PBC: MANAGEMENT OF LIVER DISEASE AND OTHER COMPLICATIONS

Robert G Gish MD

Adjunct Professor of Medicine
Stanford University

Advisor: PBCers PBC Foundation

PBC:

- Epidemiology
- Natural history
- Diagnosis
- Symptoms: look at the whole patient
- Treatment of PBC liver disease
- Treatment of extrahepatic disease

CHOLESTATIC LIVER DISEASES

- Definition
  - PBC 2 of 3
    - Alk phos > 2 x ULN
    - + AMA
    - Compatible liver biopsy
  - PSC
    - Cholangiogram abnormal
    - Compatible biopsy supportive

Impact of PBC

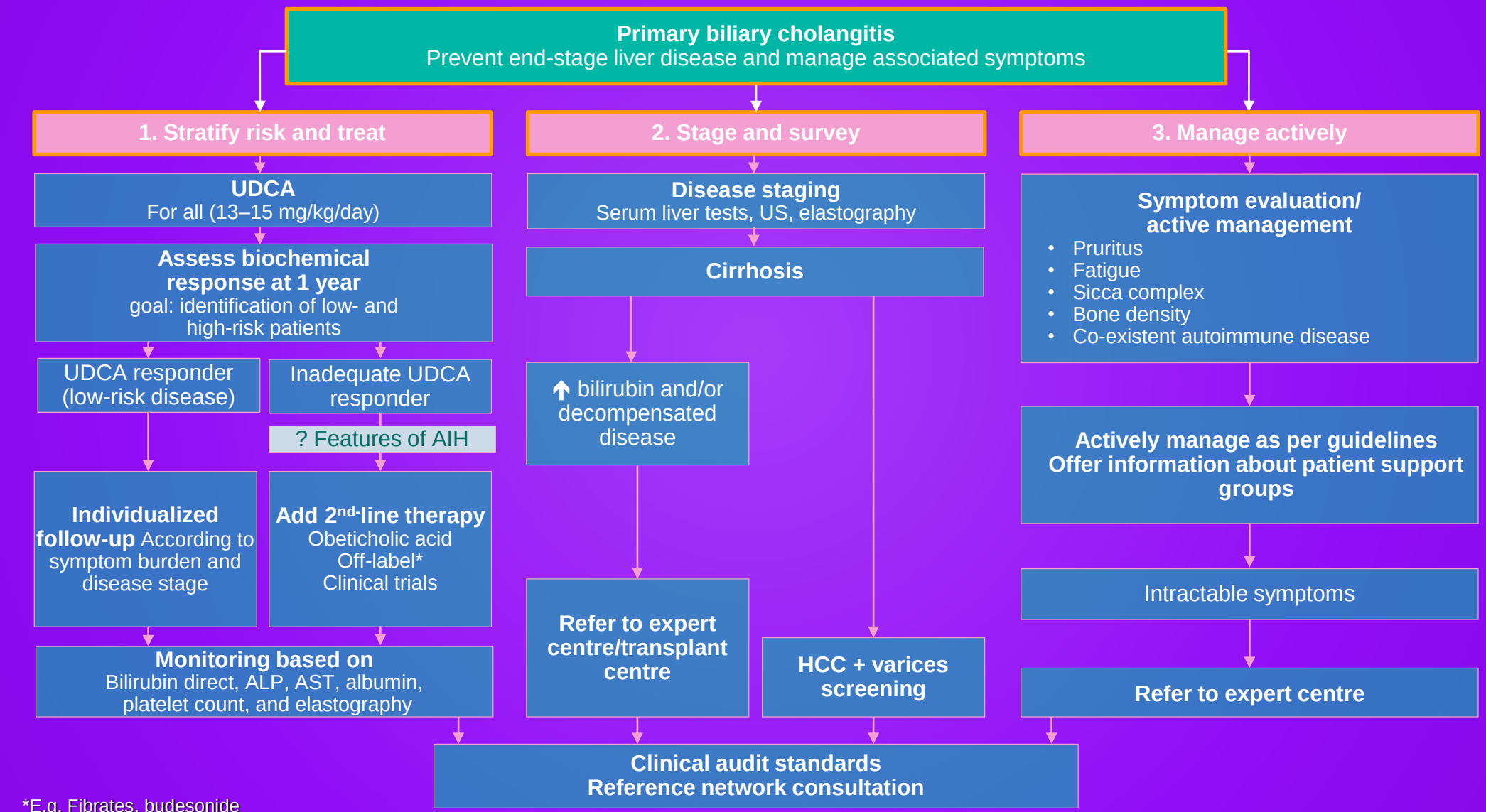
- Most Patients will progress to **end-stage liver disease if there is no treatment of their liver disease**
  - Average survival (historical) among those untreated is 9–10 years
- **Symptoms** associated with PBC **impact on QoL**, and include:
  - Pruritus
  - Sicca complex
  - Abdominal discomfort
  - Jaundice
  - Fatigue
  - Restless legs
  - Insomnia
  - Depression
  - Cognitive dysfunction

Life-long care that is **structured** and **individualized** is required

Goal is to **prevent end-stage complications** of liver disease and **manage associated symptoms*** that reduce QoL

*Statement 11 (Grade of evidence III, Grade of recommendation 1)
EASL CPG PBC. J Hepatol 2017;67:145–72

Three pillars of PBC management



*E.g. Fibrates, budesonide

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MANAGEMENT OF PBC LIVER DISEASE

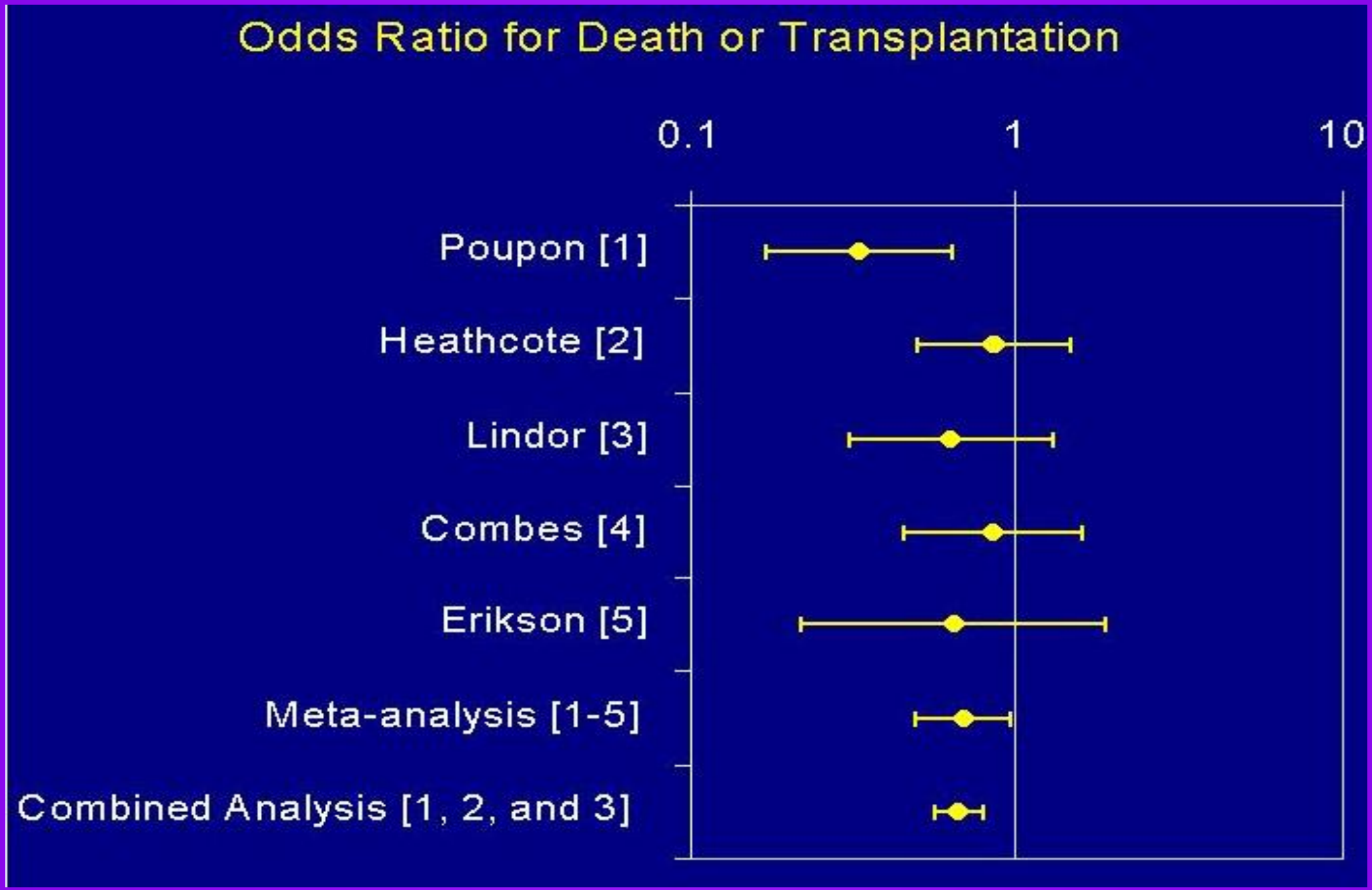
- Medical Options:

Unsuccessful	Questionable	Useful
penicillamine	steroids	UDCA 1st line
cyclosporine	**Budesonide (2018*)**	OCA 2nd line
azathioprine	methotrexate	Fenofibrate 3rd Line
thalidomide	colchicine	Bezafibrate 3Rd Line
malotilate		
chlorambucil		

