Chronic Cholestatic Liver Diseases
- EASL Clinical Practice Guidelines -

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EASL Clinical Practice Guidelines: Management of cholestatic liver diseases

European Association for the Study of the Liver*

Chronic Cholestatic Liver Diseases

EASL Clinical Practice Guidelines

- Diagnostic approach
- Therapeutic options
Diagnostic Approach to the Cholestatic Patient

Diagnostic Algorithm

1. AP i. S. → \( \gamma \text{GT or conj. Bilirubin i. S.} \) → History*, physical examination, ultrasound

* Drugs, herbal medicine, other exposure to potential toxins?
Diagnostic Approach to the Cholestatic Patient

Diagnostic Algorithm

1. History*, physical examination, ultrasound

2. AP i. S. → γGT or conj. Bilirubin i. S.

3. Dilated bile ducts
   - Bile duct stones
   - Focal liver lesion(s)
   - others

Strongly suggested diagnosis

f, 32 yrs

f, 44 yrs

Specific investigations

Diagnosis
Diagnostic Approach to the Cholestatic Patient

Diagnostic Algorithm

1. History*, physical examination, ultrasound

- Dilated bile ducts
- Bile duct stones
- Focal liver lesion(s)
- others

Strongly suggested diagnosis

Specific investigations

Differentiation of hepatocellular adenoma and focal nodular hyperplasia using $^{18}$F-fluorocholine PET/CT

Jacomina W. van den Esschert, Matthanja Bieze, Ulrich H. Beuers, Thomas M. van Gulik, Roelof J. Bennink
Eur J Nucl Med Mol Imaging 2010;epub ahead of print
Dilated bile ducts
Bile duct stones
Focal liver lesion(s)

Strongly suggested diagnosis

Diagnostic Approach to the Cholestatic Patient
Diagnostic Algorithm

AP i. S. → γGT or conj. Bilirubin i. S. →

History*, physical examination, ultrasound → Normal

AMA, ANA (IgM, ACE) →

AMA a/o PBC-specific ANA* pos. →

Strongly suggested diagnosis

• Dilated bile ducts
• Bile duct stones
• Focal liver lesion(s)
• others

Specific investigations

* multiple (6-12) nuclear dots (anti-Sp100); perinuclear rim (anti-gp210)

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
Diagnostic Approach to the Cholestatic Patient

Diagnostic Algorithm

1. History*, physical examination, ultrasound (US)
   - normal

2. AMA, ANA
   - negative, no drug history

3. Liver biopsy
   - negative

4. MRCP

Strongly suggested diagnosis
   - specific investigations

AP i. S. ↑
γGT or conj. Bilirubin i. S. ↑

Diagnosis

- Dilated bile ducts
- Bile duct stones
- Focal liver lesion(s)
- others

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
Diagnostic Approach to the Cholestatic Patient

Diagnosis

1. **AP i. S.**
2. **γGT or conj. Bilirubin i. S.**
3. **History*, physical examination, ultrasound (US)**
   - negative
4. **AMA, ANA**
   - negative, no drug history
5. **Liver biopsy**
   - negative
6. **MRCP + endoscopic US**
   - negative
7. **Observe, back to 1**
8. **ERCP**
   - negative, but clinical suspicion of sclerosing cholangitis
9. **Strongly suggested diagnosis**
10. **Diagnosis**

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
Diagnostic Approach to the Cholestatic Patient

**Diagnostic Algorithm**

1. **AP i. S.**
2. **γGT or conj. Bilirubin i. S.**
3. **History*, physical examination, ultrasound (US)**
   - normal
4. **AMA, ANA**
   - negative, no drug history
5. **Liver biopsy**
   - negative
6. **MRCP + endoscopic US**
   - normal, but clinical suspicion of sclerosing cholangitis
7. **ERCP**

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**19 yrs, m**

- AP: 196 U/L
- γGT: 262 U/L
- ALT: 121 U/L
- AST: 58 U/L
- atyp. pANCA +

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EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
The Patient with Sclerosing Cholangitis

Diagnostic Algorithm

Sclerosing Cholangitis

History, additional diagnostic procedures:
Causes of secondary sclerosing cholangitis?

