Diagnosis and Management of Primary Biliary Cholangitis and Autoimmune Liver Diseases

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UPDATE IN LIVER DISEASES 2020

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Objectives

- Primary Biliary Cholangitis (PBC)
- Autoimmune Hepatitis (AIH)
- Primary Sclerosing Cholangitis (PSC)

- Epidemiology
- Pathophysiology
- Clinical presentation
- How to establish diagnosis
- Treatment options
- Other considerations

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Case

- 42 y/o female presented with chronic symptoms of lethargy and pruritus
- PMH: HTN, Hypothyroidism, impaired fasting glucose
- FH: Cousin has PBC, Father has RA
- SH: Alcohol: 9 beers 1-2 times a week, sometimes more
- LAB: Alk Phos elevated for 6 years

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Case

Labs: ALT/AST: 138/94, ALP: 343, T.Bili: 0.3, Albumin 4.1, GGT: 366

Autoimmune markers: ANA: neg, SMA: <20, IgG: 1514, AMA: 1:320

IgM: 352

Viral hepatitis panel: HAV IgM/IgG, HBs ag, HBs ab, HCV ab all negative

Liver Biopsy:

- Decreased bile ducts with lymphocytic cholangitis and chronic portal inflammation
- Mildly increased portal fibrosis

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Epidemiology of PBC

- Commonly found in middle-aged women and occurs in adults of all ethnic groups
- Incidence rates for PBC range from 0.33 to 5.8 per 100,000 per year
  - Has remain stable in the last 20 years
- Prevalence rates range from 1.91 to 40.2 per 100,000 inhabitants
- Most epidemiological studies are from the Western world and true population-based studies are scarce
- Transplant-free survival rates have improved due to widespread ursodeoxycholic acid (UDCA)
  - Concomitant increase in prevalence

J Hepatol 2012;56(5):1181–8
Gastroenterol Hepatol 2018;16(8):1333-1341

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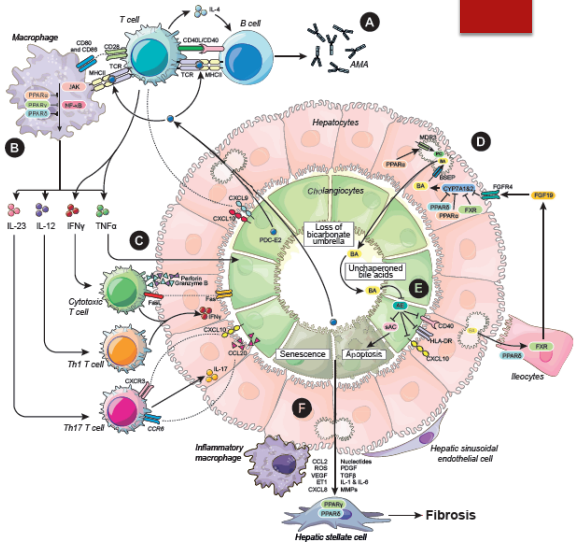
Pathophysiology

- Effective biliary secretion is essential for adequate hepatic detoxification and is integral to digestive function
- **PBC** reflects the consequences of immune and cellular injury to biliary epithelial cells, resulting in cholestasis and progressive liver fibrosis
- Loss of tolerance to some mitochondrial self-antigens in the cholangiocytes, especially the pyruvate dehydrogenase complex, subunit E2 (PDC-E2)



EASL CPG PBC. J Hepatol 2017;67:145–72

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PBC Clinical Presentation

- Most patients are asymptomatic at presentation
- Symptoms associated with PBC include:
  - **Pruritus**
  - **Sicca complex**
  - **Fatigue**
  - Abdominal discomfort
  - Jaundice
  - Restless legs
  - Insomnia
  - Depression
  - Cognitive dysfunction

J Hepatol 2017;67:145–72

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PBC Diagnosis

- Patient should have 2 out of these 3 criteria:
  - Elevated alkaline phosphatase for 6 months
    - Not explained by other cause
  - Anti-Mitochondrial Antibody
    - Or PBC specific anti-nuclear antibodies
      - SP 100/gp 210
  - Liver biopsy with nonsuppurative destructive cholangitis and destruction of interlobular bile ducts
    - May be non-specific on early stage

