Endoscopic aspects of primary sclerosing cholangitis

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Primary sclerosing cholangitis
Presentation plan

• General review

• Role of endoscopy in overall management
  – Diagnosis
  – Excluding other diseases
  – Identifying cholangiocarcinoma
  – Determining prognosis
  – Therapeutic management

• Conclusions - Guidelines
PSC: Some facts…

• Chronic cholestatic liver disease characterized by inflammation and periductal fibrosis of the intrahepatic and/or extrahepatic bile ducts
  
  *Tischendorf, Liver Transpl 14:735-746, 2008*

• Incidence: 0.9-1.3 cases/100000
  
  Prevalence: 8.5-13.6 cases/100000

  *Bambha, Gastroenterology 2003;125:1364-1269*

• Male predominance (70%), 4th decade

  *Kingham, Gastroenterology 2004; 126:1929-1930*

• Association with IBD: 63%-90% PSC develop IBD

  *Olsson, Gastroenterology 1991;100:1319-1323*
PSC: Aetiology

- Multifactorial disease, exact etiopathology remains unknown…..

Genetic predisposition
(100-fold increase among siblings)

Immunopathogenetic mechanisms
(HLA, association with IBD)

But……
- Male predisposition
- Poor response to immunosuppressive therapy
- Absence of disease specific antibodies

PSC: Clinical presentation

- No symptoms (up to 45%)
  - Mean delay between onset of biochemical manifestations and diagnosis: 4 years
- Abdominal pain
- Pruritus
- Jaundice
- Fatigue
- Weight loss
- Fever
- Signs of cirrhosis

Bergquist, J Hepatol 2005;42:252-256._
PSC: Diagnosis

• Criteria
  – Cholangiographic findings of irregularities, multifocal strictures and beading of the intrahepatic and/or extrahepatic ducts
  – Biochemical alterations (cholestasis)
  – Exclusion of other causes

ERCP: Initial gold standard

PSC: Diagnostic ERCP

• Involvement:
  – Intrahepatic/Extra hepatic: 69%
  – Intrahepatic: 25%
  – Extra hepatic: 4%

• Dominant stricture: 35%-45% (stricture < 1.5 mm of the CBD or < 1 mm of the IHBD)

• Normal cholangiogram: 2%
  – Typical biochemical and histological features of PSC
  – Small-duct disease
  – No progression to large-duct disease (different entity)

*Tischendorf, Am J Gastroenterol 2007;102:107-114

*Björnsson, Gut 2002;51:731-735*
41 y old man, PSC diagnosed 10 years ago
41 y old man, PSC diagnosed 10 years ago
41 y old man, PSC diagnosed 10 years ago, balloon dilation
PSC: MRCP

- Comparable accuracy: 90% (MRCP) vs 97% (ERCP)
- Comparable interobserver agreement for the diagnosis: MRCP, 0.83; ERCP, 0.73
- MRCP: Better accuracy for peripheral ducts (87% vs 63%)
- MRCP used for screening
- Optimal cost-effectiveness approach

Angulo, J Hepatol 2000;33:520-527
Moff, Gastrointest Endosc. 2006;64:219-23.
Moff, Gastrointest Endosc. 2006;64:219-23.
PSC: Differential diagnosis

• Excluding other diseases and/or variant forms of PSC
  – Small duct disease (normal cholangiogram, typical histology → liver biopsy)
  – Overlap with auto-immune hepatitis (liver biopsy)
  – IgG4 related sclerosing cholangitis
    • Biliary strictures with lymphoplasmacytic infiltration
    • Frequently high serum levels of IgG4
    • Association with autoimmune pancreatitis
    • Reversible and responsive to steroid therapy

PSC vs IgG4 sclerosing cholangitis

• Role of endoscopy in discriminating both forms
  – Aspect of papilla (swollen) (Sn → 63%)
  – Cholangiogram with bile duct and ampulla biopsies for detecting IgG4-plasma cells (Sn → 52%)
  – IDUS showing symmetrical bile duct wall thickness (even in non-stenotic areas)

*Kubota, Gastrointest Endosc. 2008 Dec;68(6):1204-8
Kawakami, J Gastroenterol Hepatol. 2010;25(10):1648-55
Kubota, Dig Endosc. 2011 Jan;23(1):10-6*
Kubota, Gastrointest Endosc. 2008 Dec;68(6):1204-8
PSC: Identifying cholangiocarcinoma

