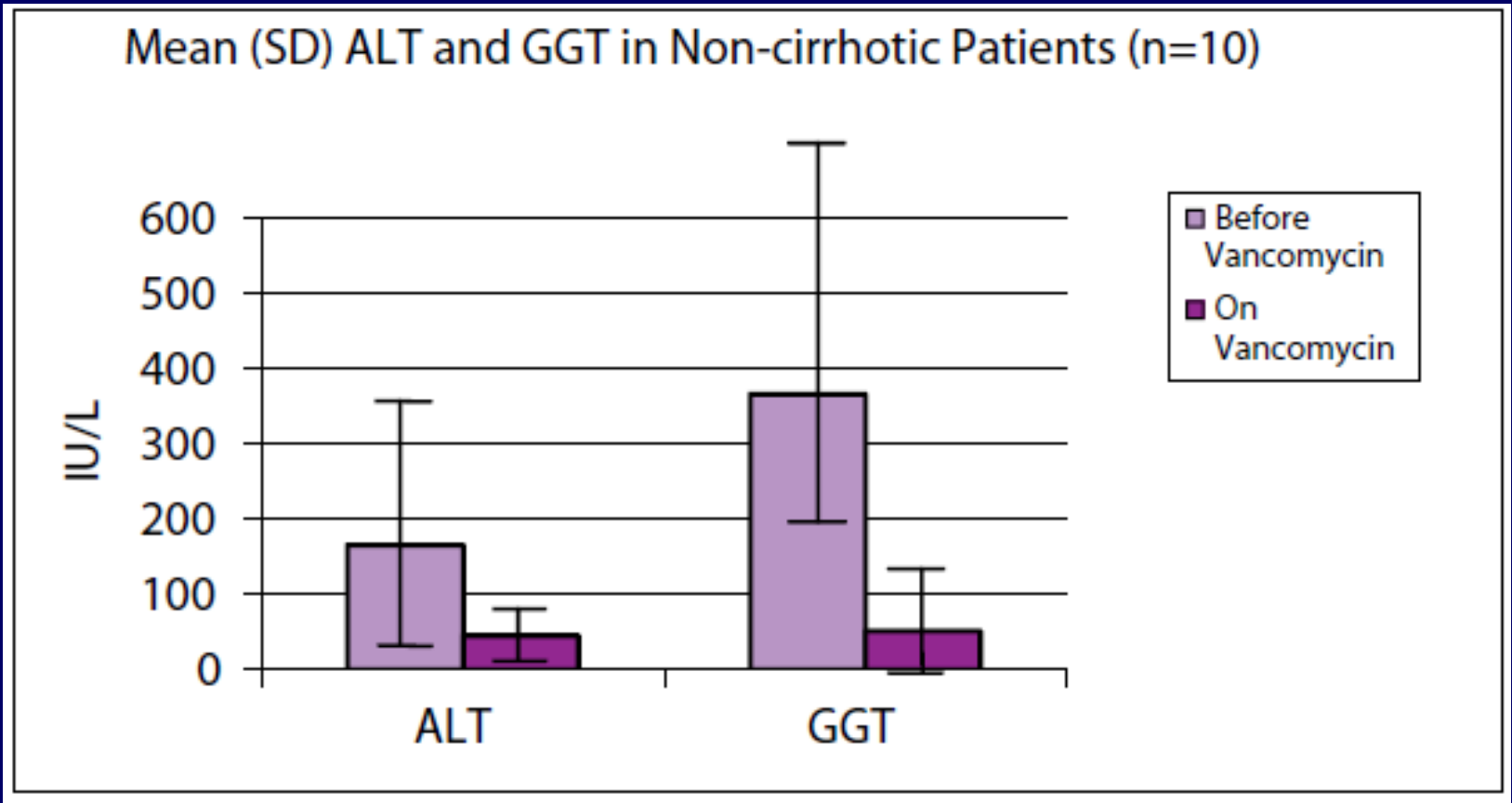
**Prior to Vancomycin**

**During Vancomycin, 500 tid po**



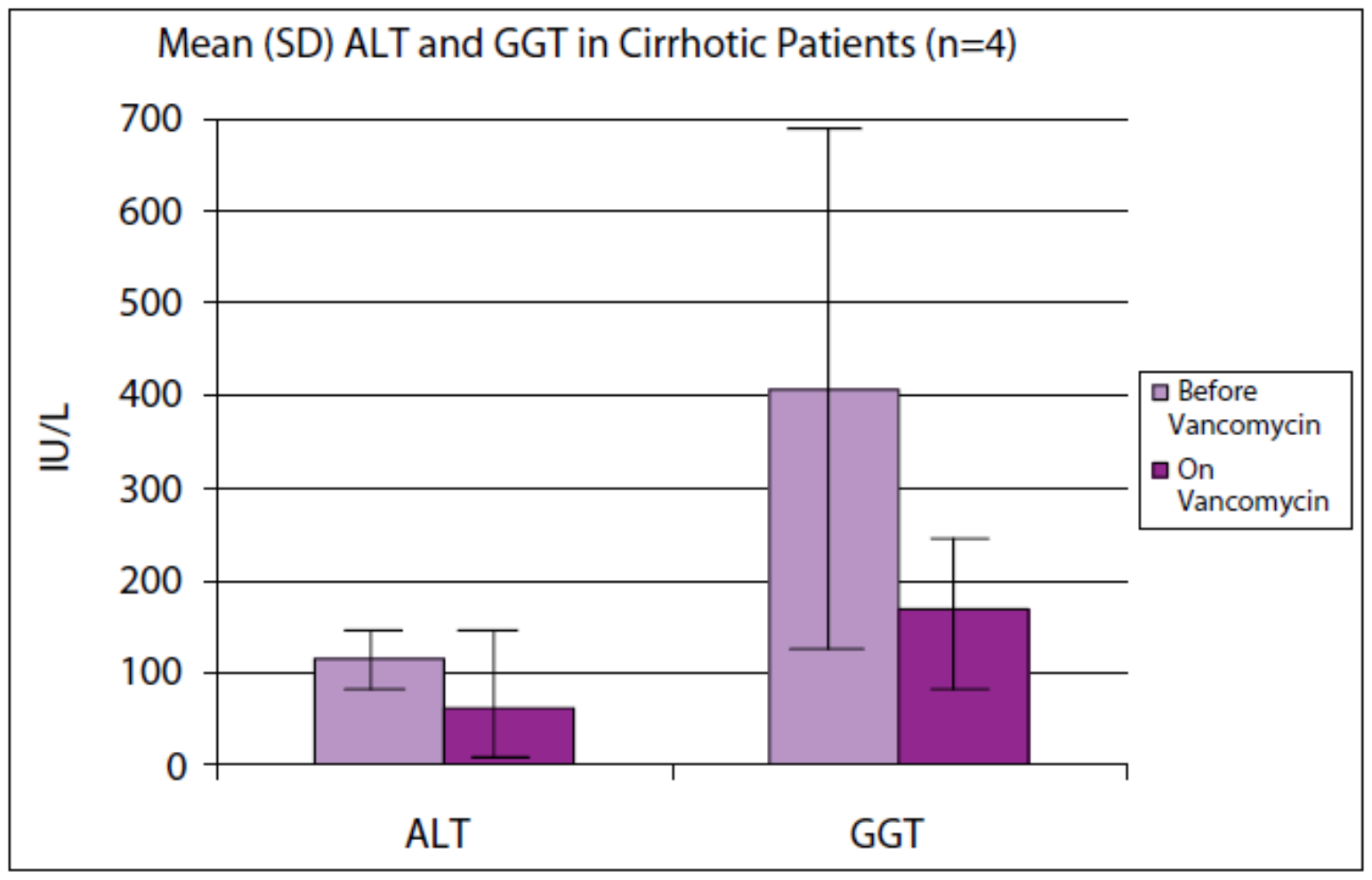

Davies YK, et al. Case Reports in Transplantation 2013. Online.