TREATMENT OF PBC - URSODIOL

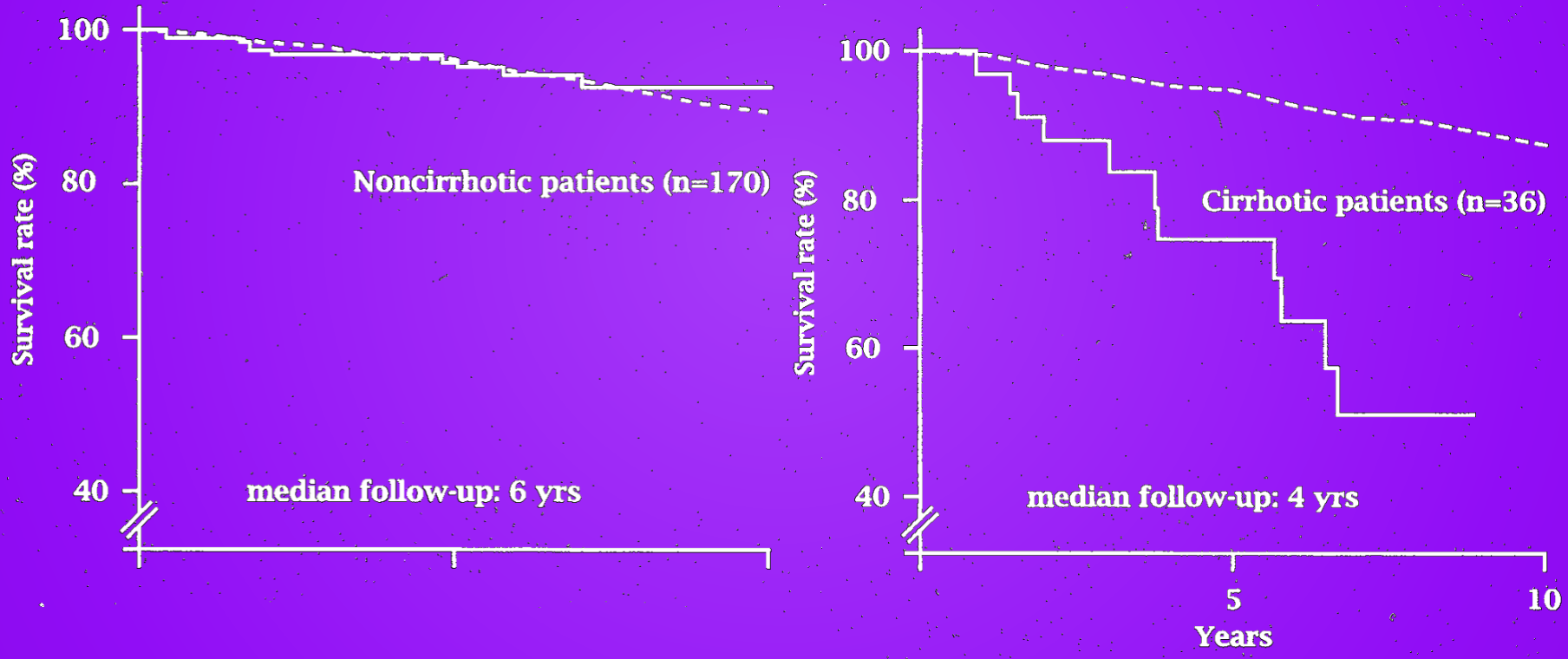
11 Randomized Trials

- various sizes of study > 1200 patients
- various doses
- various endpoints
- various duration (9 of 11 ≤ 2 years)


Odds Ratio for Death or Transplantation
0.1
1
10
Poupon [1]
Heathcote [2]
Lindor [3]
Combes [4]
Erikson [5]
Meta-analysis [1-5]
Combined Analysis [1, 2, and 3]

NATURAL HISTORY OF PBC

Effects of UDCA



Poupon RE, et al. Hepatology 1999;29:1668-1671

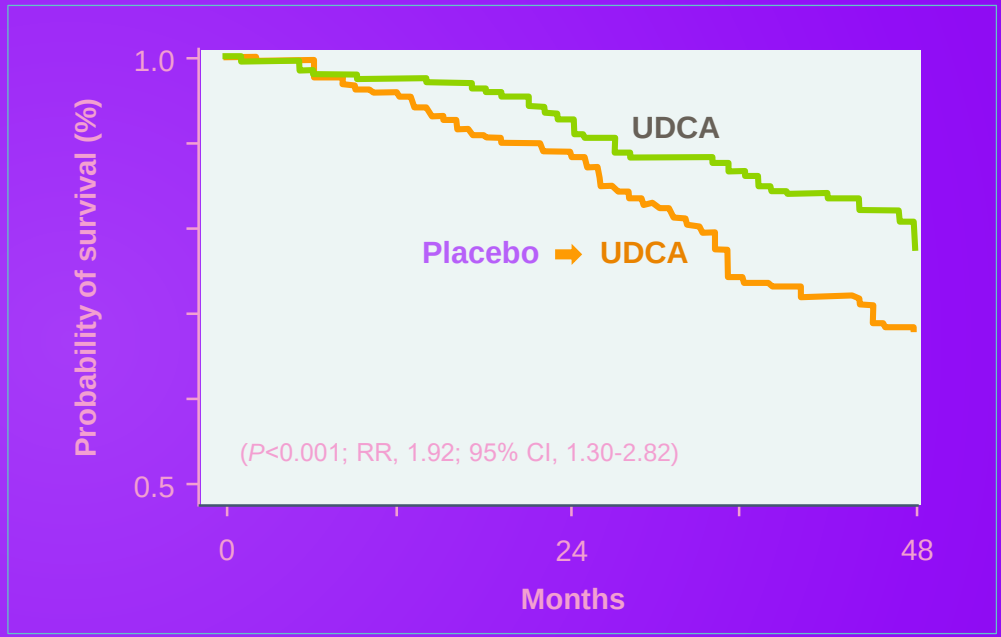
UDCA IN PBC

- Improves liver disease, survival and decreases the need for liver transplantation
- Normal AP: normal life span
- No consistent, reliable effect on pruritus

UDCA Treatment Is Associated With a Number of Beneficial Effects in PBC[1-5]

UDCA is associated with:

- Decrease in ALP[1]
- Improvements (decreases) in serum bilirubin[1,2]
- Delay in progression of fibrosis and histologic stage[1-3]
- Decreased risk for development of esophageal varices[4]
- Increases in liver–transplant-free survival[1,2,5]



CI, confidence interval; RR, relative risk.

1.EASL. *J Hepatol*. 2009;51(2):237-267.
2.Lindor KD, et al. *Hepatology*. 2009;50(1):291-308.
3.Poupon R. *Hepatology*. 2010;52(5):745-758.
4.Angulo P, et al. *J Hepatol*. 1999;30(5):830-835.
5.Poupon RE, et al. *Gastroenterology*. 1997;113(3):884-890.

Defining inadequate response to treatment

- Treatment failure must be defined on validated surrogate endpoints
  - To account for the slow progression of disease
- Qualitative biochemical response to UDCA assessed using binary definitions or continuous scoring

Binary definitions	Time (months)	Treatment failure
Rochester[1]	6	ALP ≥2 ULN or Mayo score ≥4.5
Barcelona[2]	12	Decrease in ALP ≤40% and ALP ≥1x ULN
Paris-I[3]	12	ALP ≥3x ULN or AST ≥2x ULN or bilirubin >1 mg/dl
Rotterdam[4]	12	Bilirubin ≥1x ULN and/or albumin <1x ULN
Toronto[5]	24	ALP >1.67x ULN
Paris-II[6]	12	ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin >1 mg/dl
Ehime[7]	6	Decrease in GGT ≤70% and GGT ≥1 ULN
Continuous scoring	**Time (months)**	**Scoring parameters**
UK-PBC[8]	12	**12 months:** bilirubin, ALP and AST (or ALT); **Baseline:** albumin and platelets
GLOBE[9]	12	**12 months:** bilirubin, ALP, albumin, and platelet count; **Baseline:** age

See notes for full reference list
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Some Patients May Experience Side Effects of UDCA Treatment[1]

The most common reported side effects of UDCA include[1]:

- Abdominal discomfort
- Abdominal pain
- Alopecia
- Diarrhea
- Nausea
- Pruritus
- Rash

- Patients may also experience weight gain (~5 lbs) with UDCA within the first year of treatment[2,3]

- UDCA is contraindicated in patients with complete biliary obstruction and known hypersensitivity or intolerance to UDCA or any of the components of the formulation[1]

1. URSO 250 / URSO Forte [package insert]. Bridgewater NJ: Aptalis Pharma US, Inc; 2013.
2. Poupon R. *Hepatology*. 2010;52(5):745-758.
3. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308.

Treatment: therapies to slow disease progression

- **Ursodeoxycholic acid** (UDCA) and **obeticholic acid** (OCA) approved in PBC
- **Heterogeneity of treatment efficacy** in clinical trials may be due to:
  - Variable inclusion criteria without reference to disease risk or stage

Recommendations*	Grade of evidence	Grade of recommendation
Oral UDCA: 13–15 mg/kg/day as the first-line pharmacotherapy for all patients with PBC. UDCA is usually continued for life	I	1
Oral OCA: iochemical efficacy in patients with ALP >1.67x ULN and/or bilirubin elevated <2x ULN demonstrated in a Phase 3 study • Conditionally approved for patients with PBC in **combination with UDCA** for those with an inadequate response to UDCA, or as monotherapy in those intolerant to UDCA • Consider use in such patients (initial dose 5 mg; dose titration to 10 mg according to tolerability at 6 months)	I	2
Data from Phase 3 randomized trials for **budesonide** (in non-cirrhotic patients), and **bezafibrate**, both in **combination with UDCA**, not yet published; currently, a recommendation for therapy cannot be made	II-2	2