Hepatology, VOL. 69, NO. 1, 2019

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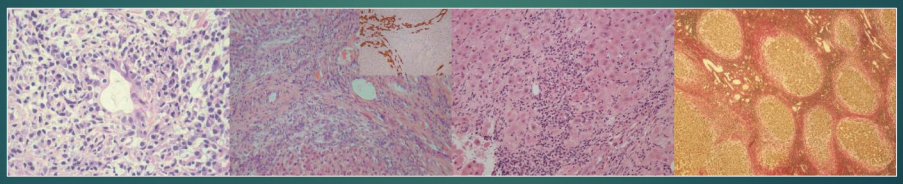
PBC Histopathology

- Liver biopsy is not generally required to diagnose PBC
  - Essential when:
    - PBC-specific antibodies are absent
    - Co-existent AIH or NASH is suspected
    - With other systemic/extrahepatic co-morbidities



Lymphocytic cholangitis | Bile duct loss and ductular reaction | Interface hepatitis | Cirrhosis

EASL CPG PBC. J Hepatol 2017;67:145–72

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PBC Treatment

- UDCA remains the first line agent
- Up to 40 % of patients are non responder or incomplete responders to UDCA

Binary definitions	Time (months)	Treatment failure
Rochester[1]	6	ALP ≥2 ULN or Mayo score ≥4.5
Barcelona[2]	12	Decrease in ALP ≤40% and ALP ≥1x ULN
Paris-I[3]	12	ALP ≥3x ULN or AST ≥2x ULN or bilirubin >1 mg/dl
Rotterdam[4]	12	Bilirubin ≥1x ULN and/or albumin <1x ULN
Toronto[5]	24	ALP >1.67x ULN
Paris-II[6]	12	ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin >1 mg/dl
Ehime[7]	6	Decrease in GGT ≤70% and GGT ≥1 ULN
Continuous scoring	Time (months)	Scoring parameters
UK-PBC[8]	12	12 months: bilirubin, ALP and AST (or ALT); Baseline: albumin and platelets
GLOBE[9]	12	12 months: bilirubin, ALP, albumin, and platelet count; Baseline: age

Journal of Hepatology 2017 vol. 67 j 145–172

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Other treatment options

- Obeticholic acid is FDA approved for PBC
  - In combination with UDCA after treatment for > 1 year with incomplete response
  - Only as monotherapy for patients intolerant for UDCA
  - FXR agonist
    - Modulates BA homeostasis
    - Decreased portal pressure
    - Anti-fibrotic
    - Anti-inflammatory

NEJM 2016; 375: 631-643

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POISE Trial: Obeticholic Acid for PBC

- 46 % of pts on OCA met the primary endpoint compared to 10% of pts on placebo
- Significant drop in ALP, AST, ALT, GGT, TB
- Significant reduction in inflammatory markers
- Reduction in HDL-cholesterol
- No change in liver stiffness scores

NEJM 2016; 375: 631-643

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Fibrates in PBC

- Bezafibrate and Fenofibrate
- PPAR agonist
  - ↑ BA detoxification and secretion
  - ↓ BA synthesis
  - ↑ Fatty acid oxidation
- Several ongoing clinical trials
- **Current off label use only**

Journal of Hepatology 2017 vol. 67 j 145–172

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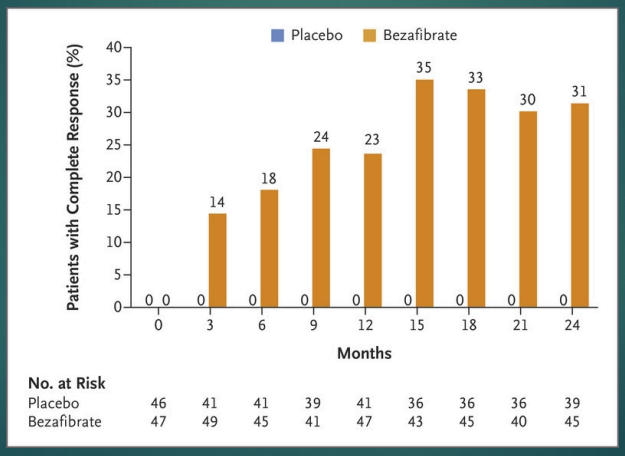
BEZURSO Trial



