Biliary tract diseases of the liver

Digestive Diseases Course
Bucharest 2016

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How important are biliary tract diseases?

- Approximately 16% of all liver transplants performed in the United States between 1988 and 2014 were for cholangiopathies.


**Hepatology 2011 53(5):1608-17**
<table>
<thead>
<tr>
<th>Classification of the Cholangiopathies</th>
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<tbody>
<tr>
<td><strong>Genetic</strong></td>
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<tr>
<td>Alagille syndrome</td>
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<tr>
<td>Caroli syndrome</td>
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<tr>
<td>Cystic fibrosis</td>
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<tr>
<td>Polycystic liver disease</td>
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<tr>
<td>ADPLD</td>
</tr>
<tr>
<td>ARPKD</td>
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<tr>
<td><strong>Idiopathic</strong></td>
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<tr>
<td>Autoimmune cholangitis</td>
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<tr>
<td>Biliary atresia</td>
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<tr>
<td>Idiopathic childhood/adult ductopenia</td>
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<tr>
<td>IgG4-associated cholangitis</td>
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<tr>
<td>Primary biliary cirrhosis</td>
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<tr>
<td><strong>Malignant</strong></td>
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<tr>
<td>Cholangiocarcinoma</td>
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<tr>
<td>Secondary sclerosing cholangitis</td>
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<tr>
<td>ABCB4 deficiency</td>
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<tr>
<td>Abdominal trauma (surgical or blunt)</td>
</tr>
<tr>
<td>AIDS cholangiopathy</td>
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<tr>
<td>Amyloidosis</td>
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<tr>
<td>Chemical/drugs (e.g., 5-fluorouracil)</td>
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<tr>
<td>Choledocholithiasis</td>
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<tr>
<td>Eosinophilic or mast cell cholangitis</td>
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<tr>
<td>Graft-vs-host disease involving the liver</td>
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<td>Iatrogenic biliary strictures</td>
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<td>Portal hypertensive biliopathy</td>
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<tr>
<td>Recurrent pyogenic cholangitis</td>
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<tr>
<td>Sarcoidosis</td>
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<tr>
<td>Sickle cell disease</td>
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<tr>
<td>Vascular/ischemic (e.g., hepatic artery stenosis after liver transplant)</td>
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</tbody>
</table>

ADPLD = autosomal dominant polycystic liver disease; ARPKD = autosomal recessive polycystic kidney disease; AHD = acquired immunodeficiency syndrome.
Proposed Pathogenetic Model for Cholangiopathies

- Microorganisms
- Xenobiotics
- Unknown environmental risks
- Exotoxins
- Endotoxins

Illicit to cholangiocyte

- Genetic predisposition
- Epigenetics
- Posttranscriptional regulation

Chronic inflammation of bile ducts

- Reactive cholangiocyte
- Local proinflammatory milieu

Persistence/progression

- Repair/resolution

Host factors

Cholangiopathy

- Malignant transformation
- Fibrosis
- Bile duct proliferation
- Ductopenia
- Cholestasis
Cytokeratin expression as an aid to diagnosis in medical liver biopsies
The normal adult human liver biopsy

Per portal tract there were:
- 2.3 +/- 2.2 interlobular bile ducts
- 2.6 +/- 2.3 hepatic arteries
- 0.7 +/- 0.7 portal veins

This meant that:
- 8% did not contain a portal vein
- 7% did not contain a bile duct
- 9% did not contain a hepatic artery

• Hepatology. 1998 Aug;28(2):323-31
• Bile duct paucity or ductopenia is usually defined in less than 50% of portal tracts containing ducts.
Diagnosis of ductopaenic liver diseases

• The size of the liver biopsy specimen is important because of the typical patchy distribution of the bile duct damage – more than 10 portal tracts should be present.

• Associated features include, feathery degeneration (with or without Mallory-Denk bodies), periportal copper deposition and cholestatic rosettes.

• CK7 immunohistochemistry is very helpful

• Canalicular cholestasis not seen until decompensated liver disease has occurred.
Liver diseases characterized by loss of native bile ducts (‘vanishing bile duct syndromes’)