- 8-14% of patients with PSC
- Risk factors:
  - Alcohol and tobacco consumption
  - Concomitant colon cancer
  - Long history of IBD
- Clinical suspicion in case of aggravating jaundice, weight loss

*Boberg, Scand J Gastroenterol 2002;10:1205-1211*

*Berquist, Hepatology 1998;27:311-316*
PSC: Identifying cholangiocarcinoma

• Diagnosis
  – Serum CA 19-9
  – CT, MRCP, PET-Scan
  – ERCP with cytological brushings:

<table>
<thead>
<tr>
<th></th>
<th>Type</th>
<th>N patients</th>
<th>Sn</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponsioen 1999</td>
<td>R</td>
<td>47</td>
<td>60%</td>
<td>89%</td>
</tr>
<tr>
<td>Boberg 2006</td>
<td>P</td>
<td>61</td>
<td>73%</td>
<td>95%</td>
</tr>
<tr>
<td>Charatcharoenwitthaya 2008</td>
<td>P</td>
<td>230</td>
<td>50%</td>
<td>97%</td>
</tr>
<tr>
<td>Barr Fritcher 2009</td>
<td>R</td>
<td>189/498</td>
<td>40%</td>
<td>97%</td>
</tr>
</tbody>
</table>

_Ponsioen, Endoscopy 1999;31:305-309_
_Barr Fritcher, Gastroenterology. 2009 Jun;136(7):2180-6_
_Boberg, J Hepatol 2006;45:568-574_
_Charatcharoenwitthaya, J Hepatol 2006;45:568-574_
PSC: Identifying cholangiocarcinoma

- What’s new?
  - Molecular markers on brushings to increase Sn
    - DNA methylation alterations
    - Fluorescence in situ hybridization (FISH)
    - Digital Imaging analysis
    - K-ras mutation analysis

Identify cells with chromosomal abnormalities

FISH can increase Sn without decreasing Sp

FISH may detect polysomic cells in brushings before other pathological or imaging techniques identify CCA

Barr Fritcher, Gastroenterology. 2009 Jun;136(7):2180-6v
Levy, Am J Gastroenterol 2008 May;103(5):1263-73
Moreno-Luca, Gastroenterology. 2006 Oct;131(4):1064-72
PSC: Identifying cholangiocarcinoma

• ERCP and imaging techniques
  – Cholangioscopy
    • 9F cholangioscope through duodenoscope over guidewire
    • Stricture morphology (irregular ulcer, villous mucosa, polypoid lesion → criteria for malignancy)
    • Sn: 92%, Sp: 93%
  – Methylene-blue aided cholangioscopy
    • Enhances images by dye uptake from inflammatory/dysplastic tissue

Tischendorf, Endoscopy 2006;38:665-669
Awadallah, Am J Gastroenterol 2006; 101: 284 – 291
Hoffman, Endoscopy 2008;40:563–571
PSC: Identifying cholangiocarcinoma

• ERCP and imaging techniques
  – IDUS
    • 20Mhz miniprobe through duodenoscope over guidewire
    • Stricture morphology (asymmetry, irregular outer margin, hypoechoic \(\rightarrow\) criteria for malignancy), abnormal lymph nodes
    • Accu: 50%-90% but limited reproducibility
  – Optical coherence tomography (OCT)
    • Light reflectance for producing cross sectional images
    • Higher resolution than IDUS (0.01mm)
    • Prospective study in biliary strictures \(\rightarrow\) can enhance Sn combined to cytology

Varadarajulu, J Gastroenterol Hepatol. 2007;22:2086-92
Levy, Am J Gastroenterol 2008 May;103(5):1263-73
Tischendorf, Scand J Gastroenterol. 2007;42: 1011-7
Arvanitakis, Endoscopy2009;41:696–701

Quality in Endoscopy: ERCP, Munich 2011
# PSC: Prognosis

## TABLE 1. Variables Used in Selected Prognostic Models for Primary Sclerosing Cholangitis

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ASAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>+</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>AP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>IBD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Variceal bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Histologic stage</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
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<tr>
<td>Cholangiographic stage</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

**Abbreviations:** AP, alkaline phosphatase; ASAT, aspartate aminotransferase; IBD, inflammatory bowel disease.

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*Tischendorf, Liver Transpl 14:735-746, 2008*
Table 1  Classification of cholangiographic findings in primary sclerosing cholangitis