# Long-Term Vancomycin: Non-cirrhotic Patients




Davies YK, ….. Cox, K. JPGN 2008;47:61-67.

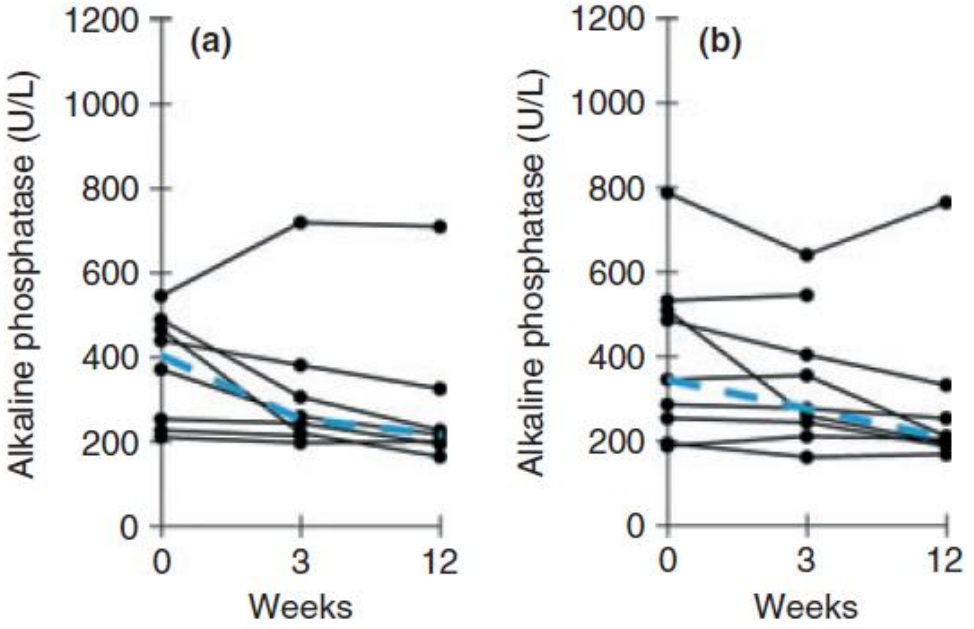
# Long-Term Vancomycin: Cirrhotic Patients




Davies YK, ….. Cox, K. JPGN 2008;47:61-67.

**Randomized Controlled Trial**

**Vancomycin: low vs high dose**
**Metronidazole: low vs high dose**




**Vancomycin Arms**
**Low dose (125 mg po q6h)**
**Vs**
**High Dose (250 mg po q6h)**

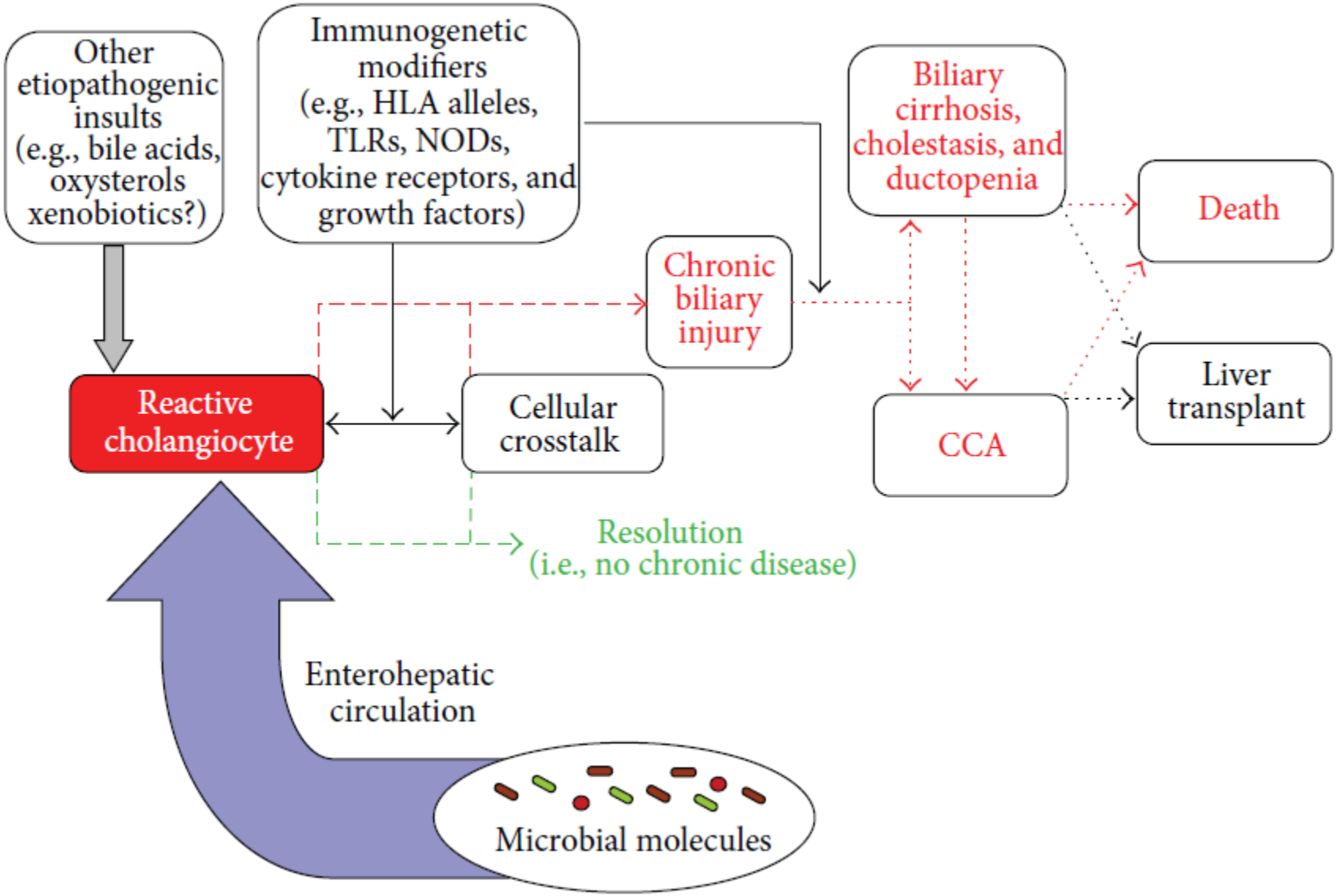
**Metronidazole Arms**
**Low dose (250 mg po tid)**
**Vs**
**High Dose (250 mg po tid)**

Tabibian JH, et al. Aliment Pharmacol Ther 2013; 37:604-612.

