Approach to the cholestatic patient

Tom Hemming Karlsen
Oslo University Hospital, Norway
ASSA SAGES, August 8th, 2015

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The cholestatic patient?

- Primary biliary cirrhosis (PBC)
- Primary sclerosing cholangitis (PSC)
- Biliary atresia
- Hereditary cholestasis
- Intrahepatic cholestasis of pregnancy
- Gallstone disease
- Polycystic liver disease
- Drug-induced liver disease

Manifestation:
- Cholestatic liver disease
- Other liver affection (e.g. hepatitis)

Consequence:
- Liver cirrhosis
- Hepatocellular cancer
- Bile duct cancer
- Pruritus
- Fatigue
- Osteoporosis

Karlsen et al., 2013
“The commonest indications for hepatic transplantation in adults included cryptogenic cirrhosis, auto-immune hepatitis and primary sclerosing cholangitis. In children **biliary atresia** was the commonest cause of liver failure.” (Groote Schuur Hospital first 10 year report, 2000)
Defects of bile formation

Trauner et al., 1998
The EASL CPG summary

[Diagram showing a flowchart with steps and decision points related to liver conditions and diagnostic procedures.]

www.easl.eu
The scientist approach
Etiological considerations

Bull et al. 1998 (PFIC1)

Strautnieks et al. 1998 (PFIC2)

Sambrotta et al. 2014 (PFIC4)

De Vree et al. 1998 (PFIC3)

Paulusma et al. 1997 (Dubin Johnson)

Karlsen et al. 2015
Etiiological considerations

A. Primary sclerosing cholangitis

B. Crohn’s disease

C. Type 1 diabetes

D. Celiac disease

Karlsen et al. 2015
Etiological considerations

Primary biliary cirrhosis

Primary sclerosing cholangitis

Autoimmune hepatitis

Liu et al. 2012, 2013
DeBoer, 2014
Is genetics the right approach?

Franke et al. 2010
Henriksen et al. 2014
Drug induced liver injury (DILI)

Flucloxacillin

Lumiracoxib

Amoxicillin-clavulunate

https://www.genome.gov/26525384
Etiological considerations

- Genetic diseases
- Complex diseases

Genetic risk fraction

Environmental risk fraction

Genetic testing useful

Genetic testing not useful

Overall disease liability

Karlsen et al. 2015
The clinician approach

EASL Clinical Practice Guidelines: Management of cholestatic liver diseases
European Association for the Study of the Liver

1. Introduction

EASL Clinical Practice Guidelines (CPG) on the management of cholestatic liver diseases define the use of diagnostic, therapeutic and preventive modalities, including non-invasive and invasive procedures, in the management of patients with cholestatic liver diseases. They are intended to assist physicians and other healthcare providers as well as patients and interested individuals in the clinical decision-making process by describing a range of generally accepted approaches for the diagnosis, treatment and prevention of specific cholestatic liver diseases. The clinical care for patients with cholestatic liver diseases has advanced considerably during recent decades thanks to growing insight into pathophysiological mechanisms and remarkable methodological and technical developments in diagnostic procedures as well as therapeutic and preventive approaches. Still, various aspects in the care of patients with cholestatic disorders remain incompletely resolved. The EASL CPG on the management of cholestatic liver diseases aim to provide current recommendations on the following issues:

- Diagnostic approach to the cholestatic patient.
- Diagnosis and treatment of primary biliary cirrhosis (PBC).
- Diagnosis and treatment of PBC–autoimmune hepatitis (AIH) overlap syndrome.
- Diagnosis and treatment of primary sclerosing cholangitis (PSC).
- Diagnosis and treatment of PSC–AIH overlap syndrome.
- Diagnosis and treatment of immunoglobulin G4-associated cholangitis (IAC).


www.easl.eu
The clinician approach
PSC and PBC

<table>
<thead>
<tr>
<th>PBC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interlobular bile duct destruction</td>
<td>Intra-extrahepatic bile ducts</td>
</tr>
<tr>
<td>Prevalence: 0.6–40 per 100,000</td>
<td>Prevalence: 0.2–14 per 100,000</td>
</tr>
<tr>
<td>Gender: F&gt;M, 10:1</td>
<td>Gender F&lt;M, 1:2</td>
</tr>
<tr>
<td>Age at onset: 50–60 years</td>
<td>Age at onset: 30–40 years</td>
</tr>
<tr>
<td>Smoking increases risk</td>
<td>Smoking decreases risk</td>
</tr>
<tr>
<td>&gt;28 known risk genes</td>
<td>&gt;16 known risk genes</td>
</tr>
<tr>
<td>Autoantibodies (AMA)</td>
<td>Autoantibodies (ANCA?)</td>
</tr>
<tr>
<td>Known T cell targets</td>
<td>Unknown T cell targets</td>
</tr>
</tbody>
</table>