*Statements 19–21
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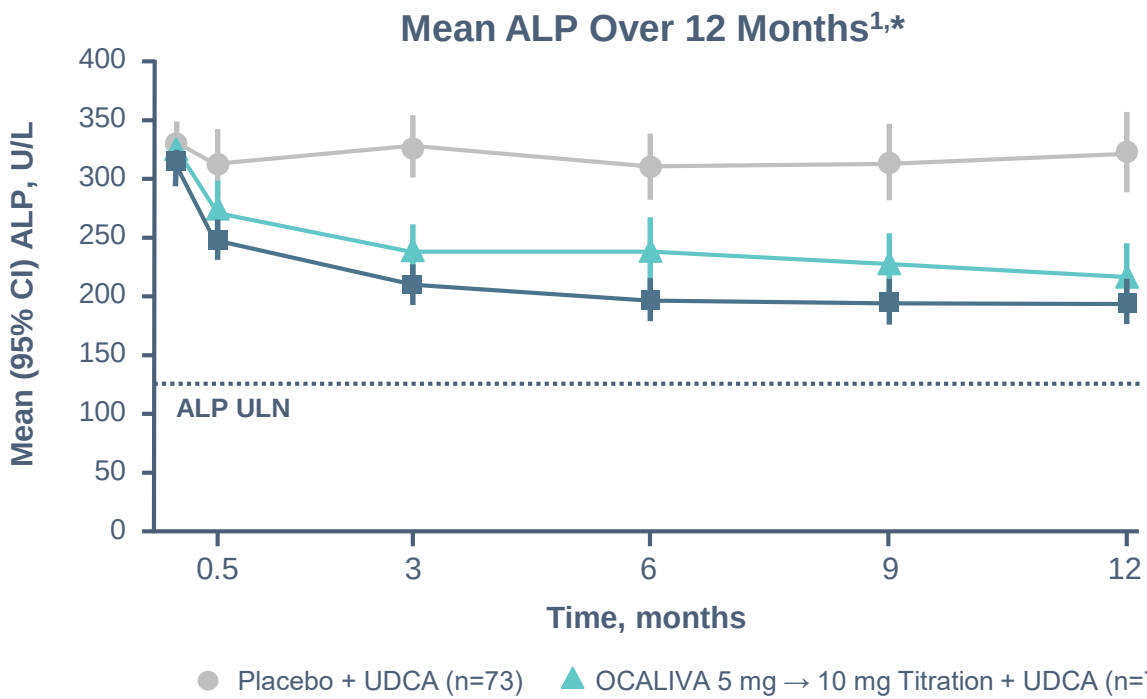
Obeticholic Acid

- Basic information
- What is new ?

OCALIVA Delivered Significant, Sustained Reductions in ALP Beyond UDCA Alone[1]



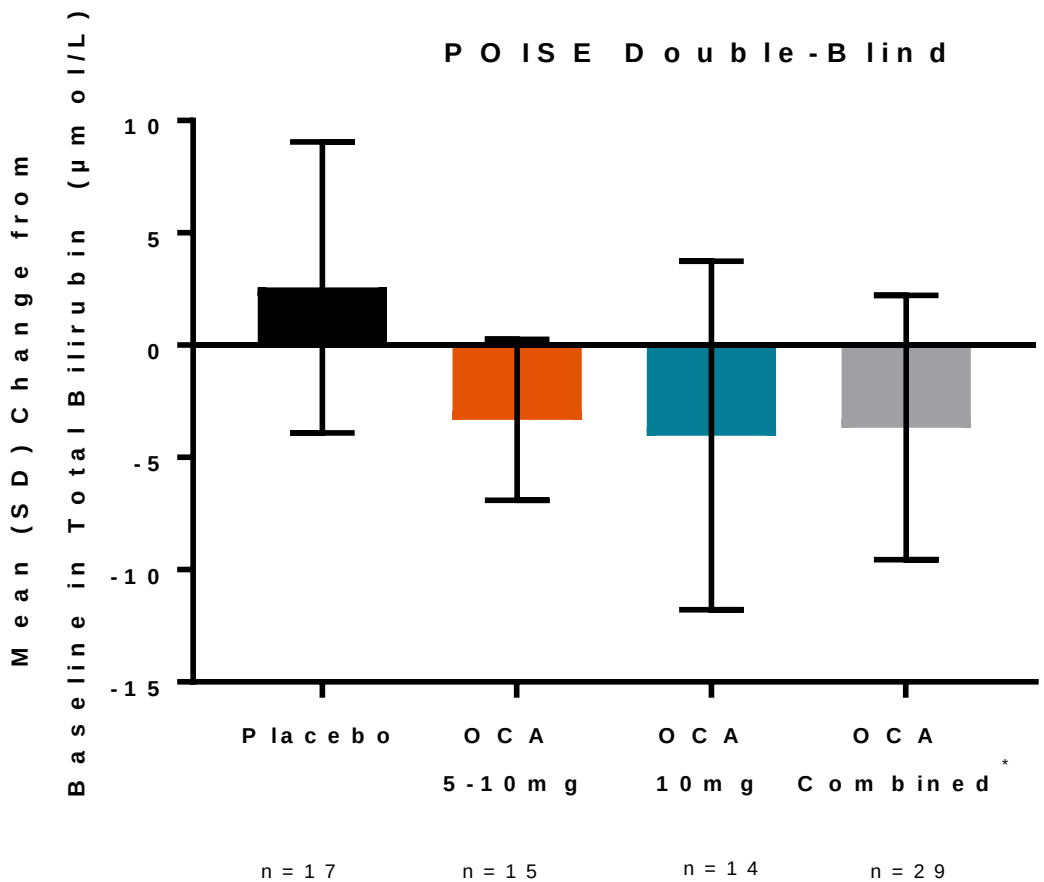
- **Patients taking OCALIVA had mean ALP reductions of >30% at 12 months vs 5% in patients taking UDCA alone[2,3]**
  - With a mean baseline ALP of 323.3 U/L, patients taking OCALIVA + UDCA had ALP reductions of approximately 100 U/L after 1 year of treatment[1,4]

CI, confidence interval.

*16 patients (7%) who were intolerant did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA 5 → 10 mg titration arm, and 5 patients (7%) in the placebo arm.

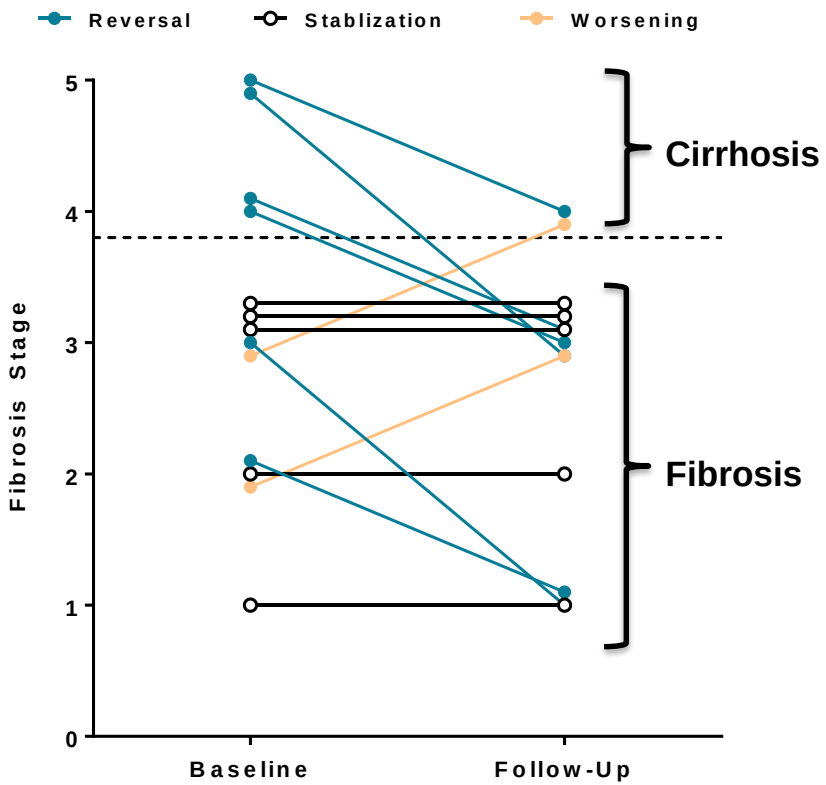
1. OCALIVA [package insert]. New York, NY: Intercept Pharmaceuticals, Inc; 2018.
2. EASL. *J Hepatol.* 2017;67(1):145-172.
3. Supplementary appendix to: Nevens F, et al. *N Engl J Med*. 2016;375(7):631-643.
4. Nevens F, et al. *N Engl J Med*. 2016;375(7):631-643.

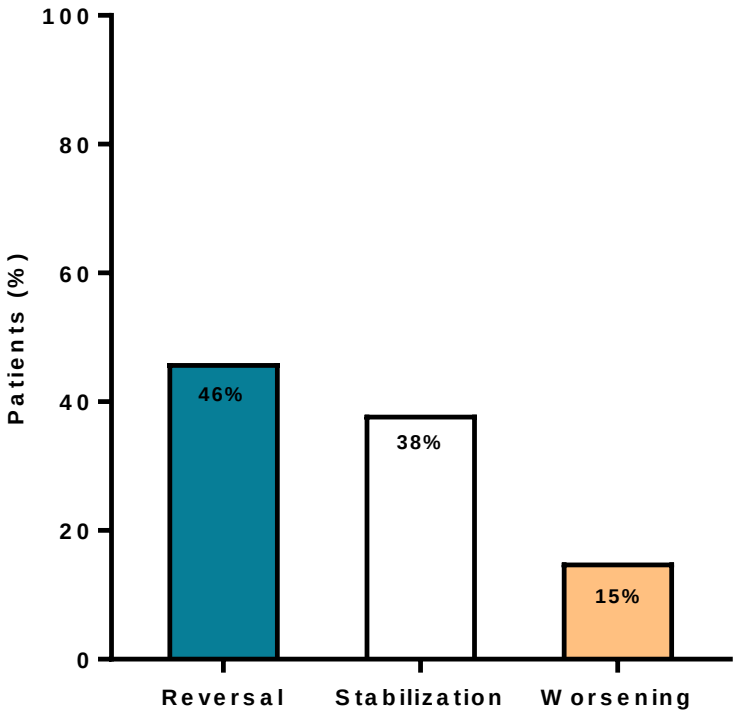
Reductions in Bilirubin Observed at 12 Months in OCA-Treated Patients With Total Bilirubin ≥0.67× ULN at Baseline



*OCA combined represents OCA-treated patients from both treatment groups with total bilirubin ≥0.67x ULN in POISE.