- Bile duct surgery
- Abdominal trauma
- Choledocholithiasis *
- Cholangiocarcinoma *
- Recurrent pancreatitis
- Ischemic cholangitis
- Eosinophilic cholangitis
- Mastcell cholangiopathy
- AIDS cholangiopathy
- Recurrent pyogenic cholangitis
- Portal hypertensive biliopathy
- IgG4-assoc. cholangitis (IAC)
- ABCB4 Deficiency
- others

Secondary sclerosing cholangitis

* may be consequence of PSC

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
The Patient with Sclerosing Cholangitis

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Secondary sclerosing cholangitis

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EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
Diagnosis of IgG4-associated Cholangitis
- HISORt Criteria -

Biliary strictures: intrahepatic, proximal and/or distal extrahepatic

A

Previous pancreatic / biliary resection or core biopsy of pancreas showing diagnostic features of AIP / IAC

Definite IAC

76 yrs, m; IgG4 12.5 g/L (n < 1.4)
Alderlieste et al., Digestion 2009;79:220

Ghazale et al., Gastroenterology 2008;134:706
EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
Diagnosis of IgG4-associated Cholangitis
- HISORt Criteria -

**Biliary strictures**: intrahepatic, proximal and/or distal extrahepatic

A

Previous pancreatic / biliary resection or core biopsy of pancreas showing diagnostic features of AIP / IAC

B

Classical imaging findings of AIP + Elevated serum IgG4

Definite IAC

71 yrs, m; IgG4 11.9 g/L (n < 1.4)
Alderlieste et al., Digestion 2009;79:220

Ghazale et al., Gastroenterology 2008;134:706
EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
Diagnosis of IgG4-associated Cholangitis

Biliary strictures: intrahepatic, proximal and/or distal extrahepatic

A

Previous pancreatic / biliary resection or core biopsy of pancreas showing diagnostic features of AIP / IAC

B

Classical imaging findings of AIP
• Elevated serum IgG4

C

Two or more of the following:
• Elevated serum IgG4
• Suggestive pancreatic imaging
• Other organ involvement
• Bile duct biopsy with > 10 IgG4-positive cells/HPF

Probable IAC

After 4 weeks of corticosteroids:
• Markedly improved biliary strictures
• Serum liver tests < 2 x ULN
• Decreasing IgG4 and CA19.9

Definite IAC

Ghazale et al., Gastroenterology 2008;134:706
EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
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Sclerosing Cholangitis

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- IgG4-assoc. cholangitis (IAC)
- ABCB4 deficiency
- others

Secondary sclerosing cholangitis

* may be consequence of PSC

Gotthardt et al. Hepatology 2008;48:1157
Denk et al. Hepatol Res 2010;40:937

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
The Patient with Sclerosing Cholangitis

Diagnostic Algorithm

Sclerosing Cholangitis

History, additional diagnostic procedures:
Causes of secondary sclerosing cholangitis?

no

Primary sclerosing cholangitis

yes

Secondary sclerosing cholangitis

- Bile duct surgery
- Abdominal trauma
- Choledocholithiasis *
- Cholangiocarcinoma *
- Recurrent pancreatitis
- Ischemic cholangitis
- Eosinophilic cholangitis
- Mastcel cholangiopathy
- AIDS cholangiopathy
- Recurrent pyogenic cholangitis
- Portal hypertensive biliopathy
- IgG4-assoc. cholangitis (IAC)
- ABCB4 deficiency
- others

* may be consequence of PSC

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
Screening in PSC

- There are at present no biochemical marker or imaging modality which can be recommended for early detection of cholangiocarcinoma. **ERCP with brush cytology (and/or biopsy) sampling should be carried out when clinically indicated (III/C2).**

---

- **III**: Opinion of respected authorities
- **C2**: Weak evidence - strong/weak recommendation (GRADE)
Screening in PSC

• There are at present no biochemical marker or imaging modality which can be recommended for early detection of cholangiocarcinoma. ERCP with brush cytology (and/or biopsy) sampling should be carried out when clinically indicated (III/C2).

• Annual **abdominal ultrasonography** should be considered for gallbladder abnormalities (III/C2).

**III** : Opinion of respected authorities  
**C1/2** : Weak evidence - strong/weak recommendation (GRADE)
Screening in PSC

- There are at present no biochemical marker or imaging modality which can be recommended for early detection of cholangiocarcinoma. **ERCP with brush cytology (and/or biopsy) sampling** should be carried out when clinically indicated (III/C2).

- Annual **abdominal ultrasonography** should be considered for gallbladder abnormalities (III/C2).