Shared hepatic features:
- Autoimmune hepatitis (~10%)
- Cholestatic liver cirrhosis
- Pruritus
- Fatigue
- Cancer
- Inflammatory bowel disease

Karlsen et al. 2013
Approaching PBC

- Diagnosis of PBC (AASLD/EASL):
  - ALP ↑
  - AMA ↑ (90-95%)
  - Biopsy (AMA negative patients, features of AIH)

- “AMA negative PBC”:
  - No genetic correlates (but underpowered)
  - Slightly different cellular composition of histological lesions
  - Other mitochondrial epitopes?
  - Mostly similar clinical behavior and UDCA response
  - Differential diagnosis: genetic cholangiopathies, SD-PSC
Approaching PSC
Diagnostic challenges in PSC

- MRC>ERC (AASLD/EASL)
- Secondary/etiologies?
- IgG4 – cut-off level?
- Autoimmune hepatitis?
- Small-duct PSC?
- IBD?
- Malignancies?
T1 (and T2) algorithms and contrast-enhancement

Banjaree et al. 2014
Diagnostic challenges in PSC

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- IgG4 – cut-off level?
- Autoimmune hepatitis?
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- Malignancies?
### SSC vs. PSC

#### Infection
- Bacterial/parasitic cholangitis
- Recurrent pyogenic cholangitis

#### Immunodeficiency related (infections)
- Congenital immunodeficiency
- Acquired immunodeficiency (e.g. HIV)
- Combined immunodeficiencies
- Angiimmune lymphadenopathy

#### Mechanic/toxic
- Cholelithiasis/choledocholithiasis
- Surgical bile duct trauma
- Intra-arterial chemotherapy

#### Ischaemic
- Vascular trauma
- Hepatic allograft arterial insufficiency
- Paroxysmal nocturnal haemoglobinuria

#### Pancreatic disease
- Chronic pancreatitis
- IgG4 related systemic disease

#### Others
- Cystic fibrosis cholangiopathy
- ABO84 associated cholangiopathy
- Sclerosing cholangitis of critical illness
- Hyperesinophilic syndrome
- Sarcoidosis
- Graft-versus-host disease
- Amyloidosis
- Systemic mastocytosis
- Caroff’s disease
- Congenital hepatic fibrosis
- Other types of ductal plate abnormalities
- Hodgkin’s disease
- Cholangitis glandularis proliferans
- Neoplastic/metastatic disease
- Langerhans cell histiocytosis
- Hepatic allograft rejection
## Cholestasis in HIV

<table>
<thead>
<tr>
<th>Finding</th>
<th>Frequency, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-induced liver injuries</td>
<td>127 (42.2)</td>
</tr>
<tr>
<td>Nonspecific hepatitis</td>
<td>51 (40.2)</td>
</tr>
<tr>
<td><strong>Cholestasis</strong></td>
<td><strong>20 (15.7)</strong></td>
</tr>
<tr>
<td>Mixed hepatitis-cholestasis</td>
<td>25 (19.7)</td>
</tr>
<tr>
<td>Submassive necrosis</td>
<td>13 (10.2)</td>
</tr>
<tr>
<td>Ductopenia/vanishing bile duct</td>
<td>11 (8.6)</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Granulomatous (drug-related)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Granulomatous inflammation</td>
<td>86 (29)</td>
</tr>
<tr>
<td>Necrotizing/nonnecrotizing</td>
<td>7 (8%) / 79 (92%)</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>61 (71%)</td>
</tr>
<tr>
<td><em>Mycobacterium avium complex</em></td>
<td>3 (3.5%)</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Drug</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>TB-IRIS-related</td>
<td>45 (52.3%)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>56 (19%)</td>
</tr>
<tr>
<td>Steatosis/steatohepatitis</td>
<td>58 (19.3%)</td>
</tr>
<tr>
<td>Steatosis</td>
<td>42 (72.4%)</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>16 (27.6%)</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>16 (5.3%)</td>
</tr>
<tr>
<td>Hepatitis C (PCR-positive)</td>
<td>10 (3.3%)</td>
</tr>
<tr>
<td>Siderosis &gt; grade 1 (50)</td>
<td>24 (8.0%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7 (2.3%)</td>
</tr>
<tr>
<td>High-grade B cell/Hodgkin's lymphoma</td>
<td>6 (8%) / 1 (1.4%)</td>
</tr>
<tr>
<td><strong>HIV/AIDS cholangiopathy</strong></td>
<td><strong>7 (2.3%)</strong></td>
</tr>
<tr>
<td>Drug-related/adaptive changes</td>
<td>7 (2.3%)</td>
</tr>
<tr>
<td>Indeterminate findings</td>
<td>5 (1.6%)</td>
</tr>
<tr>
<td>More than one pathological finding</td>
<td>49 (16.2%)</td>
</tr>
</tbody>
</table>