# Vancomycin, What's the Verdict? Friend or Foe?

1. Certainly Vancomycin does not benefit all patients
2. Unique safety consideration – emergence of vancomycin-resistent organisms
3. Not recommended for routine use – until there are more clinical trial data to support benefit and determine long-term risk

# Antibiotic Treatment to Modify the Microbiota




Tabibian JH, et al. BioMed Res International 2013. Online.

# Past Experience with Antibiotics for 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 | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | ALK | AST | ALT | GGT |
| Tetracycline[32]† | 1959 | 5 | 500 mg/day | 1–10 | −45 | −60 | −45 | – |
| Tetracycline[36]‡ | 1965 | 5 | 500 mg/day | 48 (mean) | +21 | – | – | – |
| Sulfasalazine (+UDCA)[34]§ | 1998 | 2* | – | 30 | −79 | −38 | −70 | −26 |
| | | | | 45 | −35 | −87 | −95 | −94 |
| Vancomycin[28] | 1998 | 3* | 375–1000 mg/day | 9 (mean) | – | – | −89 | −93 |
| Sulfasalazine (+UDCA)[35] | 2002 | 1 | 50 mg/kg/day | 37 | – | | −92 | −83 |
| Metronidazole (+UDCA)[38] | 2004 | 39 | 600–800 mg/day | 36 | −52.4 | −41.0 | −67.9 | – |
| Sulfasalazine[29] | 2006 | 1 | 2–4.5 g/day | 24 | −74 | – | −84 | – |
| Azithromycin (+UDCA)[33] | 2007 | 1 | 500 mg/day, 3 days/week | 5 | −72 | −31 | −33 | −54 |
| Vancomycin[27] | 2008 | 14* | 50 mg/kg/day | 54 ± 43 | – | – | −78 | −89 |
| Minocycline[39] | 2009 | 16 | 200 mg/day | 12 | −19.7 | −2.8 | – | – |

ALK, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; q.d.s., four times a day; UDCA, ursodeoxycholic acid.

Months of treatment and follow-up are absolute unless otherwise indicated.

Table adapted from Elfaki and Lindor.[37]

* Paediatric patients.

† Includes one patient who also received prednisone but was not separable from the other four patients.

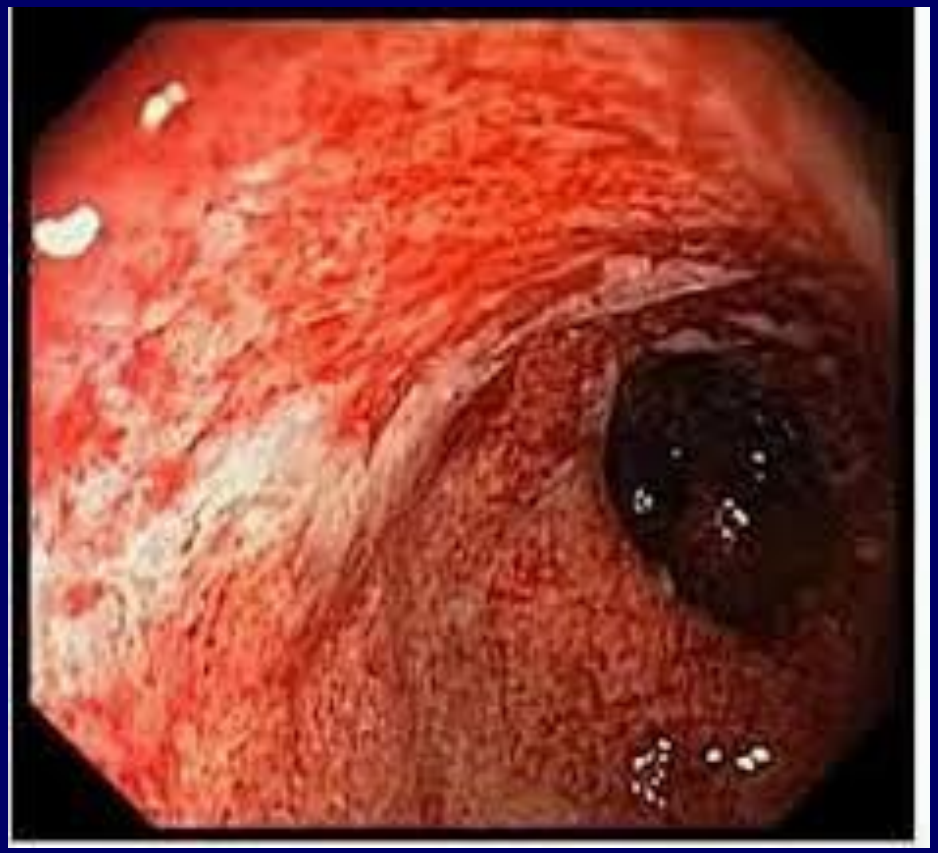
‡ Does not include two patients who received prednisone.

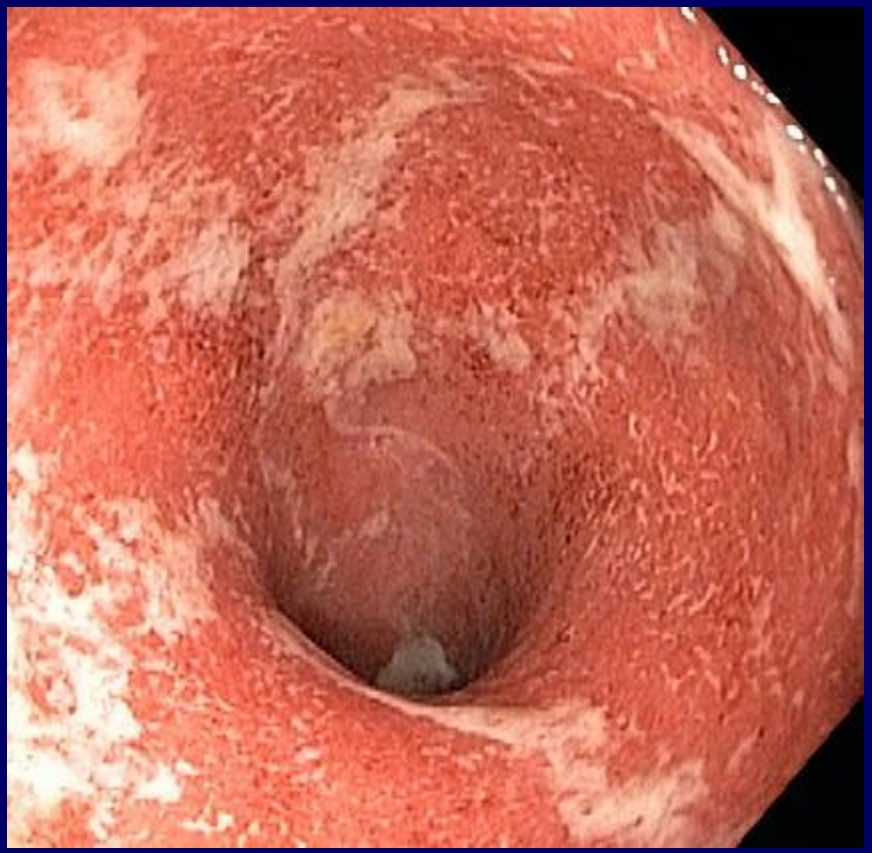
§ Does not include a third patient who also received prednisolone and mizoribine.

