PBC: MANAGEMENT OF LIVER DISEASE AND OTHER COMPLICATIONS

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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

1. Stratify risk and treat
   - UDCA
     - For all (13–15 mg/kg/day)
   - Assess biochemical response at 1 year
     - goal: identification of low- and high-risk patients
   - UDCA responder (low-risk disease)
   - Inadequate UDCA responder
     - ? Features of AIH
   - Individualized follow-up
     - According to symptom burden and disease stage
   - Monitoring based on
     - Bilirubin direct, ALP, AST, albumin, platelet count, and elastography

2. Stage and survey
   - Disease staging
     - Serum liver tests, US, elastography
   - Cirrhosis
     - ↑ bilirubin and/or decompensated disease
   - Refer to expert centre/transplant centre
   - HCC + varices screening

3. Manage actively
   - Symptom evaluation/active management
     - • Pruritus
     - • Fatigue
     - • Sicca complex
     - • Bone density
     - • Co-existent autoimmune disease
   - Actively manage as per guidelines
     - Offer information about patient support groups
   - Intractable symptoms
     - Refer to expert centre

Clinical audit standards
Reference network consultation

*E.g. Fibrates, budesonide
EASL CPG PBC. J Hepatol 2017;67:145–72
MANAGEMENT OF PBC LIVER DISEASE

- **Medical Options:**
  - Unsuccessful: penicillamine, cyclosporine, azathioprine, thalidomide, malotilate, chlorambucil
  - Questionable: steroids, Budesonide (2018*)
  - Useful: UDCA 1\textsuperscript{st} line, OCA 2\textsuperscript{nd} line, Fenofibrate 3\textsuperscript{rd} Line, Bezafibrate 3\textsuperscript{Rd} Line, Budesonide (2018*)
  - OCA 2\textsuperscript{nd} line
  - Fenofibrate 3\textsuperscript{rd} Line
  - Bezafibrate 3\textsuperscript{Rd} Line
TREATMENT OF PBC - URSODIOL

11 Randomized Trials

- various sizes of study > 1200 patients
- various doses
- various endpoints
- various duration (9 of 11 ≤ 2 years)
NATURAL HISTORY OF PBC
Effects of UDCA

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\textsuperscript{1-5}

UDCA is associated with:

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

CI, confidence interval; RR, relative risk.
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

<table>
<thead>
<tr>
<th>Binary definitions</th>
<th>Time (months)</th>
<th>Treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochester¹</td>
<td>6</td>
<td>ALP ≥2 ULN or Mayo score ≥4.5</td>
</tr>
<tr>
<td>Barcelona²</td>
<td>12</td>
<td>Decrease in ALP ≤40% and ALP ≥1x ULN</td>
</tr>
<tr>
<td>Paris-I³</td>
<td>12</td>
<td>ALP ≥3x ULN or AST ≥2x ULN or bilirubin &gt;1 mg/dl</td>
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<tr>
<td>Rotterdam⁴</td>
<td>12</td>
<td>Bilirubin ≥1x ULN and/or albumin &lt;1x ULN</td>
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<tr>
<td>Toronto⁵</td>
<td>24</td>
<td>ALP &gt;1.67x ULN</td>
</tr>
<tr>
<td>Paris-II⁶</td>
<td>12</td>
<td>ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin &gt;1 mg/dl</td>
</tr>
<tr>
<td>Ehime⁷</td>
<td>6</td>
<td>Decrease in GGT ≤70% and GGT ≥1 ULN</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Continuous scoring</th>
<th>Time (months)</th>
<th>Scoring parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK-PBC⁸</td>
<td>12</td>
<td>12 months: bilirubin, ALP and AST (or ALT); <strong>Baseline</strong>: albumin and platelets</td>
</tr>
<tr>
<td>GLOBE⁹</td>
<td>12</td>
<td>12 months: bilirubin, ALP, albumin, and platelet count; <strong>Baseline</strong>: age</td>
</tr>
</tbody>
</table>
Some Patients May Experience Side Effects of UDCA Treatment

<table>
<thead>
<tr>
<th>The most common reported side effects of UDCA include¹:</th>
</tr>
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<tbody>
<tr>
<td>• Abdominal discomfort</td>
</tr>
<tr>
<td>• Abdominal pain</td>
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<tr>
<td>• Alopecia</td>
</tr>
<tr>
<td>• Diarrhea</td>
</tr>
<tr>
<td>• Nausea</td>
</tr>
<tr>
<td>• Pruritus</td>
</tr>
<tr>
<td>• Rash</td>
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<tr>
<td>• Patients may also experience weight gain (~5 lbs) with UDCA within the first year of treatment²,³</td>
</tr>
</tbody>
</table>