Sonderup et al., 2015
Diagnostic challenges in PSC

- MRC>ERC (AASLD/EASL)
- Secondary/etiologies?
- IgG4 – cut-off level?
- Autoimmune hepatitis?
- Small-duct PSC?
- IBD?
- Malignancies?
IgG4 associated sclerosing cholangitis

Culver, courtesy sharing
Mendes et al., 2008
IgG4 associated sclerosing cholangitis

Type 1: autoimmune pancreatitis

- Clinical suspicion of pancreatic disease
- Absence of classical imaging for AIP
- Negative work-up for cancer
  
  One of the following:
  - Serum IgG4 > 2 x ULN
  - (Histologically) proven other ISD-spectrum organ involvement
  - Two of the following:
    - Elevated serum IgG4
    - Clinical/radiological evidence for other organ involvement
    - Compatible FNA histology

  Response to 2 weeks of adequate steroid treatment:
  - Significant decrease in serum IgG4
  - Markedly improved morphology as objectivated by imaging (CT, ultrasound, MRCP)

Definite diagnosis of AIP

IgG4-associated cholangitis

- Stricture(s) of intrahepatic, proximal extrahepatic or intrapancreatic ducts, with:
  
  Classical imaging findings of AIP and elevated serum IgG4

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

  Combined with following findings after 4 weeks of adequate steroid treatment:
  - Markedly improved biliary strictures allowing stent removal
  - Liver enzymes <2 x ULN
  - Significant decrease in serum IgG4 and CA19.9

Definite diagnosis of IAC

In all cases of non-response to adequate steroid treatment:
- Withdraw steroids!
- Reconsider presence of malignant disease
Diagnostic challenges in PSC

- MRC>ERC (AASLD/EASL)
- Secondary/etiologies?
- IgG4 – cut-off level?
- Autoimmune hepatitis?
- Small-duct PSC?
- IBD?
- Malignancies?
Overlap syndromes?

- IAIHG position paper (2010): diagnose each entity, not «overlap»
- Features of AIH in PBC and PSC diagnosed by ALT/IgG/biopsy
- Controversy as to the utility of the IAIHG scoring system
- Treatment response for AIH features - assessment/side effects
Diagnostic challenges in PSC

- MRC>ERC (AASLD/EASL)
- Secondary/etiologies?
- IgG4 – cut-off level?
- Autoimmune hepatitis?
- Small-duct PSC?
- IBD?
- Malignancies?
Small-duct PSC

- Patients with a cholestatic biochemical profile not otherwise explained
- Normal good quality cholangiogram
- Liver biopsy showing features of PSC:
  - Patients without IBD should have typical changes suggestive of PSC
  - Patients with concomitant IBD should have histology at least compatible with PSC