**Tabibian JH, et al. Aliment Pharmacol Ther 2013;37:604-612.**

# Inhibiting Inflammatory Responses

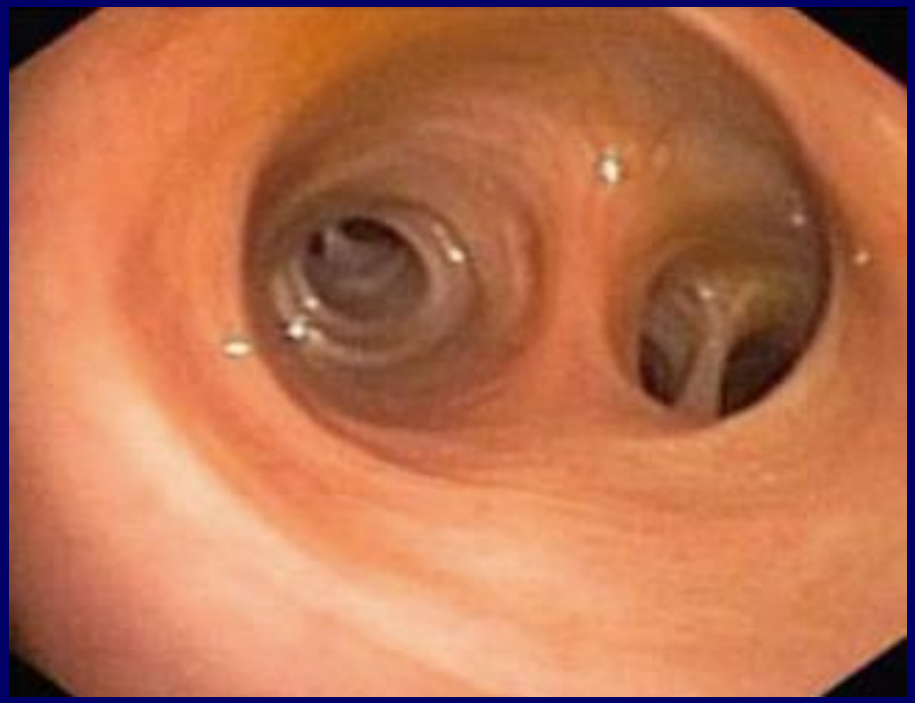
# CUC at Colonoscopy



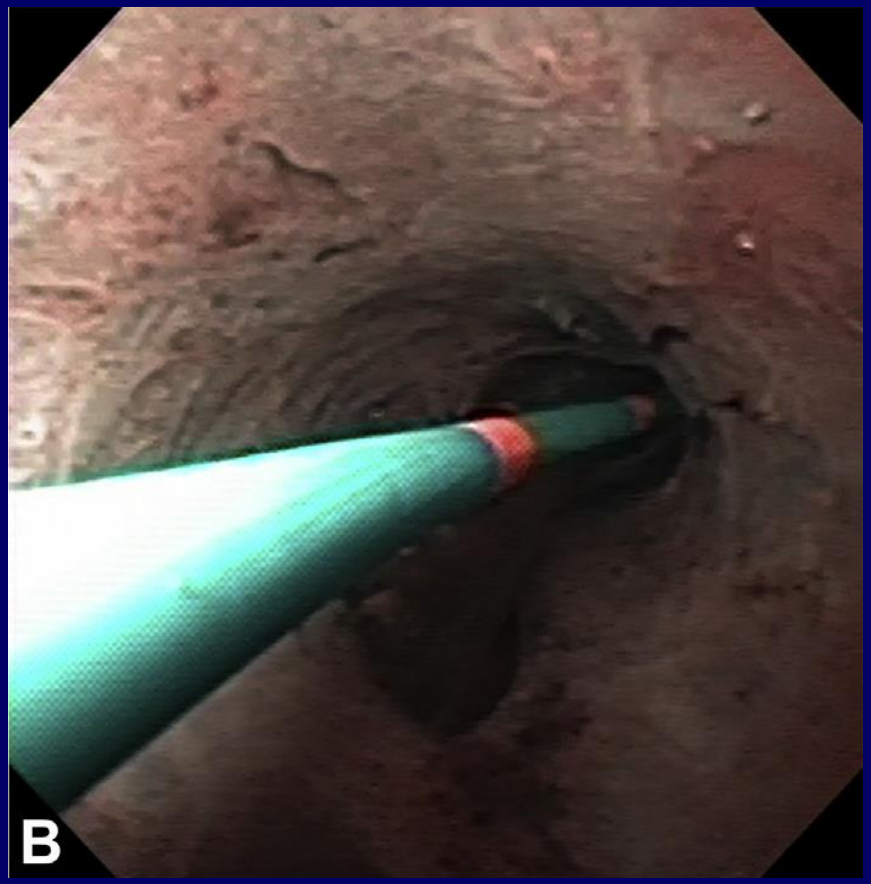


# PSC at Cholangioscopy

**Normal**

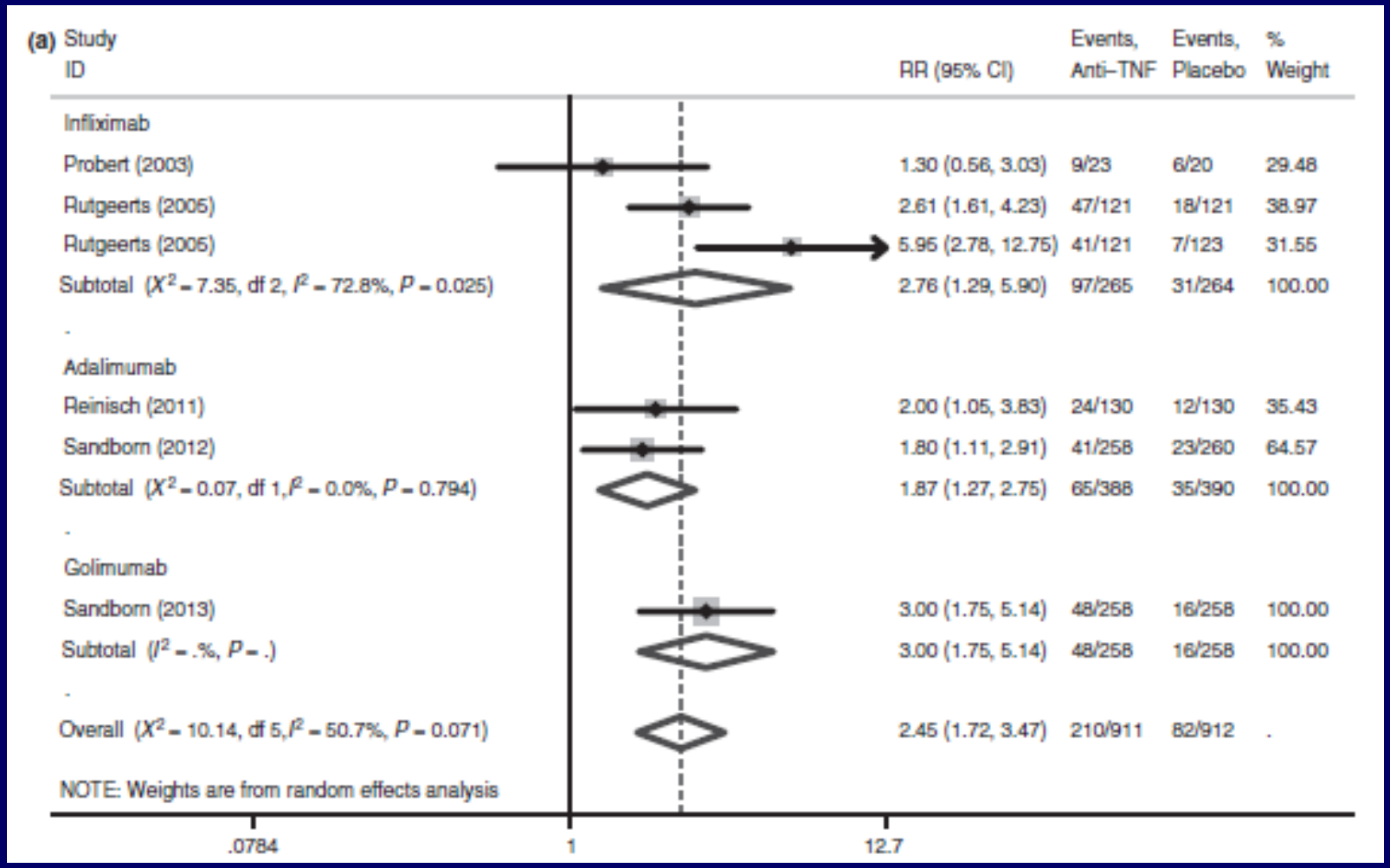