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental</td>
<td>Biliary atresias</td>
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<tr>
<td></td>
<td>Alpha-1-antitrypsin deficiency</td>
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<tr>
<td></td>
<td>Cystic fibrosis</td>
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<tr>
<td>Immune-mediated</td>
<td><strong>Primary biliary cirrhosis</strong></td>
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<td></td>
<td><strong>Primary sclerosing cholangitis</strong></td>
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<td></td>
<td>Autoimmune overlap syndromes</td>
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<td></td>
<td>IgG4-related systemic sclerosing disease</td>
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<tr>
<td></td>
<td>Sarcoïdosis</td>
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<tr>
<td></td>
<td>Chronic liver allograft rejection</td>
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<tr>
<td>Vascular</td>
<td>Arterial diseases, e.g. Hepatic artery thrombosis</td>
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<tr>
<td></td>
<td>Trauma <em>Vasculitis</em></td>
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<tr>
<td></td>
<td>Portal vein obstruction</td>
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<tr>
<td>Infective</td>
<td>Bacterial, e.g. <em>ascending cholangitis</em></td>
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<tr>
<td></td>
<td>Viral, e.g. <em>cytomegalovirus</em></td>
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<td></td>
<td>Protozoan, e.g. <em>cryptosporidia</em></td>
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<td></td>
<td>Other, e.g. <em>ruptured hydatid cyst</em></td>
</tr>
<tr>
<td>Drugs and toxins</td>
<td>Phenothiazines Antibiotics Tricyclic antidepressants Anticonvulsants</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Langerhans cell histiocytosisSystemic mastocytosisHodgkin's lymphoma</td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
</tbody>
</table>

*Histopathology 2010 56, 415–425*
A, Early primary biliary cirrhosis showing a surviving native bile duct (large arrow) and CK7+ periportal cells with an intermediate hepatobiliary phenotype (examples indicated with small arrows) before an established ductular reaction is evident. B, Advanced primary biliary cirrhosis showing absence of a native intraportal bile duct and a marked ductular reaction at the periphery of expanded portal tract.

*Histopathology* 2010 **56**, 415–425
Primary Sclerosing Cholangitis

PSC

• Approximately 60% of patients with primary sclerosing cholangitis are male, and the median age at diagnosis is 41 years.
• Associated with inflammatory bowel disease.
• Cholestatic liver function tests.
• Imaging of the biliary tree is central to making the diagnosis.
Types of PSC

- 90% involve the entire biliary tree
- 5% involve the small bile ducts, only
- 5% associated with autoimmune hepatitis overlap (35% in children)
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Diagnostic Approach and Criteria</th>
<th>Cholangiographic Features</th>
<th>Histopathological Features</th>
<th>Management</th>
<th>Other Features</th>
</tr>
</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 bili ducts</td>
<td>Mixed inflammatory-cell infiltrate, usually more intense around bile ducts; often nonspecific and nondiagnostic</td>
<td>Evaluate and treat coexisting conditions; endoscopic management of dominant stricture; liver transplantation for advanced disease</td>
<td>70-80% of patients have inflammatory bowel disease; increased risk of colon and gallbladder cancer, cholangiocarcinoma, and hepatocellular carcinoma</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>
<td>Evaluate and treat coexisting conditions; liver transplantation for advanced disease</td>
<td>May progress to classic subtype; associated with longer survival and less risk of cholangiocarcinoma than classic subtype</td>
</tr>
<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>
<td>Same as for classic subtype (see above); treatment for autoimmune hepatitis</td>
<td>Better prognosis than with classic subtype but worse prognosis than with autoimmune hepatitis alone</td>
</tr>
</tbody>
</table>

* MRCP denotes magnetic resonance cholangiopancreatography.
PSC and Liver Biopsy

• A liver biopsy is not necessary for diagnosis unless small-duct primary sclerosing cholangitis or an overlap with autoimmune hepatitis is suspected.

• Diagnostic criteria include:

  an increased serum alkaline phosphatase level that persists for more than 6 months,

  cholangiographic findings of bile-duct strictures detected by means of either MRCP or ERCP and

  exclusion of causes of secondary sclerosing cholangitis
PSC Histology

• Comparison of PSC and control (PBC and HCV) explants:

  Onion-skin fibrosis of terminal and medium size bile ducts
  Medium-size BD loss
  Bile duct scars
  Arterial fibro-intimal hyperplasia (75% of cases)
  Less inflammatory activity

