Colangitis Esclerosante Primaria: Manejo Clínico y Endoscópico

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Primary Sclerosing Cholangitis

✓ Idiopathic chronic cholestatic liver disease
✓ Characterized by stricturing of intra-extra-hepatic biliary tree
✓ Variable rate of progression
✓ Diagnosis of exclusion
✓ Unclear pathogenesis – genetic and environmental risk factors
✓ No effective medical therapy

Lazaridis . NEJM 2016 Sep 22;375(12):1161-70
• Combination of:
  – Cholestatic biochemical profile
  – Multifocal strictures on cholangiography
  – Exclusion of secondary sclerosing cholangitis

• ERCP:
  – Gold standard, but has side effects (more therapeutic than diagnostic)

• MRCP
  – Considered the initial diagnostic test of choice.
  – Sensitivity (86%) and specificity (94%)

AASLD Guidelines, Hepatology. 2010
EASL/ESGE Guidelines 2017
Diagnosis

Chronic cholestasis
- Asymptomatic
- Pruritus
- Symptoms of advanced liver disease
- Inflammatory bowel disease?

Multifocal strictures on cholangiogram
- Labs: ALP persistently high > 6 months, autoantibodies, 10% elevated IgG4
- High IgG4 possibly associated with faster progression

Liver biopsy seldom required*
- Small duct PSC
- Overlap cases

*Courtesy Dr C Levy
## PSC - Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Diagnostic Approach and Criteria</th>
<th>Cholangiographic Features</th>
<th>Histopathological Features</th>
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</thead>
<tbody>
<tr>
<td>Classic</td>
<td>MRCP or ERCP with typical cholangiographic features; elevation of alkaline phosphatase level (more than doubled) for &gt;6 mo; exclusion of causes of secondary sclerosing cholangitis</td>
<td>Affects small and large bile ducts</td>
<td>Mixed inflammatory-cell infiltrate, usually more intense around bile ducts; often nonspecific and nondiagnostic</td>
</tr>
<tr>
<td>Small-duct</td>
<td>Liver biopsy; elevation of alkaline phosphatase level (more than doubled) for &gt;6 mo; exclusion of causes of secondary sclerosing cholangitis</td>
<td>Affects only small bile ducts</td>
<td>Mixed inflammatory-cell infiltrate, usually more intense around bile ducts; often nonspecific and nondiagnostic</td>
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<tr>
<td>Associated with autoimmune hepatitis</td>
<td>Laboratory evidence of autoimmune hepatitis plus MRCP or ERCP findings of primary sclerosing cholangitis; exclusion of causes of secondary sclerosing cholangitis</td>
<td>Affects small and large bile ducts</td>
<td>Lymphoplasmacytic infiltrate, interface hepatitis</td>
</tr>
</tbody>
</table>
MRCP Is The Preferred Imaging Modality

**False-Positives**
- MRCP: cirrhosis
- ERCP: Incomplete biliary distension

**False-Negatives**
- MRCP: Very mild/early changes
- ERCP: High grade strictures

Not good as surrogate marker of disease activity and progression

Berstad et al. CGH 2006
Lazaridis et al. NEJM 2016
Schramm C et al., Hepatology 2017
Tenca, et al Liv International 2018
MRCP is good, but beware of overcall!
## Differential Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Cholangiocarcinoma</td>
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<tr>
<td>Choledocholithiasis</td>
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<tr>
<td>IgG 4–related sclerosing cholangitis</td>
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<tr>
<td>Immunodeficiency states / AIDS cholangiopathy</td>
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<tr>
<td>Ischemic cholangitis</td>
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<tr>
<td>Portal hypertensive biliopathy</td>
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<tr>
<td>Diffuse intrahepatic metastasis</td>
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<tr>
<td>Surgical biliary trauma</td>
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<tr>
<td>Recurrent pyogenic cholangitis</td>
</tr>
<tr>
<td>Recurrent pancreatitis</td>
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<tr>
<td>Sclerosing cholangitis in critically ill</td>
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<tr>
<td>Drug induced / Intra-arterial chemotherapy</td>
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</tbody>
</table>
Diagnostic Algorithm EASL/ESGE

MRCP
- Positive
  - Confirm large duct stenosis and PSC
- Negative
  - ERCP
    - Positive
      - Confirmed LD-PSC
    - Negative
      - Liver Biopsy
        - No PSC