**PSC Stricture**



# TNF-α Antagonists

# Treatment of CUC

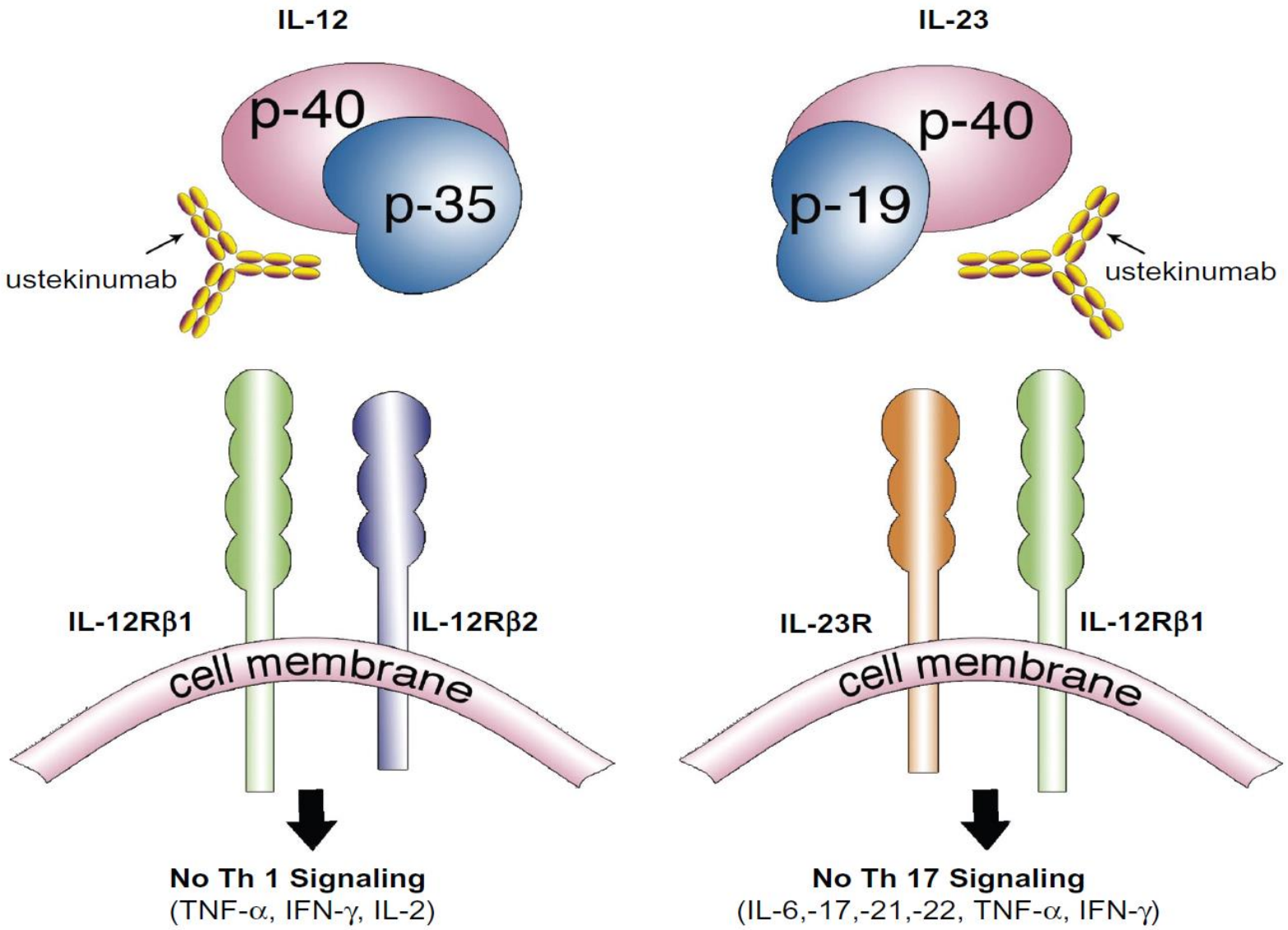



**Could this work for patients with PSC? One small study stopped early – no effect.**

Stidham RW, et al. Aliment Pharmacol Ther 2014;39:660-671.