- UDCA is contraindicated in patients with complete biliary obstruction and known hypersensitivity or intolerance to UDCA or any of the components of the formulation¹

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

<table>
<thead>
<tr>
<th>Recommendations*</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral UDCA:</strong> 13–15 mg/kg/day as the first-line pharmacotherapy for all patients with PBC. UDCA is usually continued for life</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td><strong>Oral OCA:</strong> biochemical efficacy in patients with ALP &gt;1.67x ULN and/or bilirubin elevated &lt;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)</td>
<td>I</td>
<td>2</td>
</tr>
<tr>
<td>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</td>
<td>II-2</td>
<td>2</td>
</tr>
</tbody>
</table>

*Statements 19–21
EASL CPG PBC. J Hepatol 2017;67:145–72
Obeticholic Acid

- Basic information
- What is new?
OCALIVA Delivered Significant, Sustained Reductions in ALP Beyond UDCA Alone

Patients taking OCALIVA had mean ALP reductions of >30% at 12 months vs 5% in patients taking UDCA alone.

- 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.

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.


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

Mean (SD) Change from Baseline in Total Bilirubin (µmol/L)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>17</td>
</tr>
<tr>
<td>OCA 5-10 mg</td>
<td>15</td>
</tr>
<tr>
<td>OCA 10 mg</td>
<td>14</td>
</tr>
<tr>
<td>OCA Combined</td>
<td>29</td>
</tr>
</tbody>
</table>

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

EASL 2018
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

ICP
PFIC/BRIC
HBV/HCV
Drugs
Hormones
Alcoholic hepatopathy

PBC

PSC
Cholangiocellular carcinoma
Hilar lymphadenopathy
Extrahepatic tumours/metastases
Biliary atresia

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
Lysophosphatidylcholine (LPC) → Autotaxin (ATX) → 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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ursodiol</td>
<td>15-30 mg/kg/day orally</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>4 gm, 3 to 4 times daily</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>50 mg by mouth daily</td>
</tr>
<tr>
<td>Rifampin</td>
<td>150 to 300 mg by mouth twice daily</td>
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</tbody>
</table>
SERTRALINE AS TREATMENT FOR CHOLESTATIC PRURITUS IN PBC PTS

SERTRALINE AS TREATMENT FOR CHOLESTATIC PRURITUS IN PBC PTS

FATIGUE

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

- Cause unknown
- Effect on prognosis
- UDCA not helpful
- Prozac
- Modafinil
FATIGUE IN PBC

IMPACT OF FATIGUE ON SURVIVAL IN PBC

SURVIVAL IN FATIGUED AND NON-FATIGUED PBC PATIENTS

Low fatigue controls

Low fatigue PBC pts

Transplant-Free Survival (%)

Follow-Up (Months)

$p < 0.05$

SURVIVAL IN FATIGUED AND NON-FATIGUED PBC PATIENTS

High fatigue controls

High fatigue PBC pts

$p = 0.005$

Follow-Up (Months)

MODAFANIL THERAPY FOR FATIGUE IN PBC PATIENTS

Jones DE, Newton JL. Aliment Pharmacol Ther 25:471-76
MODAFANIL IN PBC
(Epworth Sleepiness Scale)

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

<table>
<thead>
<tr>
<th>Recommendations*</th>
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</table>
| 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
Symptoms associated with PBC have a significant impact on QoL

### Management of symptoms

<table>
<thead>
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<tbody>
<tr>
<td><strong>Screening:</strong> 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</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>• First-line: cholestyramine as first-line therapy. Avoid interaction with other medications</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>• Second-line: rifampicin†</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seek and treat associated and alternate causes of fatigue</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>• Advise patients with fatigue on developing coping strategies</td>
<td>III</td>
<td>2</td>
</tr>
<tr>
<td><strong>Sicca complex:</strong> where appropriate consider expert referral</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td><strong>Miscellaneous:</strong> Refer patients with symptoms resistant to medical therapy for specialist management, regardless of disease severity</td>
<td>III</td>
<td>1</td>
</tr>
</tbody>
</table>

*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

<table>
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<th>Recommendations*</th>
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<th>Grade of recommendation</th>
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</thead>
<tbody>
<tr>
<td>Consider the <strong>risk of osteoporosis</strong> in all patients with PBC</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>To assess risk, consider use of <strong>DEXA</strong> to assess <strong>bone mineral density</strong> at presentation and at follow-up where Indicated</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>Supplement patients with PBC with <strong>calcium</strong> and <strong>vitamin D</strong>, according to local practice</td>
<td>III</td>
<td>2</td>
</tr>
<tr>
<td><strong>Bisphosphonates</strong> 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</td>
<td>II-2</td>
<td>1</td>
</tr>
</tbody>
</table>

