Management of Primary Sclerosing Cholangitis: Update on Guidelines

CYNTHIA LEVY, MD
ASSOCIATE PROFESSOR OF MEDICINE
UNIVERSITY OF MIAMI

Primary Sclerosing Cholangitis

- 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

Hirschfield GM et al. Lancet 2013
Epidemiology

- Incidence 1-3/100,000
- Prevalence 16/100,000
- 60-70% males; Mean age 30-40 yo
- Strong association with inflammatory bowel disease
  - Must refer for colonoscopy with bx at time of dx
- Accounts for roughly 10% of LT/year

PSC

IBD


Pathogenesis

Role of Microbiome

Macrophage differentiation, leukocyte trafficking

Complex genetic associations
- NOD2 and DR1
- IBD non-HLA risk loci
- Usually related to autoimmunity, T-cell signaling, dysbiosis

Toxic bile

PSC

Diagnosis

- Asymptomatic
- Pruritus
- Symptoms of advanced liver disease
- Inflammatory bowel disease?
- Labs: ALP, autoantibodies, high IgG, high IgM (50%), 10% elevated IgG4
  - High IgG4 possibly associated with faster progression
- Small duct PSC
- Overlap cases

Liver biopsy seldom required*

Special Populations – Small Duct PSC

- Prevalence: About 10% of all PSC cases
- Similar gender/age group as large duct PSC
- More Crohn’s disease
- Up to 23% progress to large duct – median time 7.4 years after presentation
- More patients progressing to large duct have cirrhosis and need LT

<table>
<thead>
<tr>
<th></th>
<th>SD-PSC (n=83)</th>
<th>LD-PSC (n=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>11 (13.1%)</td>
<td>45 (28.7%)</td>
</tr>
<tr>
<td>LT</td>
<td>8 (9.6%)</td>
<td>33 (21%)</td>
</tr>
<tr>
<td>CCA</td>
<td>1 (1.2%)</td>
<td>18 (12%)</td>
</tr>
</tbody>
</table>

Bjornsson et al. Gastroenterology 2008
Special Populations – Overlap with Autoimmune Hepatitis

Predominantly in children, adolescents and young adults (<25yo)
Diagnostic criteria not well defined
◦ More likely to have autoantibodies, ↑ globulins, higher ALT compared to PSC and higher ALP compared to AIH

Occurs in 1-17 % of all PSC
Development may be sequential
◦ Large proportion of children with AIH develop cholangiographic evidence of PSC

Retrospective studies suggest beneficial response to immunosuppressants


MRCP IS THE PREFERRED IMAGING MODALITY

ERCP  MRCP
Better sensitivity for subtle perinatal bile duct changes
Similar overall accuracy
Allows for therapeutic intervention
Non invasive
No radiation

True Positives
MRCP: fibrosis
ERCP: Complete biliary duct obstruction

False Positives
MRCP: Cirrhosis
ERCP: Incomplete biliary duct distension

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

Berstad et al CGH 2006; Talwalkar et al Hepatology 2004
Differential Diagnosis

Cholangiocarcinoma
Choledocholithiasis
IgG 4–related sclerosing cholangitis
AIDS cholangiopathy
Ischemic cholangitis
Portal hypertensive biliopathy
Diffuse intrahepatic metastasis
Surgical biliary trauma
Recurrent pyogenic cholangitis
Recurrent pancreatitis
Sclerosing cholangitis in critically ill
Intra-arterial chemotherapy

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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
Anti-mitochondrial antibody can help exclude PBC
Test for IgG4 at least once

Lindor KD et al. Am J Gastro 2015
Natural History: Survival Without Liver Transplant

Causes of death:
- CCA (32%)
- Liver failure (18%)
- LT-related complications (9%)
- CRC (8%)

Population-based cohort vs. Liver transplantation centers cohort

Patients at risk:
- 500
- 378
- 206
- 104
- 50
- 18
- 5

Time since diagnosis until LT or PSC-related death (years)