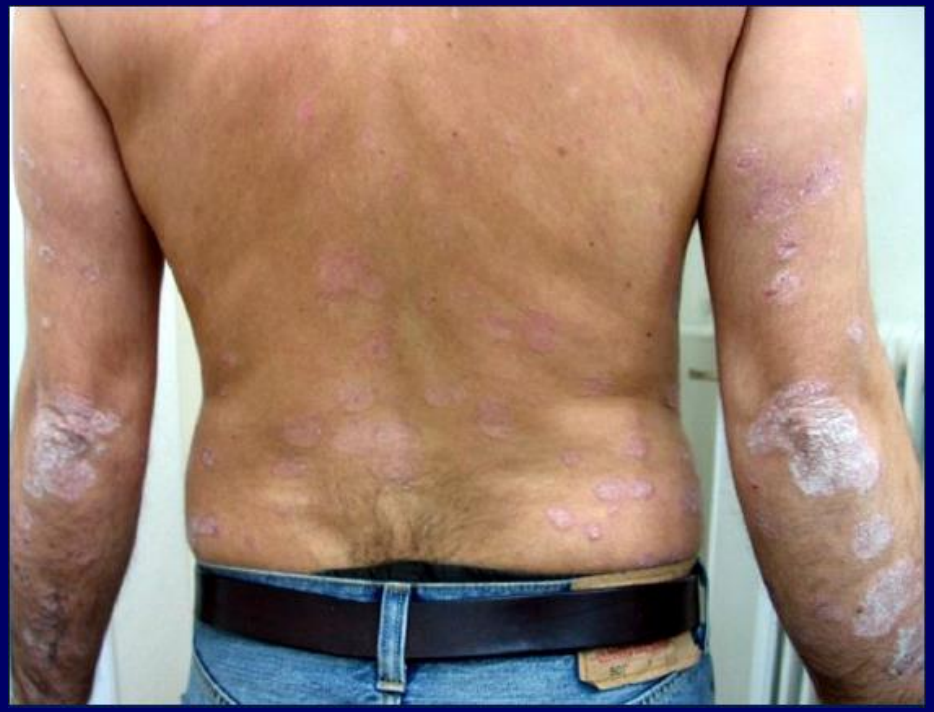
# Interleukin Blockade

# Ustekinimab Mechanism of Action

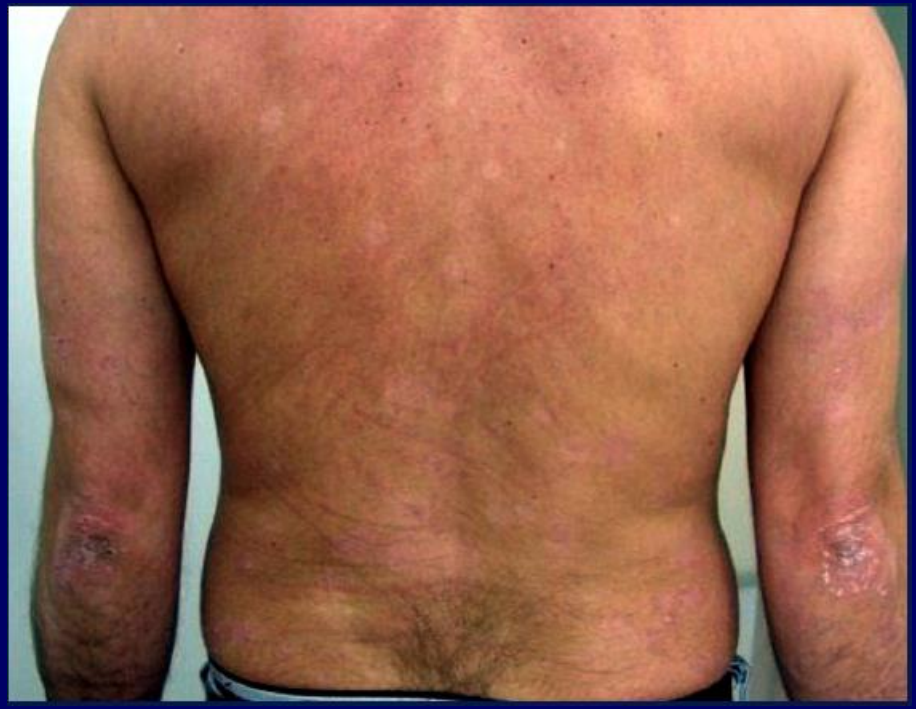


# Ustekinimab for Psoriasis

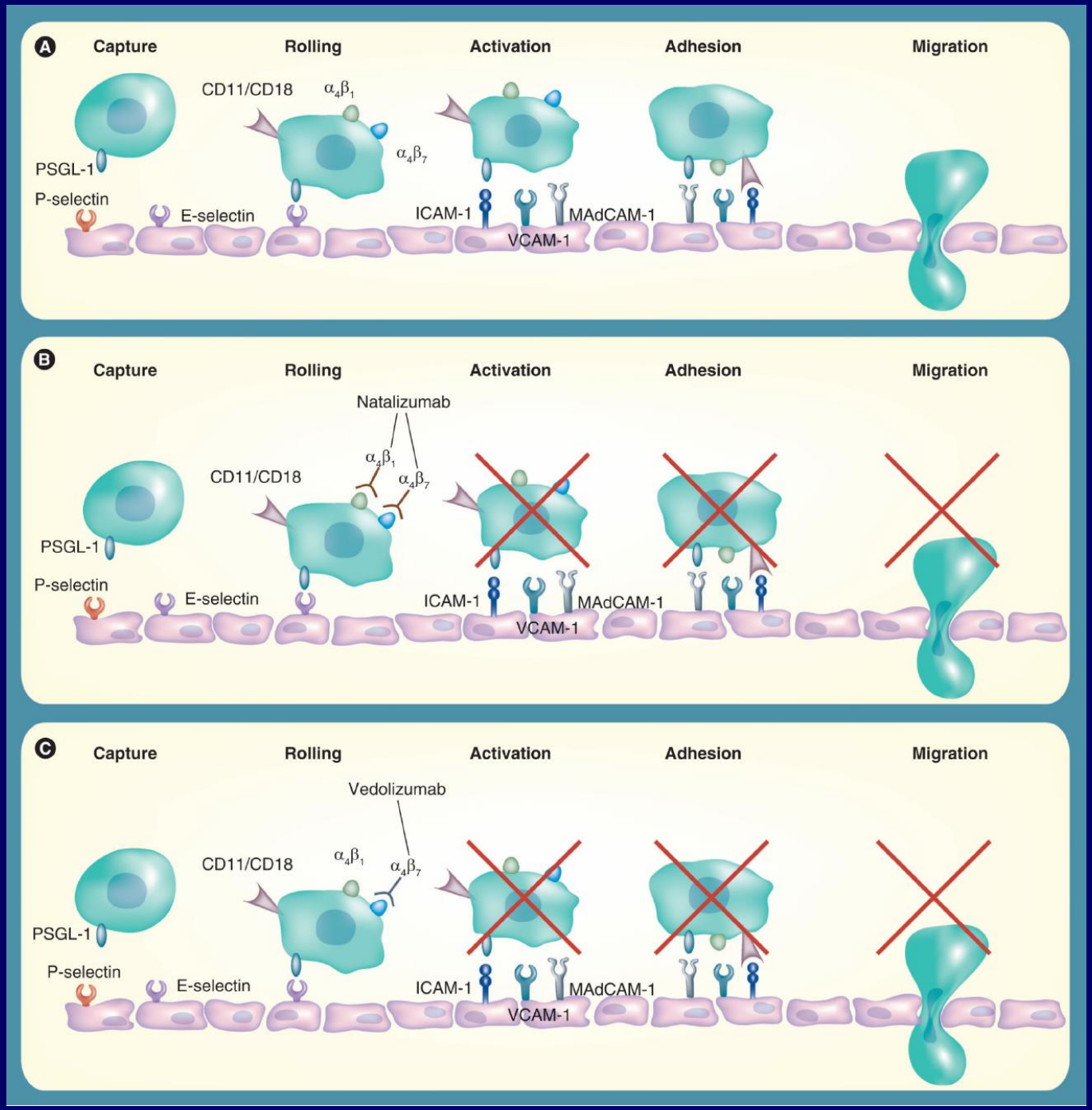
Before



After



# α-Integrin Antagonists


A
Capture
Rolling
Activation
Adhesion
Migration
CD11/CD18
$\alpha_4\beta_1$
$\alpha_4\beta_7$
PSGL-1
P-selectin
E-selectin
ICAM-1
MAdCAM-1
VCAM-1
B
Capture