Small Duct PSC

Aabakken L et al. Endoscopy 2017
EASL-ESGE / ACG / AASLD Guidelines

Recommendations for Diagnosis

MRCP is preferred over ERCP
Liver biopsy is not necessary
Liver biopsy recommended in cases of suspected small duct PSC or to exclude other conditions, such as overlap with autoimmune hepatitis
Test for IgG4 at least once
Strictures

**DIFFUSE STRICTURES**
Multiple stenosis in the intrahepatic ducts or extrahepatic ducts > 1.5mm in diameter

**DOMINANT STRicture**
Stenosis with a diameter of \(\leq 1.5 \text{ mm} \) in the CBD
or \(\leq 1 \text{ mm} \) in the intrahepatic duct within 2cm of main hepatic confluence
Endoscopic Therapy
Who and When

✓ Abnormal liver tests with or without right upper quadrant pain and:
✓ Difficult to treat pruritus
✓ Cholangitis- fever / jaundice
✓ Dominant strictures and cholestasis
✓ Common bile duct stones
✓ Strictures with alarm symptoms
  ✓ Elevated CA19.9, weight loss

Law R, Baron TH. CLD 2014
Endoscopic Therapy - Goals

- Improve liver function, minimize symptoms, and delay the need for LT.
- Rule out CCA- sampling
- Treat strictures
- Reduce the serum alkaline phosphatase
- Minimize recurrent cholangitis and other complications

Law R, Baron TH. CLD 2014
Ductal Sampling - When?

- **Brush cytology / endobiliary biopsies:**
  - Worsening symptoms (jaundice, cholangitis, pruritus);
  - Rapid increase of cholestatic enzyme levels
  - New dominant stricture or progression
  - Any alarm feature

EASL/ESGE Guidelines. J Hepatol 2017
Therapy of strictures

- ERCP with balloon dilation with diameters of 4 - 8 mm
- Dilate only the dominant stricture
- Follow up with ALP and liver enzymes.
- Success > 80%
- EASL/AASLD/ASGE recommend antimicrobial therapy before ERCP

Law R, Baron TH. CLD 2014
Lindor KD et al. Am J Gastro 2015
Endoscopic Therapy – How?

1. Sphincterotomy
   • may perform, but not effective not alone
2. Stricture dilation alone *preferred
3. Dilation and short term stenting
   – Refractory strictures and acute bacterial cholangitis
   – Supported by EASL, AASLD, ACG guidelines

EASL/ESGE Guidelines . 2017
Lindor KD et al. Am J Gastro 2015
AASLD Guidelines, Hepatology. 2010
Endoscopic therapy

(A) Dominant strictures  (B) Balloon dilatation of the strictures.  (C) Placement of a 10F plastic biliary stent above the hilar stricture.  (D) Stricture resolution noted on follow-up cholangiogram.
**Dominant Strictures**

*Stenosis with a diameter of ≤1.5 mm in the CBD or ≤1 mm in the intrahepatic duct within 2cm of main hepatic confluence.*

**First ERCP session**

- Consider sphincterotomy
- Balloon Dilate to 4 mm
- Insert Plastic Stent (7-10Fr)*

**At 1-2 weeks**

- Re-dilate (4-8 mm)
- 2-3 sessions
- Follow up

**1. REFRACTORY STRICTURES AFTER FAILURE OF DILATION * three**

**2. CHOLANGITIS**

Lindor KD et al. Am J Gastro 2015
AASLD Guidelines, Hepatology. 2010
EASL/ESGE Guidelines. 2017
DILISTENT STUDY

Stenting vs Balloon dilation – Open label trial 9 centers
Primary outcome - cumulative recurrence-free patency of the dominant stricture

- 65 randomized
  - 31 vs 34
- Stent (2 weeks) vs balloon
- Cumulative recurrence-free rate did not differ significantly between groups at 24 months
- Study terminated by DSMB early due to high side effects in the stent group -
  - Pancreatitis 24% vs 3.3%
  - Cholangitis 12% vs 3.3%

Gastroenterology 2018;155:752–759
Dominant Strictures

- Occur in ≈ 60%
- May cause sudden worsening with jaundice and cholangitis
- Up to 40% may develop DS in 5 yr of follow up
- More frequently benign
  - but 22-26% are malignant
  - Decreased survival even if benign
- Need to rule out CCA

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Dominant Strictures: Role of endoscopic therapy

- Improvement in jaundice
- Reduced rates of hospitalization
- Radiological improvement of strictures
- Retrospective studies show reduced mortality compared to predicted survival per Mayo Risk Score
  - Dilatation +/- short term stenting preferred

Beware of Cholangiocarcinoma

- CCA develops in 10% to 15% of patients with PSC
- A recent meta-analysis (>700 patients) - brush cytology is highly specific (97%) but has poor sensitivity (30%)
- In addition to routine cytologic evaluation, FISH (fluorescent in situ hybridization test) has sensitivity of 73% and specificity of 95%.