The Majority of Patients Had Reversal or Stabilization in Fibrosis Stage After 3 Years of OCA Treatment





- Six patients (46%) showed reversal in fibrosis (1 stage, n=4; 2 stages, n=2), while 2 patients (15%) showed fibrosis worsening by 1 stage
- All 4 patients with baseline cirrhosis showed reversal of fibrosis by at least 1 stage, and 3 (75%) improved to fibrosis without cirrhosis

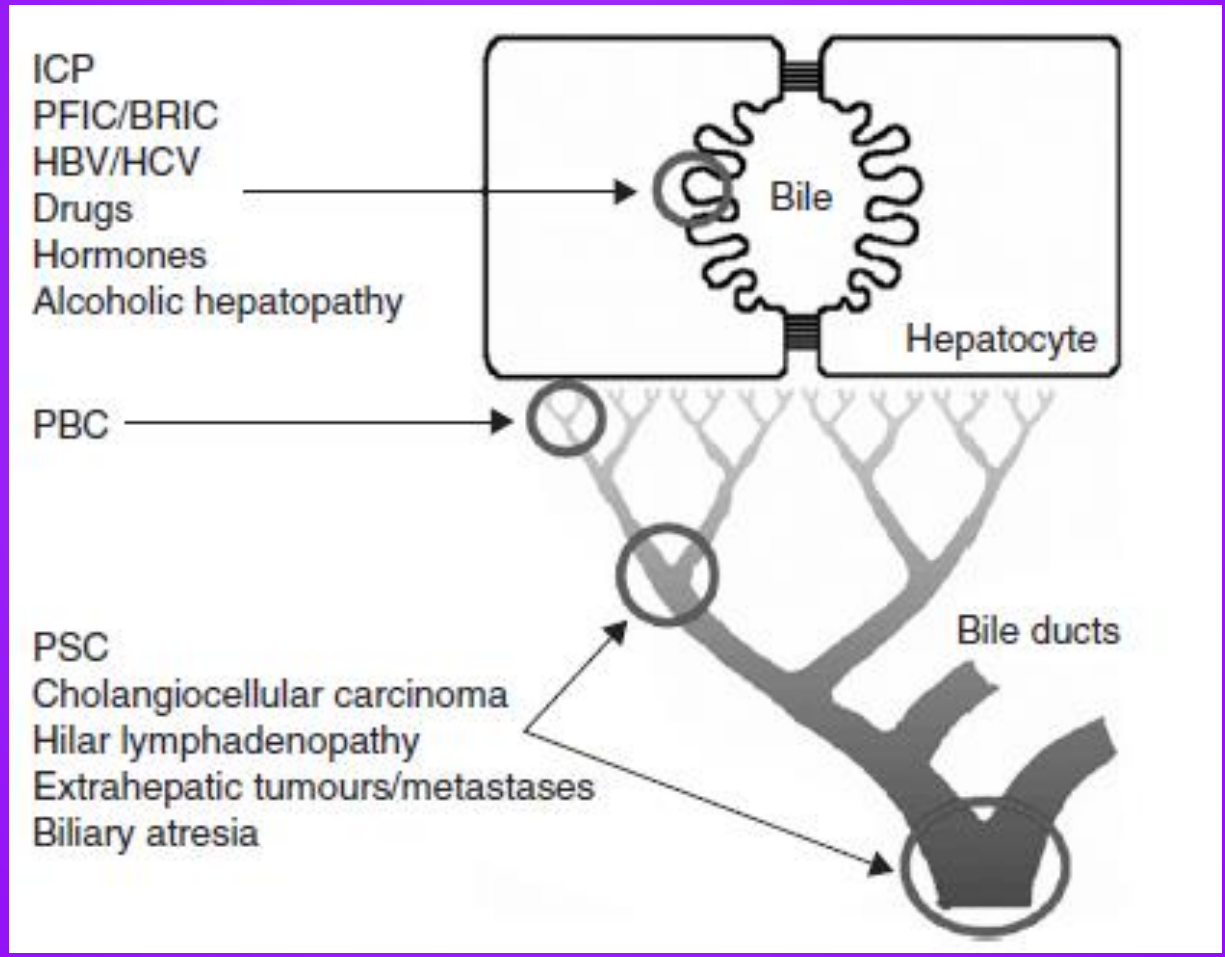
F0=no fibrosis; F1=periportal fibrosis; F2=bridging fibrosis with rare septa; F3=bridging fibrosis with many septa; F4=incomplete cirrhosis; F5=cirrhosis.

PRURITUS IN PBC

OVERVIEW

- Review of Pathogenetic Mechanics
- Potential Targets for Therapy

COMMON HEPATOBILIARY DISEASES ASSOCIATED WITH PRURITUS



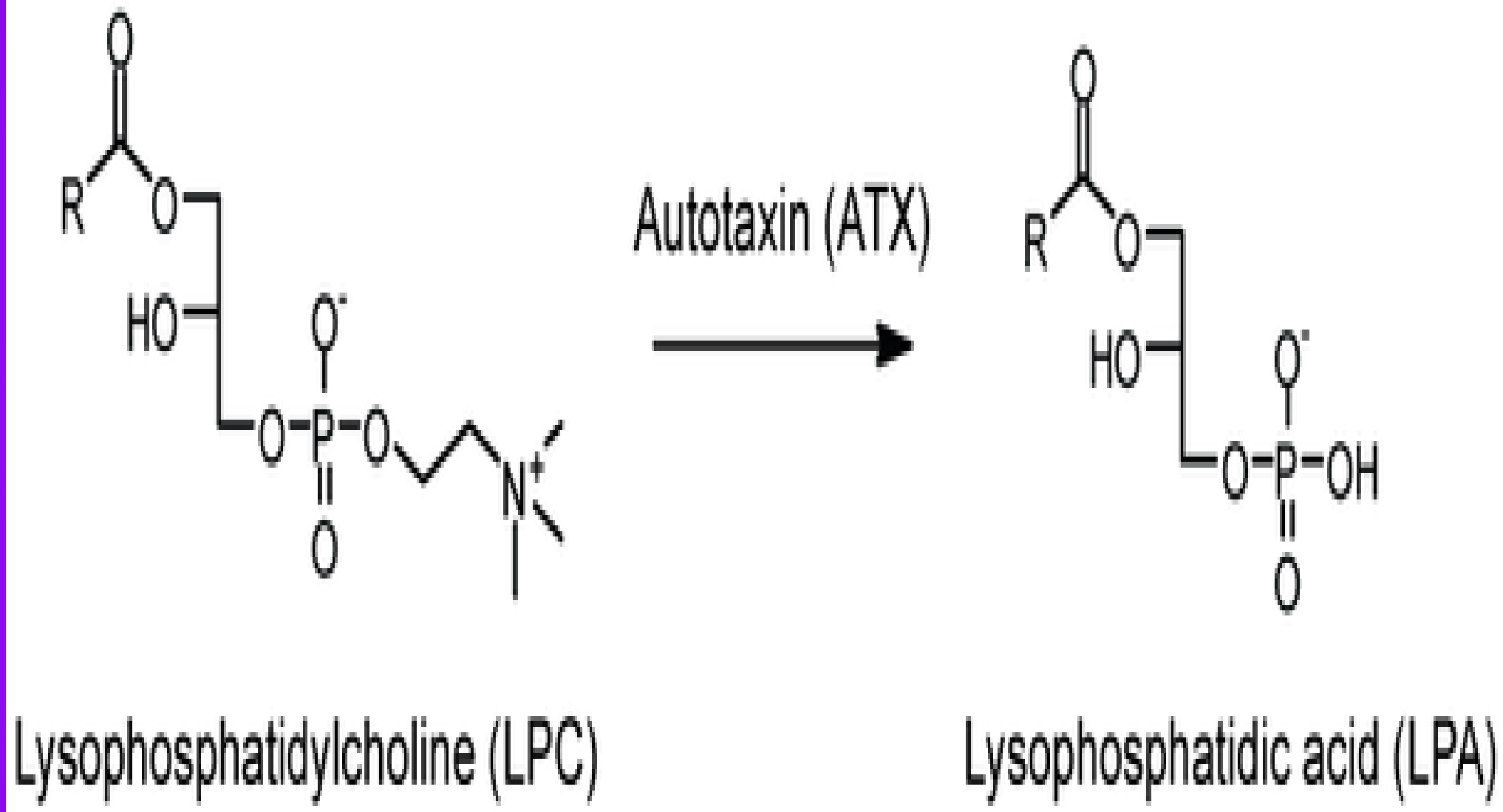
Kremer A, et al. Drugs 2008;68:2163-82

MANAGEMENT OF PRURITUS

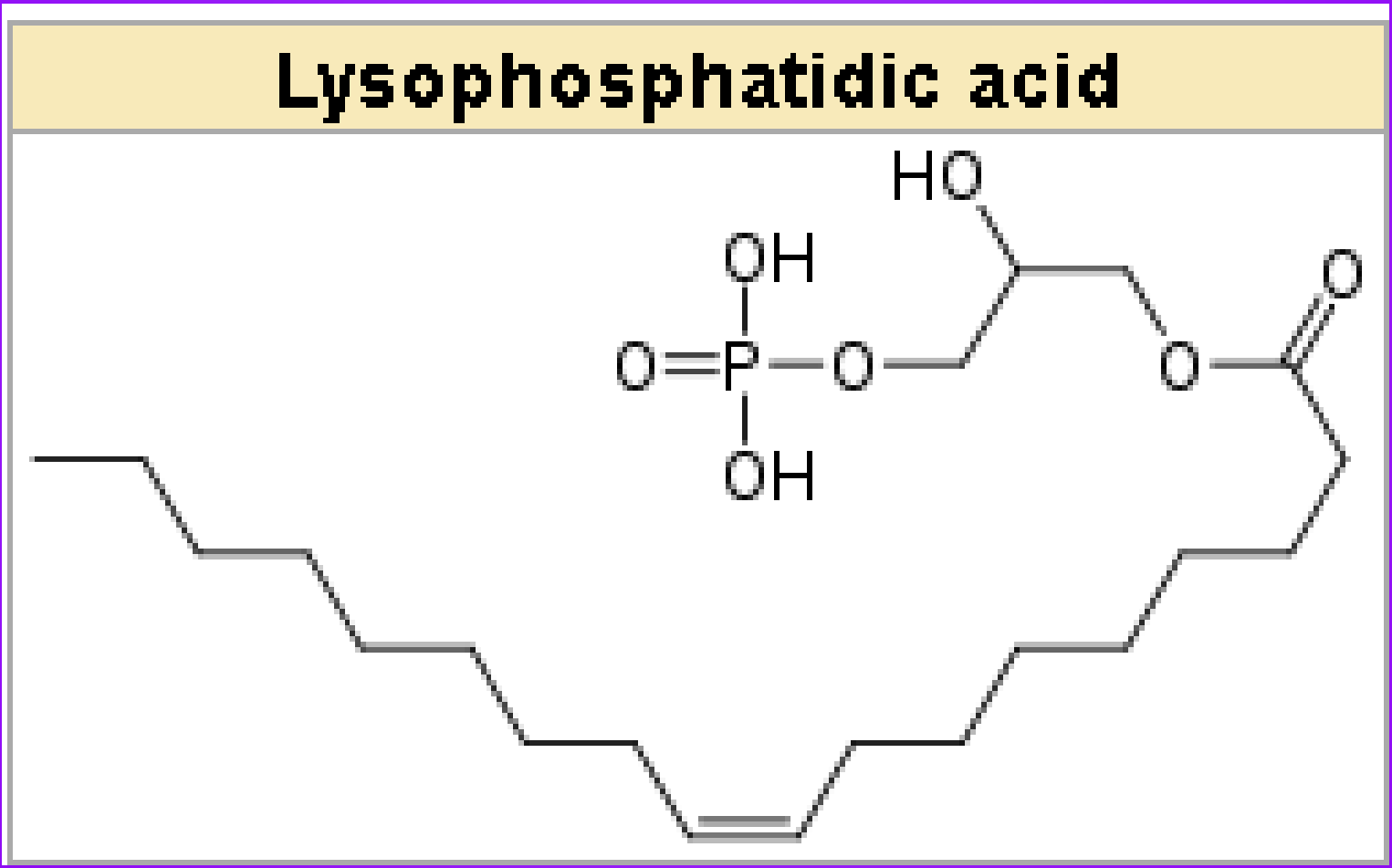
- Need to make correct diagnosis
  - Stones/Strictures/CA
  - PBC
  - PSC
  - IgG4
  - AIH