- **Total colonoscopy** with biopsies should be performed in patients in whom the diagnosis of PSC has been established without known IBD (III/C1) and should be repeated annually (or every 1-2 years in individualized patients) in PSC patients with colitis from the time of diagnosis of PSC (III/C1).

- III : Opinion of respected authorities
- C1/2 : Weak evidence - strong/weak recommendation (GRADE)
Chronic Cholestatic Liver Diseases
EASL Clinical Practice Guidelines

- Diagnostic approach
- Therapeutic options
Primary Biliary Cirrhosis: Pathogenesis

- Immune-mediated bile duct injury
- Aggravation of bile duct injury by hydrophobic bile acids
- Cholestasis with retention of hydrophobic bile acids in liver
- Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis
- Liver failure

Ursodeoxycholic acid
(13-15 mg/kg/d)

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
Potential Mechanisms and Sites of Action of UDCA in Cholestatic Liver Diseases

- UDCA
  - Stimulation of hepatocellular secretion
  - Stimulation of cholangiocellular secretion
- Cholestasis
  - Bile acids
  - Apoptosis
  - Necrosis
- Bile
  - Reduction of bile toxicity
- Antiapoptotic effects

Aggravation of bile duct injury by hydrophobic bile acids

Cholestasis with retention of hydrophobic bile acids in liver

Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis

Liver failure

Primary Biliary Cirrhosis: Future Therapy

Pathogenesis

Immunologic bile duct injury

↓

Aggravation of bile duct injury by hydrophobic bile acids

↓

Cholestasis with retention of hydrophobic bile acids in liver

↓

Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis

↓

Liver failure

Ursodeoxycholic acid

Nuclear receptor agonists?
- FXR agonists?
- PPARα agonists?

Budesonide?

Other immunosuppressive agents?

RCT

Liver transplantation
Primary Sclerosing Cholangitis

Pathogenetic model

Immunologic bile duct injury (Cytokine-mediated)

↓

Bile duct stenoses
Aggravation of injury by BA

↓

Cholestasis with retention of hydrophobic bile acids in liver

↓

Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis

↓

Liver failure
Bile duct stenoses
Aggravation of injury by BA
Cholestasis with retention of hydrophobic bile acids in liver
Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis
Liver failure

Pathogenetic model

Immunologic bile duct injury (Cytokine-mediated)

\[ \text{Ursodeoxycholic acid} \]
(15-20 mg/kg/d)

?
## Treatment of Primary Sclerosing Cholangitis with UDCA

- **Placebo-controlled studies** -

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Dose [mg/kg/d]</strong></td>
<td>13-15 (n=14)</td>
<td>13-15 (n=105)</td>
<td>20 (n=24)</td>
<td>17-23 (n=219)</td>
<td>28-30 (n=150)</td>
</tr>
<tr>
<td><strong>Duration [years]</strong></td>
<td>1</td>
<td>2.2</td>
<td>2</td>
<td>5</td>
<td>5</td>
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<tr>
<td><strong>Symptoms</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Serum liver tests</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>+</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Beuers et al., Hepatology 1992;16:707  
Lindor et al., New Engl J Med 1997;336:691  
Mitchell et al., Gastroenterology 2001;121:900  
Olsson et al. Gastroenterology 2005;129:1464  
Lindor et al., Hepatology 2009;50:1
Treatment of Primary Sclerosing Cholangitis with UDCA
- Transplant-free survival -

Survival without liver transplantation

Power analysis *a priori*: n = 346

UDCA (n=97)

Placebo (n=101)

\[ p = 0.37 \]
## Treatment of Primary Sclerosing Cholangitis with UDCA

Double blind, randomized, placebo-controlled trial

- High dose UDCA (30 mg/kg/d) for 5 years -

<table>
<thead>
<tr>
<th>Primary Endpoints</th>
<th>UDCA</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Death</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Minimal listing criteria for liver transplantation</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Development of cirrhosis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Esophageal and/or gastric varices</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total endpoints</strong></td>
<td><strong>52</strong></td>
<td><strong>29</strong></td>
</tr>
<tr>
<td>Number of patients reaching a primary endpoint</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Number of patients reaching death, orthotopic liver</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>transplantation, minimal criteria listing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lindor et al., Hepatology 2009;50:1  
n=150
Treatment of Primary Sclerosing Cholangitis with UDCA
Double blind, randomized, placebo-controlled trial
- High dose UDCA (30 mg/kg/d) for 5 years -

Patient population:

41.3% (62)    Advanced liver fibrosis / cirrhosis
58.7% (88)    Mild/no liver fibrosis
Treatment of PSC
EASL Clinical Practice Guidelines

The available data base shows that UDCA (15-20 mg/kg/d) improves serum liver tests and surrogate markers of prognosis (I/B1), but does not reveal a proven benefit on survival (III/C2). The limited data base does not yet allow a specific recommendation for the general use of UDCA in PSC.