N Engl J Med 2018; 378:2171-2181

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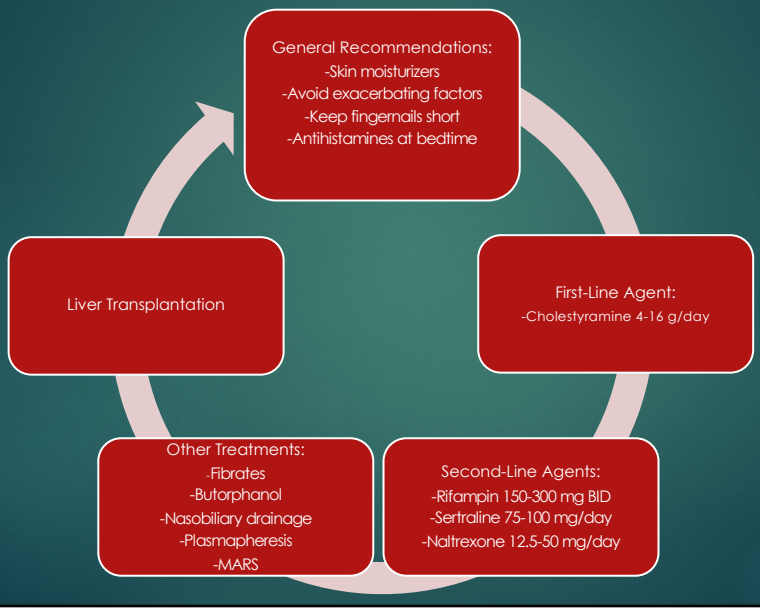
How we manage itching?



Clin Liver Dis 2018; 22: 517-532

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Other considerations

- DEXA scan at the time of diagnosis
  - Then every 2 years
- Check fat soluble vitamins
- Cirrhotic patients
  - EV screening
  - HCC screening
  - OLT evaluation
    - Even in non cirrhotic with refractory pruritus

Hepatology, VOL. 69, NO. 1, 2019

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Case

- 19-year old woman (body mass index [BMI] 45.6 kg/m^2) presented with a 6-week history of malaise, nausea and progressive jaundice, without features of liver decompensation and no history of alcohol use. Serum tests showed an alanine aminotransferase (ALT) of 592 IU/L (upper limit of normal [ULN] 40 IU/L), bilirubin of 25.6 mg/dL, serum IgG 2,089 mg/dL (ULN 1,610 mg/dL), and seropositivity for anti-nuclear antibodies (ANA; titer 1:100; homogeneous) and anti-smooth muscle antibodies (ASMA). An extended viral screen was negative (hepatitis A, B, C and E; EBV; HIV and CMV). Abdominal US without biliary dilation. Liver biopsy showed features of acute lobular hepatitis with plasmacytic infiltrates. There was moderately severe inflammatory activity including foci of bridging necrosis. No steatosis was evident.

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Epidemiology

- Affects predominantly females
  - Female-to-male ratio of 4:1
- Can affect children and adults of all ages
  - Bimodal age distribution with peaks in adolescence years and in the mid-thirties
- Incidence 1-2 cases per 100,000 habitants
- Prevalence ranges from 42.9 per 100,000 inhabitants in Alaska Natives to 4.82 per 100,000 inhabitants in South Korea
- Slowly progressive disease
  - 15 % of complications at 5 years with survival rate of 87%

Am J Gastroenterol 2002;97(9):2402–7
PLoS One 2017;12(8)

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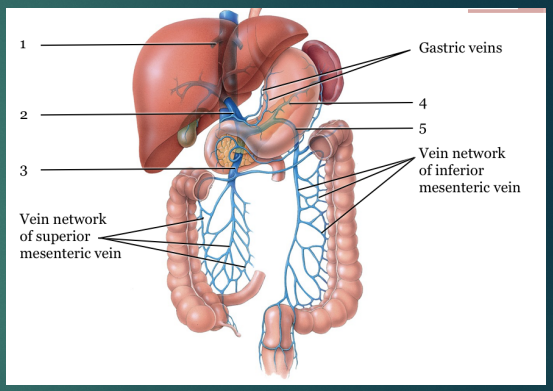
AIH Pathophysiology