<table>
<thead>
<tr>
<th>HLA-A†</th>
<th>Large duct PSC (n = 485), Freq</th>
<th>Small duct PSC (n = 87), Freq</th>
<th>Small duct PSC with IBD (n = 53), Freq</th>
<th>Small duct PSC without IBD (n = 29), Freq</th>
<th>Controls (n = 1117), Freq</th>
<th>Large duct PSC controls, OR (95%CI)</th>
<th>Large duct PSC vs. small duct PSC, OR (95%CI)</th>
<th>Large duct PSC vs. small duct PSC with IBD, OR (95%CI)</th>
<th>Large duct PSC vs. small duct PSC without IBD, OR (95%CI)</th>
<th>Large duct PSC with IBD vs. small duct PSC without IBD, OR (95%CI)</th>
<th>Small duct PSC with IBD vs. small duct PSC without IBD, OR (95%CI)</th>
<th>Small duct PSC with IBD vs. small duct PSC, OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30%</td>
<td>19%</td>
<td>21%</td>
<td>18%</td>
<td>17%</td>
<td>2.1 (1.7–2.5)</td>
<td>1.8 (1.2–2.7)</td>
<td>1.6 (1.0–2.6)</td>
<td>1.8 (0.9–3.7)</td>
<td>1.3 (0.8–2.0)</td>
<td>1.1 (0.5–2.2)</td>
<td>1.2 (0.5–3.0)</td>
</tr>
<tr>
<td>8</td>
<td>33%</td>
<td>20%</td>
<td>26%</td>
<td>5%</td>
<td>13%</td>
<td>3.3 (2.6–4.0)</td>
<td>1.9 (1.3–2.9)</td>
<td>1.4 (0.9–2.2)</td>
<td>6.8 (2.3–20.5)</td>
<td>2.4 (1.5–3.7)</td>
<td>0.4 (0.1–1.3)*</td>
<td>5.7 (1.7–19.2)*</td>
</tr>
<tr>
<td>07</td>
<td>50%</td>
<td>40%</td>
<td>46%</td>
<td>25%</td>
<td>34%</td>
<td>1.8 (1.5–2.2)</td>
<td>1.4 (1.0–1.9)</td>
<td>1.1 (0.7–1.7)</td>
<td>2.6 (1.4–5.0)</td>
<td>1.6 (1.1–2.4)</td>
<td>0.7 (0.4–1.2)</td>
<td>2.4 (1.2–5.1)</td>
</tr>
<tr>
<td>03</td>
<td>34%</td>
<td>18%</td>
<td>25%</td>
<td>4%</td>
<td>14%</td>
<td>2.9 (2.4–3.6)</td>
<td>2.2 (1.4–3.3)</td>
<td>1.5 (0.9–2.4)</td>
<td>9.6 (2.7–34.3)</td>
<td>1.9 (1.2–3.1)</td>
<td>0.3 (0.1–1.0)*</td>
<td>7.3 (1.8–29.2)*</td>
</tr>
<tr>
<td>04</td>
<td>8%</td>
<td>15%</td>
<td>11%</td>
<td>22%</td>
<td>19%</td>
<td>0.4 (0.2–0.9)†</td>
<td>0.6 (0.3–0.9)</td>
<td>0.9 (0.4–1.7)</td>
<td>0.4 (0.2–0.8)</td>
<td>0.5 (0.2–0.9)</td>
<td>1.2 (0.6–2.3)</td>
<td>0.4 (0.2–1.0)</td>
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<tr>
<td>07</td>
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<td>9%</td>
<td>16%</td>
<td>13%</td>
<td>0.4 (0.3–0.6)</td>
<td>0.4 (0.3–0.8)</td>
<td>0.6 (0.3–1.2)</td>
<td>0.3 (0.1–1.0)</td>
<td>0.8 (0.4–1.6)</td>
<td>1.4 (0.7–2.9)</td>
<td>0.5 (0.2–1.4)</td>
</tr>
<tr>
<td>11</td>
<td>3%</td>
<td>7%</td>
<td>6%</td>
<td>11%</td>
<td>6%</td>
<td>0.5 (0.4–0.8)</td>
<td>0.5 (0.3–1.1)</td>
<td>0.6 (0.3–1.6)</td>
<td>0.4 (0.1–1.0)</td>
<td>0.9 (0.4–2.0)</td>
<td>1.7 (0.7–4.0)</td>
<td>0.6 (0.2–2.0)</td>
</tr>
<tr>
<td>13:01</td>
<td>15%</td>
<td>11%</td>
<td>13%</td>
<td>6%</td>
<td>6%</td>
<td>2.7 (2.0–3.6)</td>
<td>1.3 (0.8–2.3)</td>
<td>0.6 (0.7–2.7)</td>
<td>1.0 (0.4–2.4)</td>
<td>2.0 (1.0–3.9)</td>
<td>2.4 (1.1–5.5)</td>
<td>0.8 (0.3–2.1)</td>
</tr>
</tbody>
</table>