Rolling
Activation
Adhesion
Migration
Natalizumab
$\alpha_4\beta_1$
$\alpha_4\beta_7$
CD11/CD18
PSGL-1
P-selectin
E-selectin
ICAM-1
MAdCAM-1
VCAM-1
C
Capture
Rolling
Activation
Adhesion
Migration
Vedolizumab
CD11/CD18
$\alpha_4\beta_1$
$\alpha_4\beta_7$
PSGL-1
P-selectin
E-selectin
ICAM-1
MAdCAM-1
VCAM-1

# FXR Agonists

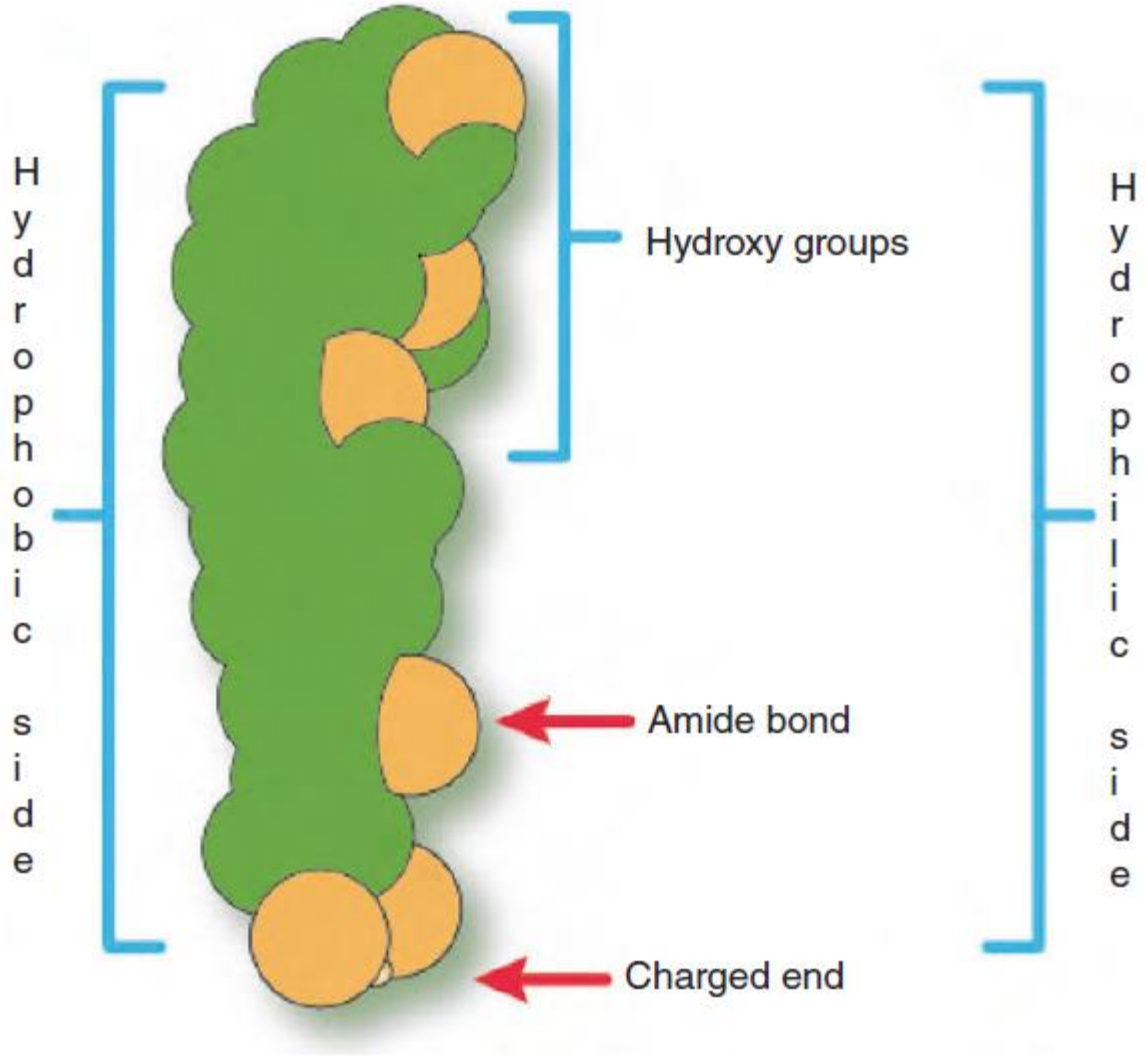
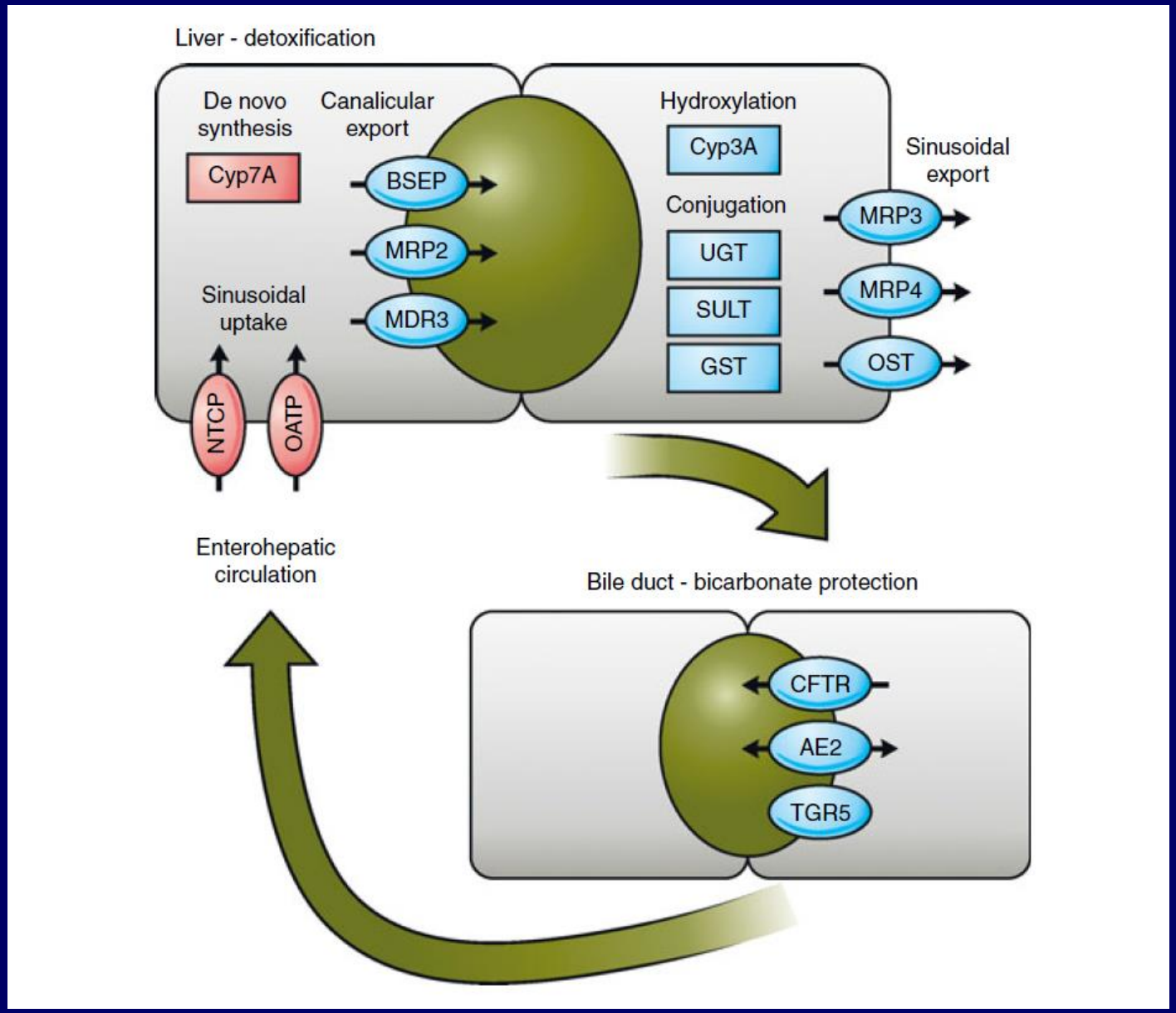