Differential diagnosis of PSC

**Obstructive:**
- Tumors
- Stones
- Previous surgery

**Inflammatory:**
- PBC
- IgG4-associated cholangitis
- AIDS cholangiopathy
- Ischemic cholangiopathy etc.
<table>
<thead>
<tr>
<th>Cause</th>
<th>Proposed Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal trauma</td>
<td>Damage and subsequent strictures of the biliary tree</td>
</tr>
<tr>
<td>AIDS-related cholangiopathy</td>
<td>Biliary strictures associated with infection, most commonly due to <em>Cryptosporidium parvum</em></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Systemic disease involving the biliary tree</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>New development of cancer that mimics clinical presentation of primary sclerosing cholangitis</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>Strictures due to a stone or stones within the biliary tree</td>
</tr>
<tr>
<td>Eosinophilic cholangiopathy</td>
<td>Systemic disease involving the biliary tree</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td>Systemic disease involving the biliary tree</td>
</tr>
<tr>
<td>Hepatic inflammatory pseudotumor</td>
<td>Inflammatory condition that mimics cholangiographic features of primary sclerosing cholangitis</td>
</tr>
<tr>
<td>Histiocytosis X</td>
<td>Systemic disease involving the biliary tree</td>
</tr>
<tr>
<td>Iatrogenic biliary strictures</td>
<td>Strictures due to surgery or ERCP</td>
</tr>
<tr>
<td>IgG4-associated cholangitis</td>
<td>Systemic disorder that is characterized by high serum IgG4 levels and IgG4-positive lymphoplasmacytic infiltration of affected organs (the pancreas and bile ducts) and that causes biliary strictures</td>
</tr>
<tr>
<td>Intraarterial chemotherapy</td>
<td>Biliary strictures due to infusion of fluorouracil chemotherapy through the hepatic artery</td>
</tr>
<tr>
<td>Ischemic cholangiopathy</td>
<td>Inadequate arterial supply of the biliary tree</td>
</tr>
<tr>
<td>Mast-cell cholangiopathy</td>
<td>Systemic disease involving the biliary tree</td>
</tr>
<tr>
<td>Portal hypertensive biliopathy</td>
<td>Extrahepatic portal venous obstruction causing compression and strictureing of the biliary tree</td>
</tr>
<tr>
<td>Recurrent pyogenic cholangitis</td>
<td>Progressive and diffuse biliary stricturing, eclusias, and local stone formation; common in East Asia</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Systemic disease involving the biliary tree</td>
</tr>
</tbody>
</table>

* AIDS denotes acquired immunodeficiency syndrome, and ERCP endoscopic retrograde cholangiopancreatography.
PSC scoring

- No specific scoring system for PSC
- Ludwig and Nakanuma systems (developed to assess PBC)
- **Degree of fibrosis** is of important prognostic value
- Nakanuma system shows strongest predictive power: fibrosis and **orcein deposition** predicted transplant-free survival and time to liver transplant.

Journal of Hepatology 2015 vol. 63 j 1212–1219
Approximately 10% of patients with primary sclerosing cholangitis have increased serum IgG4 levels, and these patients have a poorer outcome.

The condition of such patients should not be confused with that of patients who have IgG4-associated cholangitis, which is a systemic disorder characterized by:

- High serum IgG4 levels,
- IgG4-positive lympho-plasmacytic infiltration of affected organs,
- The abrupt onset of jaundice,
- Biliary strictures that often respond to treatment with glucocorticoids,
- The absence of inflammatory bowel disease.
PSC and Gall bladder disease

- Gallstones have been reported in 25% of patients.
- A mass has been reported in 6 to 14% of patients - approximately 60% of these are adenocarcinomas.
- Gallbladders that were removed before or at liver transplantation in patients revealed dysplasia in 37% of patients and adenocarcinoma in 14%.
PSC and Inflammatory Bowel Disease

• The prevalence of PSC-IBD is 60%-80% in western countries.

• Inflammatory bowel disease occurs in most patients with primary sclerosing cholangitis:
  ulcerative colitis  75-80%
  Crohn’s disease  10-15%
  Unspecified  5-10%

• 8% of cases of UC have PSC

• Colonoscopy is indicated in all patients who have received a new diagnosis.

Br Med Bull. 2015 Jun;114(1):53-64; Dig Dis. 2015;33 Suppl 2:140-8,
PSC and Inflammatory Bowel Disease

• In one study, almost all patients with coexisting primary sclerosing cholangitis and inflammatory either ulcerative colitis or Crohn’s disease had bowel disease affecting the entire colon.

• The risk of colon cancer among patients with primary sclerosing cholangitis and concomitant inflammatory bowel disease is 4X as high as the risk among patients with inflammatory bowel disease, alone.

Br Med Bull. 2015 Jun;114(1):53-64; Dig Dis. 2015;33 Suppl 2:140-8
PSC and Cholangiocarcinoma
PSC and Cholangiocarcinoma

• In developed countries, primary sclerosing cholangitis is the most common risk factor for cholangiocarcinoma.

• The risk of cholangiocarcinoma among patients with primary sclerosing cholangitis is 400 times as high as the risk in the general population.

• Among patients with primary sclerosing cholangitis, the annual risk of cholangiocarcinoma is 2%.
PSC and Bile duct dysplasia

- high frequencies of mucinous metaplasia, pyloric metaplasia, and pancreatic acinar metaplasia, which did not differ between cholangiocarcinoma and non-cholangiocarcinoma livers.

- livers with cholangiocarcinoma were more likely to harbor intestinal metaplasia, dysplasia, and high-grade dysplasia, and also contained greater numbers of dysplastic ducts than non-cholangiocarcinoma cases.

- bile duct dysplasia is still a relatively frequent finding, seen at least focally in 36% of benign end-stage PSC explants.