AUTOTAXIN

- Ectonucleotide pyrophosphatase/ phosphodiesterase 2 (NPP2 or ENPP2)
- Lipid signaling molecule lysophosphatidic acid (LPA)
- Protein functions as a phosphodiesterase
- Growth factor-like responses


Autotaxin (ATX)
Lysophosphatidylcholine (LPC)
Lysophosphatidic acid (LPA)

LYSOPHOSPHATIDIC ACID



LYSOPHOSPHATIDIC ACID (LPA)

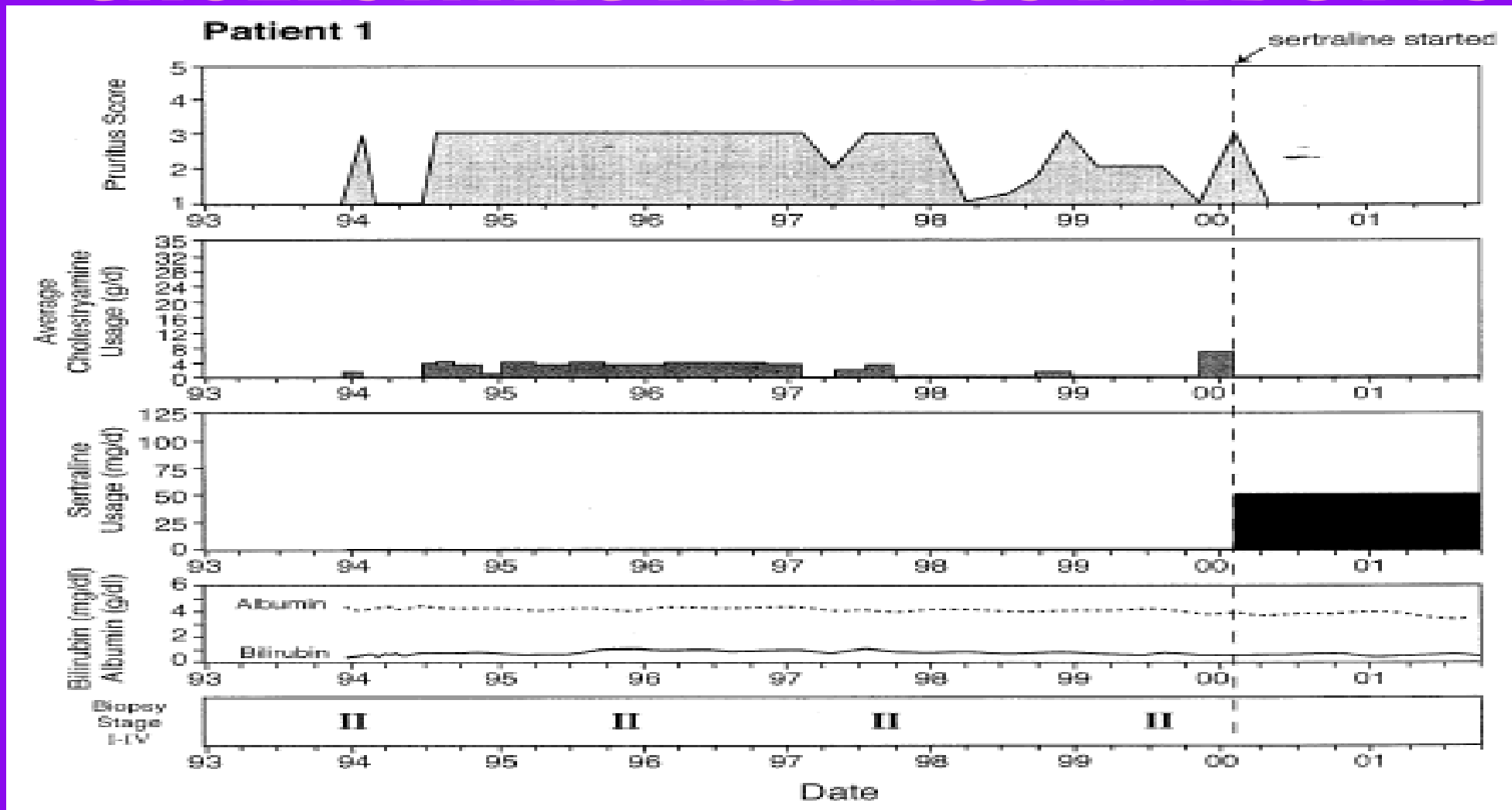
- Stimulates cell proliferation
- May contribute to oncogenesis
- May be the cause of pruritus in cholestatic diseases

MANAGEMENT OF CHOLESTASIS

Pruritus

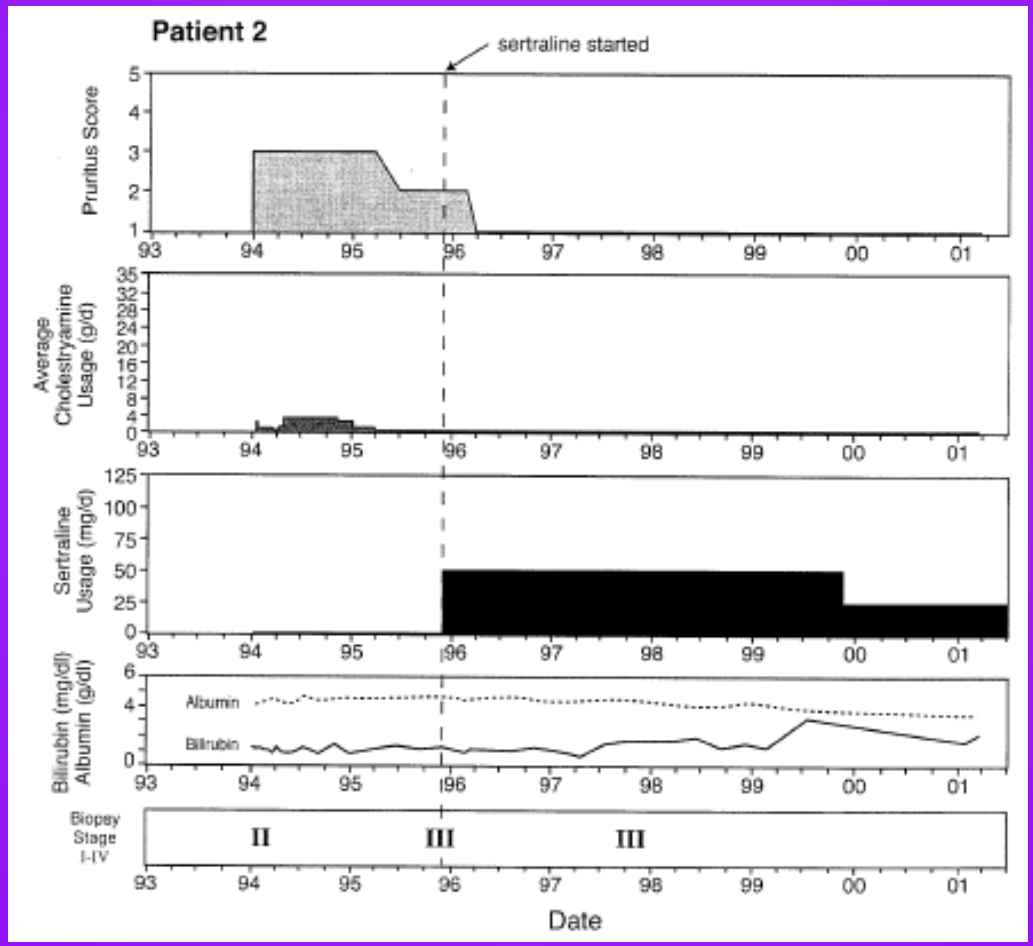
Medication	Dosage
Ursodiol	15-30 mg/kg/day orally
Cholestyramine	4 gm, 3 to 4 times daily
Naltrexone	50 mg by mouth daily
Rifampin	150 to 300 mg by mouth twice daily