<table>
<thead>
<tr>
<th>Type of duct involvement/classification</th>
<th>Cholangiographic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrahepatic (IHD)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>No visible abnormalities</td>
</tr>
<tr>
<td>I</td>
<td>Multiple strictures; normal calibre of bile ducts or minimal dilatation</td>
</tr>
<tr>
<td>II</td>
<td>Multiple strictures, saccular dilatations, decreased arborisation</td>
</tr>
<tr>
<td>III</td>
<td>Only central branches filled despite adequate filling pressure; severe pruning</td>
</tr>
<tr>
<td>Extrahaepatic (EHD)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>No visible abnormalities</td>
</tr>
<tr>
<td>I</td>
<td>Slight irregularities of duct contour; no stricture</td>
</tr>
<tr>
<td>II</td>
<td>Segmental stricture</td>
</tr>
<tr>
<td>III</td>
<td>Stricture of almost entire length of duct</td>
</tr>
<tr>
<td>IV</td>
<td>Extremely irregular margin; diverticulum-like outpouchings</td>
</tr>
</tbody>
</table>

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\[ PI = 1.13 \times X_3 + 1.98 \times X_4 + 0.024 \times Y \]

Table 2  Resultant SUMIHD-EHD” score from intrahepatic (IHD) and extrahaepatic (EHD) disease. The score can be read from the intersection of the pertaining EHD row and IHD column (the combination 0–0 is non-existent because it would preclude a diagnosis of primary sclerosing cholangitis)

<table>
<thead>
<tr>
<th>IHD</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>4</td>
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<tr>
<td>III</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
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</table>

Ponsioen, Gut 2002;51:562–566

Quality in Endoscopy: ERCP, Munich 2011
<table>
<thead>
<tr>
<th>Age</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
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<tbody>
<tr>
<td>Points</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td>11</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Points</td>
<td>0</td>
<td>8</td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>89</td>
</tr>
</tbody>
</table>

*Ponsioen, Endoscopy* 2010;42:742–747

Quality in Endoscopy: ERCP, Munich 2011
### Table 2. Prognostic Significance of Variables in 273 PSC Patients at Time of Diagnosis by Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>Hazard Ratio</th>
<th>Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.028</td>
<td>1.029</td>
<td>1.014–1.043</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low albumin</td>
<td>0.885</td>
<td>2.423</td>
<td>1.236–4.750</td>
<td>0.01</td>
</tr>
<tr>
<td>Persistent bilirubin elevation</td>
<td>1.065</td>
<td>2.902</td>
<td>2.902–1.866</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>0.872</td>
<td>2.391</td>
<td>1.578–3.622</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>0.618</td>
<td>1.856</td>
<td>1.215–2.835</td>
<td>0.004</td>
</tr>
<tr>
<td>Dominant bile duct stenosis</td>
<td>0.827</td>
<td>2.286</td>
<td>1.596–3.273</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intrahepatic and extrahepatic ductal changes</td>
<td>0.899</td>
<td>2.457</td>
<td>1.651–3.656</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

![Cumulated survival](cumulated_survival.png)

**Figure 4.** Kaplan-Meier survival of the five risk classes (P < 0.0001). The prognostic score (PSC score) was divided into the 25%, 50%, 75%, and 87.5% quantiles resulting in these five risk classes.

*Tischendorf, Am J Gastroenterol. 2007 Jan;102(1):107-14*
PSC: Endoscopic treatment

- Dominant strictures in up to 50% of PSC patients
- Bile contaminated in 50% of cases with dominant strictures and this may contribute to liver function deterioration
- ERCP with additional investigations (cytological brushings, molecular analysis, cholangioscopy…) to exclude malignancy