Cholangioscopy
Digital cholangioscopy

First Generation SpyGlass System

SpyGlass DS System

Stricture

Biopsy

First Generation SpyGlass System

SpyGlass DS System

Stone

Normal Ducts
Cholangioscopy

- Allows direct visualization of the bile ducts with the ability to obtain biopsies and/or perform interventions (i.e., stone removal).
- May be difficult to pass the cholangioscope into narrowed ducts.
- May lead to a greater diagnostic yield in the evaluation of CCA.
Few data

For diagnosis of Cholangioca in PSC:

**Pooled sensitivity 65% (95% CI, 35-87%)**

**Specificity 97% (95% CI, 87-99%)**

   Njei B, McCarty TR, Varadarajulu S, Navaneethan U.
   PMID: 27590963
   Similar articles

2. Systematic review with meta-analysis: endoscopic retrograde cholangiopancreatography-based modalities for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis.
   Njei B, McCarty TR, Varadarajulu S, Navaneethan U.
   PMID: 27696456
   Similar articles

3. Prospective evaluation of the clinical utility of single-operator peroral cholangioscopy in patients with primary sclerosing cholangitis.
   Arnelo U, von Seth E, Bergquist A.
   PMID: 25820274
   Similar articles

4. Cholangioscopy with narrow-band imaging in patients with primary sclerosing cholangitis undergoing ERCP.
   Azeem N, Gostout CJ, Knipschild M, Baron TH.
   PMID: 24205748
   Similar articles
**Guidelines PSC**

<table>
<thead>
<tr>
<th>Endoscopy</th>
<th>Clinical Practice Guidelines</th>
</tr>
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<tbody>
<tr>
<td>- ERCP with pruritus</td>
<td></td>
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<tr>
<td>- PSC with cytology</td>
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<tr>
<td>- PSC pathology</td>
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**Role of endoscopy in primary sclerosing cholangitis: European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) Clinical Guideline**

European Society of Gastrointestinal Endoscopy, European Association for the Study of the Liver

- Routine stenting after dilatation is not required. Short term stenting may be needed for severe strictures.
PSC is a diagnosis of exclusion
MRCP is the preferred initial diagnostic test
ERCP confirms diagnosis and allows therapy
Medical therapy is mostly ineffective
Endoscopic therapy with dilation alone for:
  - Dominant strictures without cholangitis
  - Short term stenting + dilation for bacterial cholangitis and refractory strictures
CCA should always be ruled out!
Thanks for your attention!
Clinical Picture IgG4-Related Sclerosing Cholangitis

- Biliary manifestation of IgG4-related disease
- Most are male (8M : 1F)
- Middle aged
- Obstructive jaundice; pruritus
- 90% have pancreatic involvement: anorexia, steatorrhea, weight loss
- History of allergies/ atopy; high IgE in 40-60%
- Presence of IBD more suggestive of PSC
  - 5% of patients with IgG4-SC have IBD

Beuers U, et al Dig Dis. 2015;
# Diagnosis – HISORt Criteria

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<tr>
<th>Diagnostic Criterion</th>
<th>Description</th>
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<td>Histology of bile duct</td>
<td>Bile duct bx with &gt; 10 IgG4+ cells/HPF (or &gt;50 if surgical specimen)</td>
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<tr>
<td>Imaging of bile duct</td>
<td>One or more strictures IH, proximal EH, or intrapancreatic. Fleeting biliary strictures</td>
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<td>Serology</td>
<td>Increased IgG 4 levels</td>
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<tr>
<td>Other organ involvement</td>
<td>Pancreas – classic features of AIP, or suggestive features* Retropertitoneal fibrosis Renal lesions (low attenuation, round, wedge-shaped or diffuse patchy) Salivary / lacrimal gland enlargement</td>
</tr>
<tr>
<td>Response to Steroids</td>
<td>Normalization of enzymes and resolution of strictures</td>
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