Karlsen et al. 2013
Naess et al. 2014
Diagnostic challenges in PSC

- MRC>ERC (AASLD/EASL)
- Secondary/etiologies?
- IgG4 – cut-off level?
- Autoimmune hepatitis?
- Small-duct PSC?
- IBD?
- Malignancies?
The inflammatory bowel disease

Hirschfield et al. 2013
Liu et al. in submission
Sclerosing cholangitis in IBD

Mendes et al., 2006
Diagnostic challenges in PSC

- MRC>ERC (AASLD/EASL)
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- IBD?
- Malignancies?
Malignancy surveillance in PSC

- Cholangiocarcinoma (5-20%) – no validated screening protocol

- Colorectal carcinoma (5x) – annual/biannual colonoscopy
Malignancy surveillance in PSC

- **Cholangiocarcinoma (5-20%) – no validated screening protocol**
  - EASL:
    - Annual abdominal ultrasonography should be considered for gallbladder abnormalities.
    - There is at present no biochemical marker or imaging modality which can be recommended for early detection of CCA. ERCP with brush cytology (and/or biopsy) sampling should be carried out when clinically indicated.
    - Liver transplantation is recommended in patients with late-stage PSC and may be considered in patients with evidence of cholangiocyte dysplasia or severe recurrent cholangitis.
  - AASLD:
    - We recommend evaluation for CCA in patients with deterioration of their constitutional performance status or liver biochemical-related parameters.
    - In patients with CCA and the absence of cirrhosis, we suggest that surgical resection may be performed.
    - In patients with early stage CCA not amenable to surgical resection, we recommend that such patients be considered for liver transplantation following neoadjuvant therapy by experienced transplant centres.

- **Colorectal carcinoma (5x) – annual/biennial colonoscopy**
Malignancy surveillance in PSC

- Cholangiocarcinoma (5-20%) – no validated screening protocol

- Colorectal carcinoma (5x) – annual/biennial colonoscopy

<table>
<thead>
<tr>
<th>EASL</th>
<th>AASLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Total colonoscopy with biopsies should be performed in patients in whom the diagnosis of PSC has been established without known IBD 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</td>
<td>• We recommend a full colonoscopy with biopsies in patients with a new diagnosis of PSC and no previous history or symptoms of IBD</td>
</tr>
<tr>
<td>• Currently there is suggestive but limited evidence for the use of UDCA for chemoprevention of colorectal cancer in PSC. UDCA may be particularly considered in high risk groups such as those with a strong family history of colorectal cancer, previous colorectal neoplasia or long-standing extensive colitis</td>
<td>• In patients with IBD and PSC, we recommend surveillance colonoscopy with biopsies at 1-year to 2-year intervals from the time of diagnosis of PSC to exclude colorectal neoplasia</td>
</tr>
<tr>
<td></td>
<td>• We recommend against the use of UDCA as chemoprevention for colorectal cancer in patients with ulcerative colitis and PSC</td>
</tr>
<tr>
<td></td>
<td>• We recommend that patients with IBD and PSC should be treated according to guidelines for IBD</td>
</tr>
</tbody>
</table>
The cholestatic patient

- Primary biliary cirrhosis (PBC)
- Primary sclerosing cholangitis (PSC)
- Biliary atresia
- Hereditary cholestasis
- Intrahepatic cholestasis of pregnancy
- Gallstone disease
- Polycystic liver disease
- Drug-induced liver disease

Diseases

ManIFESTATION

- Cholestatic liver disease

Consequence

- Liver cirrhosis
- Hepatocellular cancer
- Bile duct cancer
- Pruritus
- Fatigue
- Osteoporosis

- Other liver affection (e.g. hepatitis)

Karlsen et al., 2013
Summary points

- Molecular and structural abnormalities of heterogeneous etiologies
- Accounting for ~10% of European OLTs and common indication in SA
- Low threshold of MRC in IBD patients with abnormal hepatic biochemistries
- Molecular entities of inflammatory bowel diseases: UC, cCD, iCD, PSC-IBD
- «Overlap syndrome» should not be diagnosed, individual diseases should
- AMA-negative PBC and small-duct PSC without IBD: re-consider diagnosis
- The clinical utility of serum IgG4 remains challenging
- Further reading: www.easl.eu