*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**

  Fat-soluble vitamin malabsorption: Can occur in PBC, particularly with prolonged jaundice. Supplementation should be considered on an individual basis

<table>
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<tr>
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<tr>
<td>Fat-soluble vitamin malabsorption: Can occur in PBC, particularly with prolonged jaundice. Supplementation should be considered on an individual basis</td>
<td>III</td>
<td>2</td>
</tr>
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</table>

- 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

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<thead>
<tr>
<th>Recommendations†</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>III</td>
<td>2</td>
</tr>
</tbody>
</table>

*Statement 38; †Statement 39
EASL CPG PBC. J Hepatol 2017;67:145–72
Hyperlipidemia Is Common Among Patients With PBC\textsuperscript{1}

- As a result of cholestasis, hyperlipidemia is common in PBC, affecting 75\%-95\% of patients\textsuperscript{1}
- In early disease, elevated very low–density lipoprotein and LDL-C concentrations are reported, as well as significantly elevated HDL-C values\textsuperscript{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\textsuperscript{2,3}

<table>
<thead>
<tr>
<th>AASLD Guideline Recommendations\textsuperscript{3}</th>
<th>EASL Guideline Recommendations\textsuperscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>• UDCA will lower LDL-C levels and is the initial step</td>
<td>• 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</td>
</tr>
<tr>
<td>• 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</td>
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Management of complications of liver disease

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

<table>
<thead>
<tr>
<th>Recommendations*</th>
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<th>Grade of recommendation</th>
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</thead>
<tbody>
<tr>
<td>Varices: Baveno-VI guidelines for screening and management of varices apply equally to patients with PBC</td>
<td>III</td>
<td>2</td>
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</table>

- 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

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<thead>
<tr>
<th>Recommendations†</th>
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<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular carcinoma: In patients with suspected cirrhosis, HCC surveillance according to EASL guidelines is indicated</td>
<td>III</td>
<td>2</td>
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</tbody>
</table>

*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**

<table>
<thead>
<tr>
<th>Liver transplantation</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consider patients</strong></td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td><strong>for transplant</strong></td>
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<td></td>
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<tr>
<td><strong>assessment</strong></td>
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<tr>
<td><strong>when presenting</strong></td>
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<td></td>
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<tr>
<td><strong>with complications</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>of cirrhosis, markers</strong></td>
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<tr>
<td><strong>of disease severity</strong></td>
<td>[e.g. persistent elevated bilirubin values [50 μmol/l or 3 mg/dl] or MELD &gt;15], or severe medically resistant pruritus. Follow local (usually national) guidelines]</td>
<td></td>
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<tr>
<td><strong>In patients with</strong></td>
<td>II-2</td>
<td>2</td>
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<tr>
<td><strong>proven or likely</strong></td>
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<tr>
<td><strong>recurrent PBC</strong></td>
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<tr>
<td><strong>post-liver transplant, use of UDCA is safe and can improve liver biochemistry</strong></td>
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</tbody>
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*Statements 42, 43
EASL CPG PBC. J Hepatol 2017;67:145–72
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

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

*Statements 44–47
EASL CPG PBC. J Hepatol 2017;67:145–72
## Proposed clinical care standards for PBC

<table>
<thead>
<tr>
<th>Standard</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Exclude alternate aetiologies for cholestasis:</strong></td>
<td>Undertake abdominal US in all patients with suspected PBC as part of baseline assessment</td>
</tr>
<tr>
<td><strong>1st line treatment:</strong></td>
<td>UDCA at 13–15 mg/kg/day in all patients with PBC</td>
</tr>
<tr>
<td><strong>Identify patients at risk of progressive disease:</strong></td>
<td>Document risk using biochemical response indices after 1 year of UDCA therapy</td>
</tr>
<tr>
<td><strong>Recognize impact on QoL:</strong></td>
<td>Ensure appropriate investigation and treatment of symptoms (particularly pruritus, sicca complex, fatigue)</td>
</tr>
<tr>
<td><strong>Maximise opportunity for timely LTx:</strong></td>
<td>Discuss all established patients with bilirubin &gt;50 μmol/L (3 mg/dl) or evidence of decompensated liver disease* with a hepatologist linked to a transplant programme</td>
</tr>
<tr>
<td><strong>Optimize prevention of osteoporotic bone fractures:</strong></td>
<td>Assess risk of osteoporosis in all patients. Treat/follow-up in line with national guidelines</td>
</tr>
<tr>
<td><strong>Diagnose and treat of PBC with features of AIH promptly:</strong></td>
<td>Recognize as rare and when suspected, perform liver biopsy with expert clinicopathological assessment</td>
</tr>
</tbody>
</table>

*Variceal bleed, ascites, encephalopathy
EASL CPG PBC. J Hepatol 2017;67:145–72
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