Eaton et al. J Gastroenterol Hepatol Dec 2015 [epub ahead of print]

Role of MR Elastography

Liver Stiffness cut-off 4.93 kPa optimal to detect F4
Serum ALP < 1.5 x ULN excluded presence of advanced LS
LS was associated with development of decompensated liver disease (HR 1.55)
Medical Therapy

- No established medical therapy

Role of UDCA in PSC

**Low dose 13-15 mg/kg/d**
- Improves biochemistries
- No change in survival

**Median dose 17-23 mg/kg/d**
- Improves biochemistries
- Trend towards improved survival
- Study underpowered (n=219)

**High dose 25-30 mg/kg/d**
- Increased rates of treatment failure compared to placebo

High Dose UDCA: Endpoints

<table>
<thead>
<tr>
<th>Primary Endpoints</th>
<th>UDCA</th>
<th>Placebo</th>
</tr>
</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</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Development of cirrhosis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Esophageal /gastric varices</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total endpoints</td>
<td>52</td>
<td>29</td>
</tr>
<tr>
<td>N reaching primary endpoint</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>N reaching death, LT, minimal listing criteria</td>
<td>22</td>
<td>15</td>
</tr>
</tbody>
</table>

Hazard Ratio:
- Primary endpoint
  - 2.27 (1.24-4.16)
- Death, LT, minimal listing
  - 2.11 (1.04-4.28)

High dose UDCA was associated with increased risk for colorectal neoplasia in the setting of PSC/IBD

LINDOR ET AL. HEPATOLOGY 2009; EATON JE ET AL. AM J GASTRO 2011

UDCA discontinuation led to worsening liver chemistries

Wunsch et al. Hepatology 2014;50:931
Prognostic Value of ALP in PSC

<table>
<thead>
<tr>
<th>Author</th>
<th>Site</th>
<th>ALP measure</th>
<th>% meeting ALP reduction</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Mamari</td>
<td>UK</td>
<td>ALP &lt; 1.5x ULN</td>
<td>40%</td>
<td>0% vs. 48% clinical decompensation or death</td>
</tr>
<tr>
<td>Lindstrom</td>
<td>Scandinavia</td>
<td>&gt;40% drop</td>
<td>43%</td>
<td>Improved survival</td>
</tr>
<tr>
<td>Stanich</td>
<td>USA</td>
<td>Normalization</td>
<td>40%</td>
<td>14% vs. 33% reached clinical endpoint</td>
</tr>
<tr>
<td>Rupp</td>
<td>Germany</td>
<td>ALP &lt; 1.5x ULN (+ all above)</td>
<td>57%</td>
<td>Survival free of LT: 22.6 yrs vs. 16.2 yrs</td>
</tr>
<tr>
<td>De Vries</td>
<td>Netherlands</td>
<td>Normalization or reduction of ALP to &lt; 1.5xULN</td>
<td></td>
<td>PSC related death Liver transplantation Cholangiocarcinoma</td>
</tr>
</tbody>
</table>

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Recommendation for Medical Treatment

UDCA in doses >28 mg/kg/day should not be used for management of PSC

“(...) patients who normalize liver biochemistries (...) have a better prognosis. This has led some to revisit the issue of UDCA treatment for PSC; many practitioners are using a dose of ≈ 20 mg/kg/day although data from well controlled clinical trials are lacking.”

Lindor KD et al. ACG 2015
UDCA use in clinical practice

ALP > 1.5x ULN; Assess symptoms

Initial MRCP evaluation; r/o Dom Stricture; need ERCP?