“PBC”
• The disease previously known as:
  ‘Primary Biliary Cirrhosis’

  will now be called:

  “Primary Biliary Cholangitis”
AGA SECTION

Changing Nomenclature for PBC: From ‘Cirrhosis’ to ‘Cholangitis’

Ulrich Beuers, M. Eric Gershwin, Robert G. Gish, Pietro Invernizzi, David E. J. Jones, Keith Lindor, Xiong Ma, Ian R. Mackay, Albert Pares, Atsushi Tanaka, John M. Vierling, and Raoul Poupet

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Primary Biliary Cholangitis
Fibrosis in PBC

- Absent / few septa 44%
- Numerous septa 31%
- Cirrhosis 25%

Liver International. 2004;24(3)
Primary biliary cholangitis

• **Cons:**
  *Tautological*
  *Sounds too much like “primary sclerosing cholangitis”*

• **Pros:**
  *Inaccurate*
  *Stigma*

*Am J Gastroenterol* 2015; 110:1536–1538
PBC

- Autoimmune chronic cholestatic disease
- Middle-aged females
- Fatigue, pruritus
- Elevated Alkaline Phosphatase
- AMA positive (95% of patients)
- Elevated IgM
- UDCA therapy slows disease progression in 2/3 of patients

Gastroenterology 2014; 147; 1338–1349
Histology of PBC I

• PBC is characterized by chronic, nonsuppurative cholangitis that mainly affects interlobular and septal bile ducts.

• When focal lesions show intense inflammatory changes and necrosis around bile ducts, the term “florid duct lesion” is applied.

• The infiltrate consists essentially of lymphocytes and mononuclear cells in close contact with the basal membrane of cholangiocytes undergoing necrosis.

• Epithelioid granulomas are present more often in the early stage of disease.
• Portal venules are often compressed and occluded by the inflammatory reaction.

• Terminal hepatic venules are often retained in their central location with progression of fibrosis and sometimes even in cirrhosis.

• Nodular regenerative hyperplasia is a known complication.
Grading and Staging of PBC

• Scheuer/Ludwig
  Stage 1: florid duct lesion
  Stage 2: ductular proliferation and more inflammation with interface hepatitis and lymphoid aggregates
  Stage 3: fibrosis and mild duct loss
  Stage 4: cirrhosis and ductopaenia

• Kakuda
  Grading: hepatitis and cholangitis
  Staging: fibrosis, copper binding accumulation and duct loss

Overlap syndromes

• AMA-negative PBC
• AIH and PBC
• PBC and PSC
AMA-Negative PBC

- Lack AMA but whose clinical presentation, liver histology, and natural history are nearly identical to patients with typical AMA-positive PBC.
- Nearly all of these patients have antinuclear and/or antismooth muscle antibodies.
- Minimal differences in histopathology, immunology, and human leukocyte antigen status.
- The diagnosis of AMA-negative PBC requires a liver biopsy that demonstrates the typical features of PBC. The diagnosis is more certain if granulomas are present.
Overlap of AIH with PBC

• There is no formal definition.

• AIH in patients who have a diagnosis of AMA-positive PBC and not to patients with AIH who have coincidental AMA.

• Limited data suggests that response to therapy with UDCA for PBC/AIH overlap is no different from that observed in patients with PBC alone.

• A PBC/AIH overlap syndrome may also refer to patients with sequential PBC followed by AIH
Overlap of AIH with PBC

• Diagnosed by looking for 2 of the 3 following features:
  1. ALT activity 5 times upper limits of normal
  2. IgG 2x the upper limits of normal and/or positive SMA and
  3. liver biopsy with moderate or severe periportal inflammation.

UDCA with or without immunosuppressive therapy has been used with no clear consensus on optimal therapy.
Differential Diagnosis of PBC

Duct damage and ductopaenia
- PSC
- Drug induced liver disease
- Hodgkin’s lymphoma
- Chronic Rejection
- Graft versus Host Disease
- Idiopathic adulthood ductopaenia

Granulomas
- Sarcoidosis

Chronic hepatitic features
- Autoimmune hepatitis
- HCV
Indications for liver biopsy in PBC

• The combination of AP >1.5 times the ULN and AST <5 times the ULN yielded a 98.2% positive predictive value of PBC diagnosis on liver biopsy in AMA-positive subjects.

• These results were corroborated by cross-validation in an independent set of patients.

• Liver biopsy would be beneficial to establish the diagnosis of PBC in only a minority of AMA-positive patients with AP <1.5 times the ULN or AST >5 times the ULN.

Inspector: Is there any point to which you wish to draw my attention?

Gregory: To the curious incident of the dog in the night-time.

Holmes: The dog did nothing in the night-time.

Gregory: That was the curious incident.