SERTRALINE AS TREATMENT FOR CHOLESTATIC PRURITUS IN PBC PTS



Browning J, et al. Am J Gastroenterol 2003;98:2736-41

SERTRALINE AS TREATMENT FOR CHOLESTATIC PRURITUS IN PBC PTS



Browning J, et al. Am J Gastroenterol 2003;98:2736-41

FATIGUE

- Cause unknown
- Effect on prognosis
- UDCA not helpful
- Prozac
- Modafinil

FATIGUE

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- Effect on prognosis
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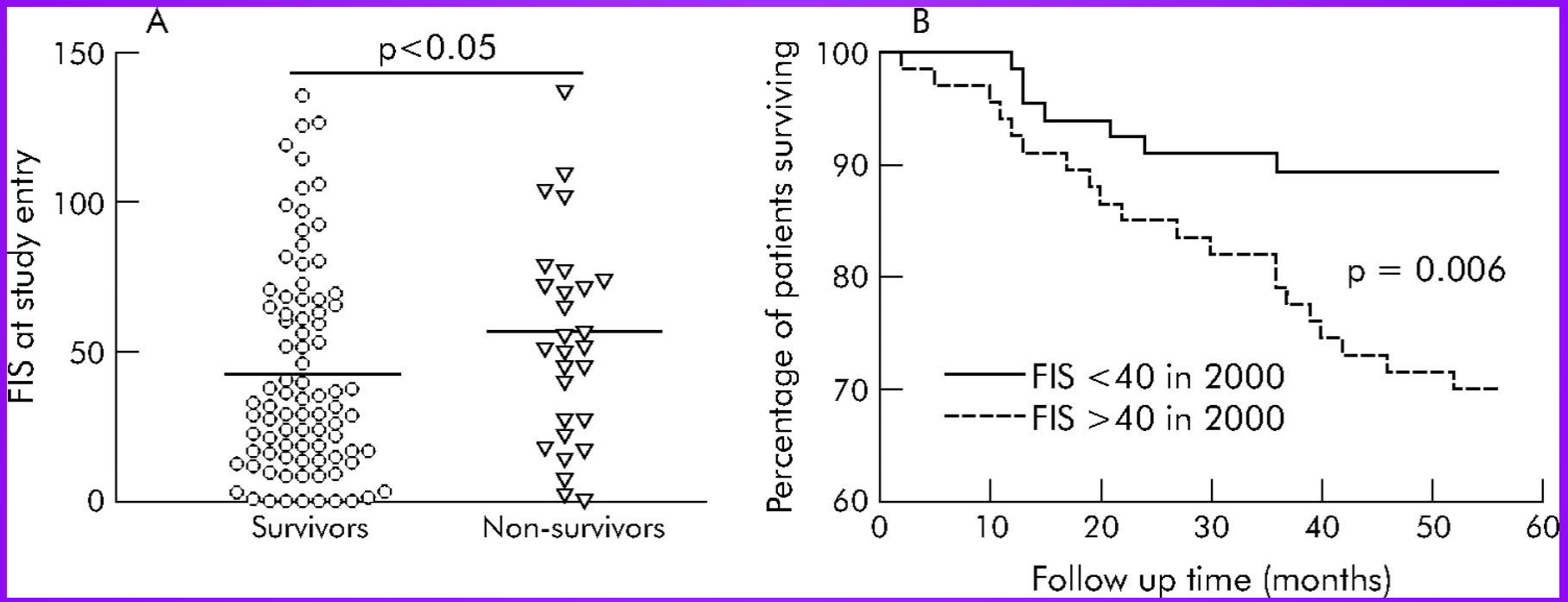
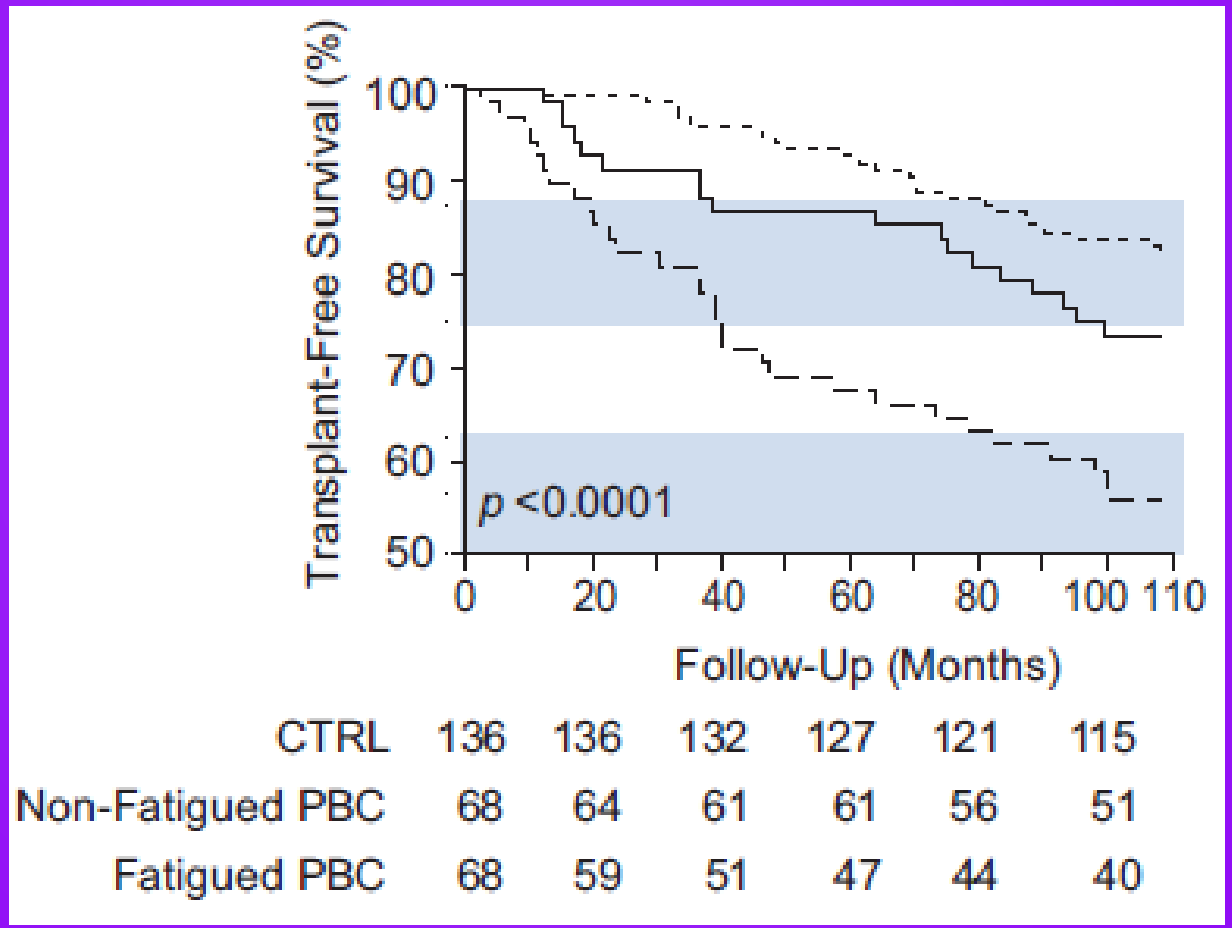
FATIGUE IN PBC



Jones DEJ, et al. Gut;2006;55:536-41

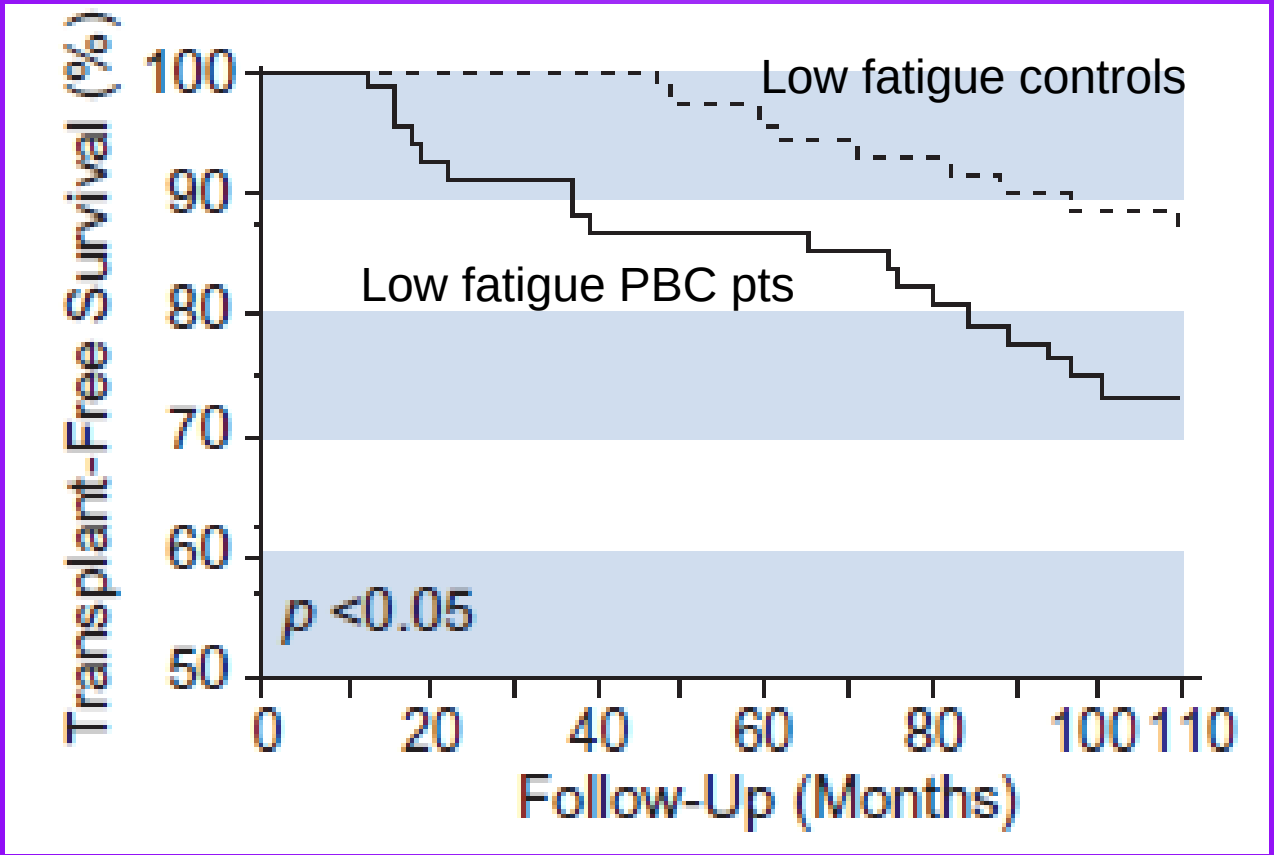
IMPACT OF FATIGUE ON SURVIVAL IN PBC



CTRL	136	136	132	127	121	115
Non-Fatigued PBC	68	64	61	61	56	51
Fatigued PBC	68	59	51	47	44	40