Consider UDCA 17-23 mg/kg/d vs. awaiting for new drugs

Re-evaluate in 6 months

Tabibian and Lindor. Hepatology 2014; 60:787

Biliary Complications

Dominant Strictures
Bacterial cholangitis
Malignancy _ CCA and GB cancer
Dominant Strictures

Stenosis < 1.5 mm in the CBD or < 1mm in the hepatic ducts within 2 cm from bifurcation

Occur in ≈ 50%

May cause sudden worsening with jaundice and cholangitis

More frequently benign, but 22-26% are malignant

Need to rule out CCA

![Graph of 18 yr-Survival]

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

Bacterial Cholangitis

- May be the initial presentation of PSC
- Associated with bacterial colonization of the biliary tree
- Risk Factors:
  - dominant strictures
  - intraductal stones
  - endoscopic/percutaneous intervention
  - surgical exploration
- Often require therapeutic drainage in addition to antibiotics

Culver EL and Chapman R. AP&T 2011

Malignancy Risk

Cumulative risk of CCA and high-grade colon dysplasia or CRC in PSC patients.

Boonstra et al. Hepatology 2013

398-fold increased risk of developing CCA
Cholangiocarcinoma & PSC

Half of cases are diagnosed in the first year after initial diagnosis of PSC

Yield of diagnosis can be increased by FISH technique → sensitivity of cytology increases from 30 to 64%

Serial polysomy associated with 70% PPV

Value of CA 19-9 is limited

Other techniques:
- Cholangioscopy
- Confocal laser microscopy
- Intraductal ultrasound
- Pet CT

Burak K et al. AJG 2004

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Endoscopic Management

- ERCP with balloon dilatation is recommended for dominant strictures causing pruritus and/or cholangitis to relieve symptoms
- PSC with dominant stricture seen on imaging should have ERCP with cytology/bx/FISH to exclude cholangiocarcinoma
- PSC patients undergoing ERCP should always receive prophylactic antibiotics
- Routine stenting after dilatation is not required. Short term stenting may be needed for severe stricture
ACG Guidelines - Surveillance

<table>
<thead>
<tr>
<th>Surveillance Strategies: Hepatobiliary and GB CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on expert opinion, very low quality of evidence</td>
</tr>
<tr>
<td>Cross sectional imaging q 6-12 months</td>
</tr>
<tr>
<td>Serum CA 19-9 q 6-12 months</td>
</tr>
<tr>
<td>Cholecystectomy for polyps &gt; 8 mm</td>
</tr>
</tbody>
</table>

Current guidelines do not support surveillance for cholangiocarcinoma in children

Lindor KD et al. AJG 2015

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Risk of Colorectal Neoplasia

Risk is increased 4-5X compared to IBD alone

Possible benefit of low dose UDCA in chemoprevention - not enough data

Annual colonoscopy with bx recommended in PSC/IBD patients
Liver Transplantation

Definitive treatment for patients with decompensated liver disease

Considerations for requesting MELD exemption points:
- >2 episodes of bacterial cholangitis or >1 episode of sepsis
- CCA < 3cm, no mets, undergoing strict IRB-approved protocol
- Intractable itching

5 yr survival 80-85%

Recurrence: 20% at 5 years
- UC post transplant and younger age are risk factors
- 4x increase in risk of death


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General Management

<table>
<thead>
<tr>
<th>Condition</th>
<th>Management/Screening</th>
</tr>
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<tbody>
<tr>
<td>Pruritus</td>
<td>Bile acid resin, rifampin, naltrexone, sertraline</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>Screen if plat &lt;150,000</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Screen with DEXA at baseline</td>
</tr>
<tr>
<td>Fat-soluble vitamin malabsorption</td>
<td>Screen in advanced liver disease</td>
</tr>
</tbody>
</table>
PSC – Key Points

At diagnosis:
- Measure IgG4
- Refer for screening colonoscopy w bx
- If platelets <150,000 or suspicion for cirrhosis ➔ EGD to r/o varices
- Use of UDCA should be individualized

During follow-up:
- Monitor labs quarterly
- If IBD: annual colonoscopy w bx
- Every 6-12 months: Cross- sectional imaging and CA 19-9

Dominant strictures (initial or symptomatic) ➔ ERCP with brush cytology + FISH.
- May need dilatation
- If stents are placed, prefer short duration (<2 wks)

Clinical decompensation, MELD >14 or suspicion for CCA ➔ refer for Liver Transplant