Rational for endoscopic therapy

Björnsson, Am J Gastroenterol. 2004;99:502-8
Pohl, Eur J Gastroenterol Hepatol. 2006;18: 69-74
## PSC: Endoscopic treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>R/P</th>
<th>Tech</th>
<th>Bioch</th>
<th>FU</th>
<th>Compl</th>
<th>OLT free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Millgen 1996</td>
<td>21</td>
<td>R</td>
<td>Stents</td>
<td>+</td>
<td>29 mo</td>
<td>14%</td>
<td>NA</td>
</tr>
<tr>
<td>Ponsoenen 1999</td>
<td>32</td>
<td>R</td>
<td>Stents</td>
<td>83%</td>
<td>4 y</td>
<td>15%</td>
<td>NA</td>
</tr>
<tr>
<td>Kaya 2001</td>
<td>71</td>
<td>R</td>
<td>Balloon/stents</td>
<td>no diff</td>
<td>24 mo</td>
<td>14%/54%</td>
<td>NA</td>
</tr>
<tr>
<td>Baluyut 2001</td>
<td>63</td>
<td>R</td>
<td>Balloon/Stents</td>
<td>NA</td>
<td>34 mo</td>
<td>20%</td>
<td>83% 5y</td>
</tr>
<tr>
<td>Stiehl 2002</td>
<td>52</td>
<td>P</td>
<td>Balloon</td>
<td>NA</td>
<td>5 y</td>
<td>9%</td>
<td>93% 5y</td>
</tr>
<tr>
<td>Enns 2003</td>
<td>104</td>
<td>R</td>
<td>Balloon/stents</td>
<td>52%</td>
<td>NA</td>
<td>14%</td>
<td>NA</td>
</tr>
<tr>
<td>Gluck 2008</td>
<td>84</td>
<td>R</td>
<td>Balloon</td>
<td>NA</td>
<td>8 y</td>
<td>7.3%</td>
<td>+</td>
</tr>
<tr>
<td>Gotthardt 2010</td>
<td>96</td>
<td>P</td>
<td>Balloon</td>
<td>NA</td>
<td>7.1 y</td>
<td>3.8%</td>
<td>81% 5y</td>
</tr>
</tbody>
</table>
## PSC: Endoscopic treatment Complications

- Post-ERCP pancreatitis
- Cholangitis
- Bile leaks

<table>
<thead>
<tr>
<th></th>
<th>N patients</th>
<th>N procedures</th>
<th>Complic</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etzel 2008</td>
<td>30</td>
<td>85</td>
<td>13%</td>
<td>Similar overall complication rate with non PSC patients</td>
</tr>
<tr>
<td>Bangarulingam 2009</td>
<td>168</td>
<td>308</td>
<td>11%</td>
<td>More cholangitis than non PSC patients</td>
</tr>
<tr>
<td>Alkhatib 2011</td>
<td>75</td>
<td>185</td>
<td>8%</td>
<td>Experience Cirrhosis BS, dilation</td>
</tr>
</tbody>
</table>

**Alkhatib, Dig Dis Sci. 2011 Jul 26.**  
**Bangarulingam, Am J Gastroenterol. 2009;104:855-60**  
**Etzel, Gastrointest Endosc. 2008 Apr;67(4):643-8**  

Quality in Endoscopy: ERCP, Munich 2011
PSC: Endoscopic treatment

- Endoscopic therapy can improve clinical status and liver function tests
- Sequential balloon dilations are the preferred therapy (stents can lead to occlusion and cholangitis)
- Complications rates are similar to non PSC patients (except for cholangitis – prophylactic antibiotics)
- Endoscopic therapy can improve transplantation-free survival rates
- However, one study with 125 PSC patients (45% dominant strictures) who did not undergo endoscopic therapy showed similar rates of cholestasis
- RCT are lacking....

Björnsson, Am J Gastroenterol. 2004;99:502-8
PSC and Cholangiocarcinoma
Endoscopy and palliation

• Biliary stenting
• Photodynamic therapy in cholangiocarcinoma
  – RCT (PDT and stenting (n=20) vs stenting alone (n=19))
  – Prolongation of survival
  – Better biliary drainage
  – Better QoL

Ortner, Gastroenterology 2003;125:1355-1363
PSC: The role of endoscopy

- ERCP has been the gold standard for the diagnosis of PSC but MRCP has been recently the method of choice for initial diagnosis and screening.
- ERCP, bile duct brushings and biopsies (bile duct and ampulla) for detecting IgG4-plasma cells can differentiate PSC with IgG4 sclerosing cholangitis which is reversible and responds to steroids.
- ERCP with bile duct brushings are performed in patients with dominant strictures to exclude cholangiocarcinoma.
- Sn of brushings is limited, therefore additional cytological technics are performed (FISH), to detect chromosomal abnormalities.
PSC: The role of endoscopy

- Additional technics during ERCP (cholangioscopy, IDUS, OCT) can contribute in detecting cholangiocarcinoma.
- The cholangiographic stage illustrated during ERCP can determine prognosis concerning transplantation-free survival (PSC score, PI).
- Endoscopic drainage can help in patients with dominant strictures (clinical and liver function improvement, better transplantation-free survival) but RCT are missing.
- Sequential balloon dilation is preferred to stenting because of the risk of cholangitis at stent occlusion.
- In case of PSC with cholangiocarcinoma, palliation can include biliary drainage with PDT.