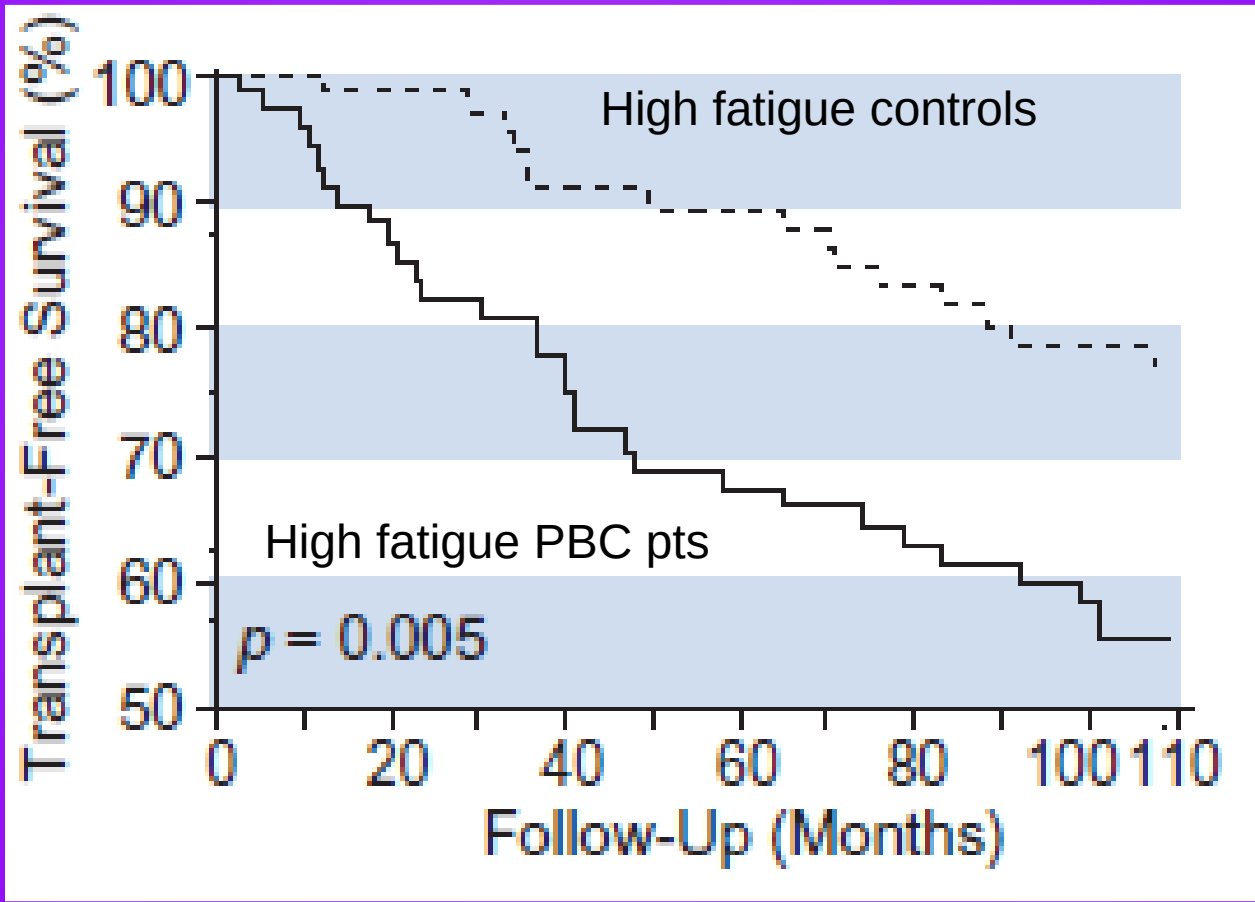
Jones DE, et al. J Hepatol 2010;53:911-17

SURVIVAL IN FATIGUED AND NON-FATIGUED PBC PATIENTS



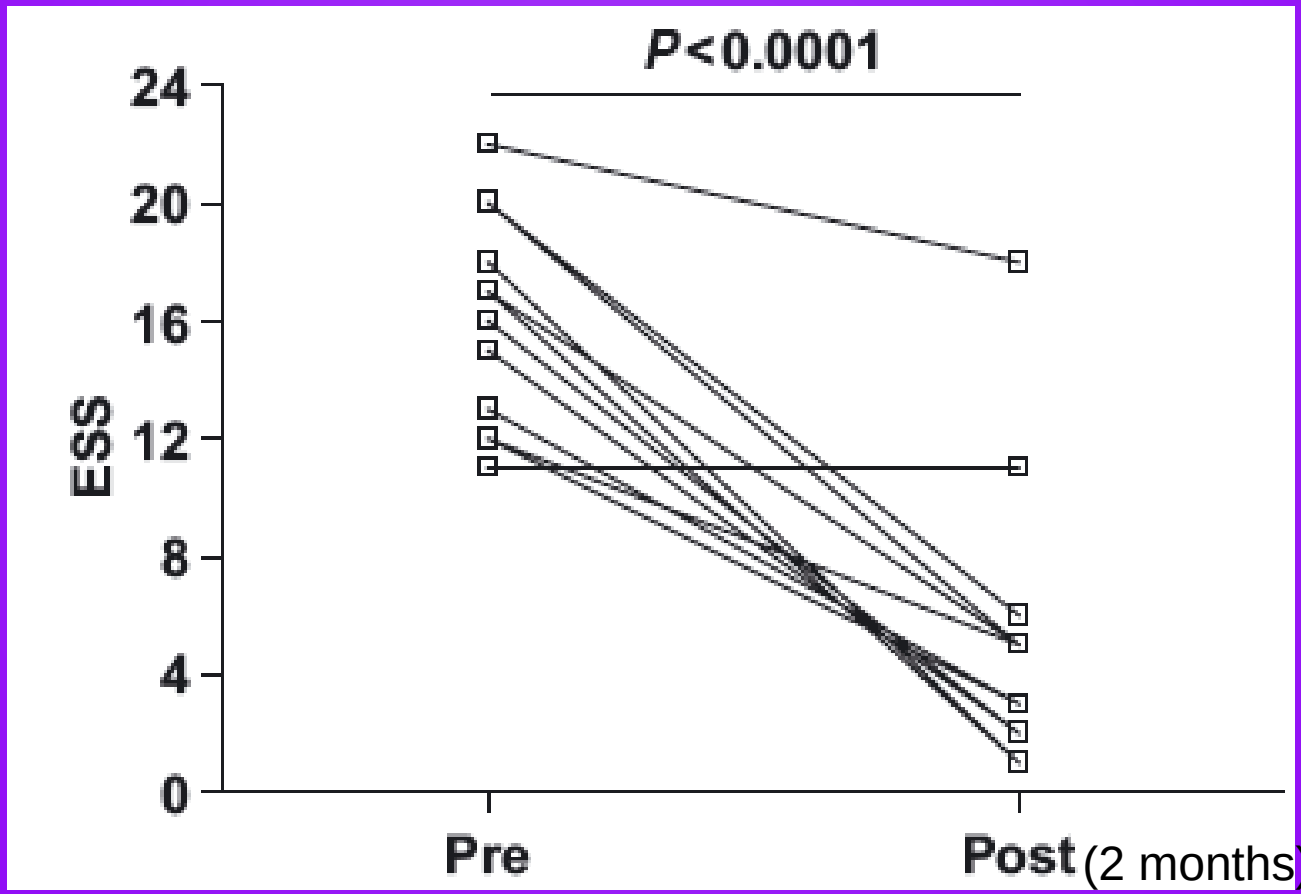
Jones DE, et al. J Hepatol 2010;53:911-17

SURVIVAL IN FATIGUED AND NON-FATIGUED PBC PATIENTS



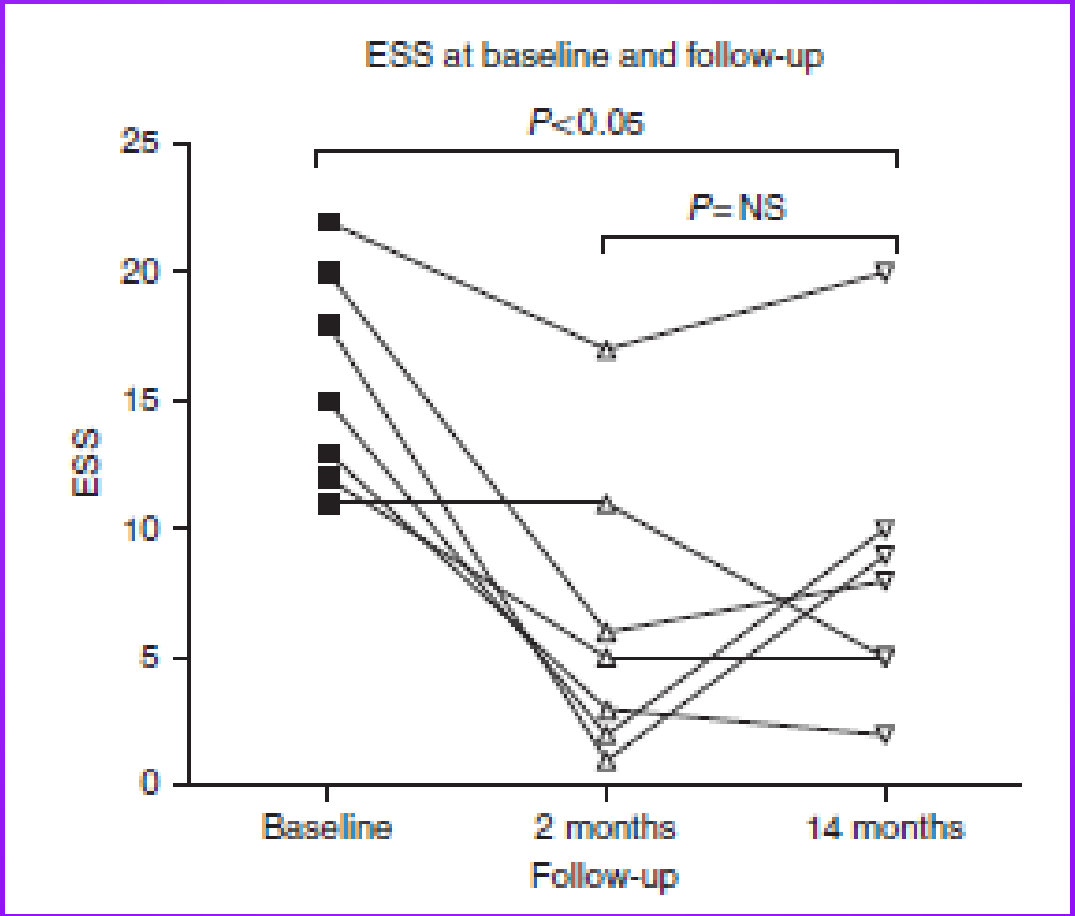
Jones DE, et al. J Hepatol 2010;53:911-17