Figure 1 Graphic representation of a bile-acid molecule (taurocholate).

# Enterohepatic Circulation of Bile Acids



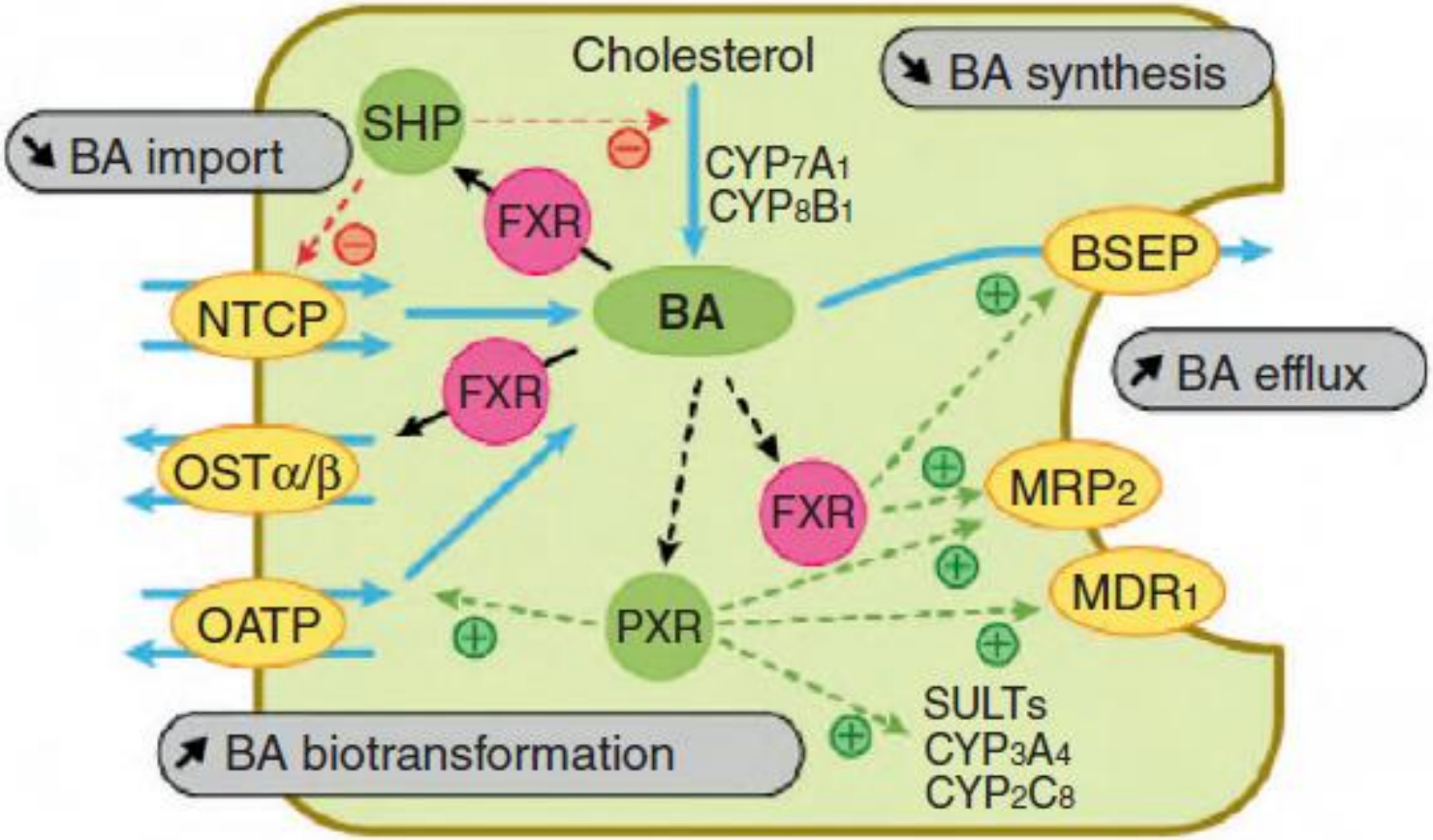



Figure 3 Diagrammatic representation of the cellular adaptive response to cholestasis.

# Obeticholic Acid

1. PBC Trial, Phase 3: Placebo 73 pts, OCA 5 mg 70 pts, OCA 10 mg 73 pts. Met endpoints for Alk Phos and Bili. But, pruritus in 68% in 10 mg/d arm – only 6% withdrew for pruritus. ?Will FDA approve for PBC?

2. NAFLD Trial: Beneficial biochemical effects. Question of dyslipidemia?

# Anti-fibrotics

**LOX-L2 inhibitor**

**Galectin inhibitor**

**Others**

# Conclusion about Treatment

**The Future looks promising –**

**Hopefully the options for treatment will Expand and improve!!**