- I: Randomized, placebo-controlled trials, meta-analyses
- III: Opinion of respected authorities
- B1: Moderate evidence – strong recommendation (GRADE)
- C2: Weak evidence - weak recommendation (GRADE)
In adult patients with PSC, we recommend against the use of UDCA as medical therapy (IA).

IA : Strong recommendation – strong evidence

Chapman et al., AASLD PG PSC. Hepatology 2010;51:660
Bile duct stenoses
Aggravation of injury by BA
Cholestasis with retention of hydrophobic bile acids in liver
Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis
Liver failure

PSC: Pathogenetic model

Immunologic bile duct injury (Cytokine-mediated)
Bile duct stenoses
Aggravation of injury by BA
Cholestasis with retention of hydrophobic bile acids in liver
Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis
Liver failure

Therapy
Endoscopic dilatation
Ursodeoxycholic acid (15-20 mg/kg/d)
Liver transplantation
Bile duct stenoses
Aggravation of injury by BA

Cholestasis with retention of hydrophobic bile acids in liver

Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis

Liver failure

Future Therapy

Pathogenetic model

Immunologic bile duct injury (Cytokine-mediated)

Endoscopic dilatation

Ursodeoxycholic acid (15-20 mg/kg/d)

Liver transplantation

norUDCA ?

Nuclear receptor agonists ?
- PPARα agonists ?
- PXR agonists ?

Liver transplantation
Extrahepatic Manifestations of PBC and PSC

(> 50% asymptomatic at diagnosis)

- Fatigue
- Pruritus
- others

Sherlock and Summerfield, 1979
## Pruritus of Cholestasis

### Therapy 2010

<table>
<thead>
<tr>
<th>Line</th>
<th>Therapy</th>
</tr>
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<tbody>
<tr>
<td>1st line</td>
<td>Cholestyramine (1-2 x 4 g/d, max. 16 g/d)</td>
</tr>
<tr>
<td>2nd line</td>
<td>Rifampicin (2 x 150 – 300 mg/d)</td>
</tr>
<tr>
<td>3rd line</td>
<td>Naltrexone (25 - 50 mg/d)</td>
</tr>
<tr>
<td>4th line</td>
<td>Sertraline (75 - 100 mg/d)</td>
</tr>
</tbody>
</table>

### Experimental
- Cannabinoids
- Ondansetron
- Albumin dialysis; plasma separation / anion absorption
- Nasobiliary drainage
- Liver transplantation

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
Identification of a Neural Activator in Serum of Pruritic Patients

Molecular weight < 3 kD
- no peptide

Proteinase K

Pertussis toxine
- G-protein coupled receptor
- amphiphilic; after protonation: hydrophobicity ↑

filter

Bligh & Dyer

LPA (= lysophosphatidic acid)

Kremer et al. Gastroenterology 2010;139:1008
Autotaxin Activity in Cholestatic Patients vs Controls

\[ r = 0.7764 \]

\[ p < 0.0001 \]
## Therapeutic Options in Cholestatic Liver Diseases

<table>
<thead>
<tr>
<th></th>
<th><strong>EASL CP Guidelines</strong></th>
<th>Future therapies ?</th>
</tr>
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<tbody>
<tr>
<td><strong>PBC</strong></td>
<td>UDCA (13-15 mg/kg/d)</td>
<td>PPARα agonist ?</td>
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<tr>
<td></td>
<td>LTx</td>
<td>FXR agonist ?</td>
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<td></td>
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<td>GR/PXR agonist ?</td>
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<tr>
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<td><strong>PBC / AIH</strong></td>
<td>UDCA + Azathiothrine / Corticosteroids</td>
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<tr>
<td><strong>IAC</strong></td>
<td>Corticosteroids / Azathiothrine</td>
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<tr>
<td><strong>ICP</strong></td>
<td>UDCA (10-15 mg/kg/d)</td>
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<tr>
<td><strong>Pruritus</strong></td>
<td>Cholestyramine</td>
<td>Autotaxin inhibitors ?</td>
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