MODAFANIL THERAPY FOR FATIGUE IN PBC PATIENTS



Jones DE, Newton JL. Aliment Pharmacol Ther 25:471-76

MODAFANIL IN PBC (Epworth Sleepiness Scale)



Hardy T, et al. Liver Int 2010;30:1551-52

Special settings: pregnancy

- A minority of women diagnosed with PBC are of reproductive age
- UDCA is safe during conception, pregnancy and post-partum according to expert clinical opinion

Recommendations*	Grade of evidence	Grade of recommendation
Expert consultation is required for all pregnant patients to guide therapy. **Pregnancy is typically well tolerated in non-cirrhotic patients with PBC** • Continue **UDCA** in pregnancy, even though data are limited • Pruritus management is important and may require specialist advice; **rifampicin** has been used by experts during third trimester	III	1
Pregnancy in patients with **cirrhosis carries a higher risk of maternal and foetal complications** • Offer pre-conception counselling and relevant specialist monitoring	III	1

*Statements 22, 23
EASL CPG PBC. J Hepatol 2017;67:145–72

Management of symptoms

- Symptoms associated with PBC have a significant impact on QoL

Recommendations*	Grade of evidence	Grade of recommendation
Screening: Evaluate all patients for presence of symptoms, particularly pruritus, sicca complex and fatigue. Severity of symptoms not necessarily correlated with stage of disease in PBC	III	1
Pruritus		
Treat using a step-wise approach. Severe pruritus may indicate an aggressively ductopenic variant of PBC. These patients have a poor prognosis and should be referred to an expert centre	III	1
• First-line: cholestyramine as first-line therapy. Avoid interaction with other medications	II-2	1
• Second-line: rifampicin†	II-2	1
Fatigue		
• Seek and treat associated and alternate causes of fatigue	III	1
• Advise patients with fatigue on developing coping strategies	III	2
Sicca complex: where appropriate consider expert referral	III	1
Miscellaneous: Refer patients with symptoms resistant to medical therapy for specialist management, regardless of disease severity	III	1

*Statements 26–33;
†150–300 mg daily. Monitor serum liver tests after initial use (after 6 and 12 weeks) and after dose increase. Stop if hepatotoxicity observed
EASL CPG PBC. J Hepatol 2017;67:145–72

Management of complications of liver disease

- **Osteoporosis** is a common complication in PBC

Recommendations*	Grade of evidence	Grade of recommendation
Consider the **risk of osteoporosis** in all patients with PBC	III	1
To assess risk, consider use of **DEXA** to assess **bone mineral density** at presentation and at follow-up where Indicated	III	1
Supplement patients with PBC with **calcium** and **vitamin D**, according to local practice	III	2
Bisphosphonates are safe and effective treatments for patients with PBC and significantly elevated fracture risk from osteoporosis. Use with caution in patients with varices. Initiate therapy according to specific osteoporosis guidelines	II-2	1

*Statements 34–37
EASL CPG PBC. J Hepatol 2017;67:145–72

Management of complications of liver disease

- Fat soluble vitamin malabsorption can occur in PBC

Recommendations*	Grade of evidence	Grade of recommendation
Fat-soluble vitamin malabsorption: Can occur in PBC, particularly with prolonged jaundice. Supplementation should be considered on an individual basis	III	2

- Serum lipids can be elevated in up to 80% of patients with PBC
  - Underlying mechanism is different to that of other conditions
  - No substantial evidence to support an elevated CV risk

Recommendations†	Grade of evidence	Grade of recommendation
Hyperlipidaemia: In patients with PBC and metabolic syndrome (high cholesterol, low HDL-C cholesterol, high LDL-C, consider cholesterol-lowering agents on a case-by-case basis; treatment is not contraindicated	III	2

*Statement 38; †Statement 39
EASL CPG PBC. J Hepatol 2017;67:145–72

Hyperlipidemia Is Common Among Patients With PBC[1]

- As a result of cholestasis, hyperlipidemia is common in PBC, affecting 75%-95% of patients[1]
- In early disease, elevated very low–density lipoprotein and LDL-C concentrations are reported, as well as significantly elevated HDL-C values[2]
  - As disease progresses, HDL-C decreases while LDL-C may increase further
- Evidence suggests that there is no increased risk of cardiovascular disease in patients with PBC and hyperlipidemia[2,3]

AASLD Guideline Recommendations[3]
• UDCA will lower LDL-C levels and is the initial step • When there is also a family history of lipid abnormalities or cardiovascular disease it may still be considered appropriate, depending on the lipid pattern, to treat with cholesterol-lowering drugs

EASL Guideline Recommendations[2]
• In the subgroup of patients with PBC and metabolic syndrome (with high cholesterol, low HDL-C and high LDL-C levels), EASL suggests considering a pharmacologic approach with cholesterol-lowering agents on a case-by-case basis; treatment is not contraindicated

1. Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575.
2. EASL. *J Hepatol*. 2017;67(1):145-172.
3. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308.

Management of complications of liver disease

- Patients with PBC may develop portal hypertension as a result of biliary cirrhosis
  - Associated with a poor prognosis

Recommendations*	Grade of evidence	Grade of recommendation
Varices: Baveno-VI guidelines for screening and management of varices apply equally to patients with PBC	III	2

- HCC is one of the most serious complications of PBC
  - Incidence of HCC in those with diagnosed PBC is 0.36 per 100 person years

Recommendations†	Grade of evidence	Grade of recommendation
Hepatocellular carcinoma: In patients with suspected cirrhosis, HCC surveillance according to EASL guidelines is indicated	III	2

*Statement 40; †Statement 41
EASL CPG PBC. J Hepatol 2017;67:145–72

Management of complications of liver disease

- PBC as an indication for liver transplant is declining
  - Despite increasing prevalence of PBC
- Outcome post-liver transplant is usually favourable and better for most other liver transplant indications
  - 5-year survival of 80–85%

Recommendations*	Grade of evidence	Grade of recommendation
Liver transplantation		
• Consider patients for transplant assessment when presenting with complications of cirrhosis, markers of disease severity (e.g. persistent elevated bilirubin values [50 mol/l or 3 mg/dl] or MELD >15), or severe medically resistant pruritus. Follow local (usually national) guidelines	II-2	1
• In patients with proven or likely recurrent PBC post-liver transplant, use of UDCA is safe and can improve liver biochemistry	II-2	2

*Statements 42, 43
EASL CPG PBC. J Hepatol 2017;67:145–72

Organisation of clinical care delivery

- Advent of stratified therapy has increased the complexity of managing patients with PBC
- Optimal care models must be flexible
  - Effectively manage high-risk patients/those with a high symptom burden
  - Avoid over-management of low-risk asymptomatic patients

Recommendations*	Grade of evidence	Grade of recommendation
Care pathways:		
• All patients with PBC should have **structured life-long follow-up**	III	1
• Develop care pathway for PBC based on these guidelines	III	2
Clinical care standards: Use standardized clinical audit tools to document and improve the quality of care delivered to patients	III	2
Patient support: Inform patients of support available from patient support groups, including access to patient education material	III	2

*Statements 44–47
EASL CPG PBC. J Hepatol 2017;67:145–72

Proposed clinical care standards for PBC

Exclude alternate aetiologies for cholestasis: Undertake abdominal US in all patients with suspected PBC as part of baseline assessment	•**Standard 90%**
1st line treatment: UDCA at 13–15 mg/kg/day in all patients with PBC	•**Standard 90%** of patients receiving therapy at adequate dose or documented to be intolerant
Identify patients at risk of progressive disease: Document risk using biochemical response indices after 1 year of UDCA therapy	•**Standard 80%** of patients receiving UDCA to have response status and criteria used recorded
Recognize impact on QoL: Ensure appropriate investigation and treatment of symptoms (particularly pruritus, sicca complex, fatigue)	•**Standard 90%** of patients have the presence/ absence of pruritus, sicca complex and fatigue recorded in notes in the last year
Maximise opportunity for timely LTx: Discuss all established patients with bilirubin >50 µmol/L (3 mg/dl) or evidence of decompensated liver disease* with a hepatologist linked to a transplant programme	•**Standard 90%** documentation that discussion has taken place within 3 months of relevant clinical event and the actions taken recorded
Optimize prevention of osteoporotic bone fractures: Assess risk of osteoporosis in all patients. Treat/follow-up in line with national guidelines	•**Standard 80%** assessment within the last 5 years
Diagnose and treat of PBC with features of AIH promptly: Recognize as rare and when suspected, perform liver biopsy with expert clinicopathological assessment	•**Standard 90%** of patients with diagnosis of PBC with features of AIH have liver biopsy confirmation and clinicopathological discussion noted

*Variceal bleed, ascites, encephalopathy

EASL CPG PBC. J Hepatol 2017;67:145–72

Acknowledgements

- Intercept
- Gideon Hirschfeld
- Keith Lindor
- Kris Kowdley
- Eric Gershwin
- John Vierling
- Patients and their families
- PBCers
- PBC Foundation
- EASL Guidelines Committee
- AASLD