- Environmental triggers mainly through molecular mimicry
  - Viruses (HCV, HBV, HAV, HEV, HSV, and CMV)
  - Drugs (nitrofurantoin, minocycline, anti-TNF, statins, interferon)
- Genetic predisposition
  - HLA region on chromosome 6, DRB1 *0301and *0401 alleles
- Failure of immune tolerance
- All result in humoral and cellular mediated immune attack of the liver



J Hepatol 2015;63:971–1004

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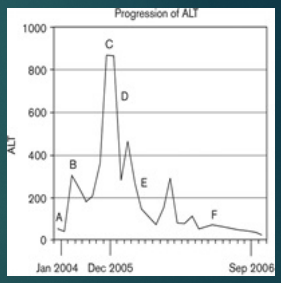
AIH Clinical Presentation

- Variable, from asymptomatic to acute hepatitis and even fulminant liver failure
- Initial presentation is most often insidious
- Fatigue, nausea, abdominal pain, jaundice, anorexia, and arthralgia
- Cirrhosis is found in a third of newly diagnosed patients
- The disease may have a fluctuating course, with periods of spontaneous remissions alternating with flare-ups



Hepatology 2010;51(6):2193–213
N Engl J Med 2006;354(1): 54–66

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AIH DIAGNOSIS

- The diagnosis of AIH requires compatible histological findings and is further supported by the following features:
  - (1) elevated serum aminotransaminase levels
  - (2) elevated serum IgG level and/or positive serological marker(s)
    - ANA, ASMA, Anti LKM, SLA
  - (3) exclusion of viral, hereditary, metabolic, cholestatic, and drug-induced diseases that may resemble AIH

J Hepatol 2015;63:971–1004
HEPATOLOGY, VOL. 72, NO. 2, 2020

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AIH Simplified Score

Feature	Discriminator	Score
ANA or SMA +	≥ 1:40	+1
ANA or SMA +	≥ 1:80	+2
or LKM +	≥ 1:40	+2
or SLA/LP +	Any titer	+2
IgG or Y-globulin level	> ULN > 1.1 x ULN	+1 +2
Liver histology (evidence of hepatitis is necessary)	Compatible with AIH Typical of AIH Atypical	+1 +2 0
Absence of viral hepatitis		0 +2

J Hepatol 2015;63:971–1004
HEPATOLOGY, VOL. 72, NO. 2, 2020

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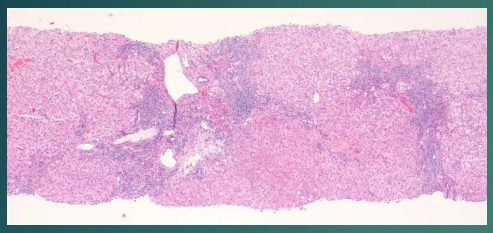
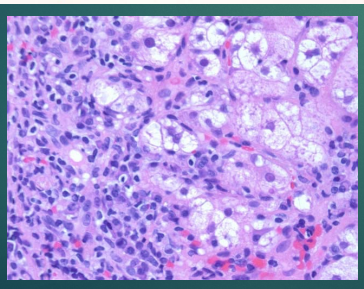
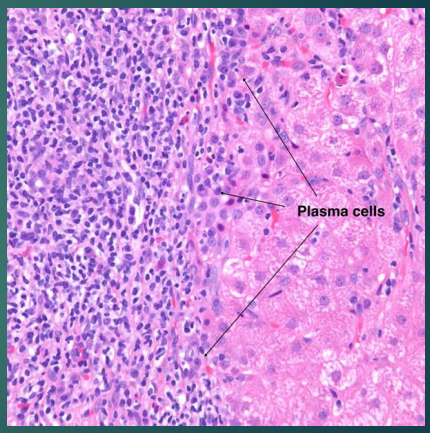
AIH Liver Biopsy







Clinical Liver Disease 2014; 3(2)

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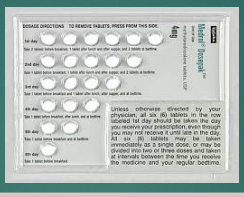
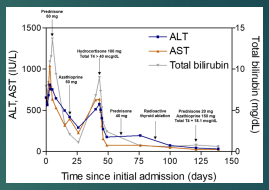
AIH Treatment

First liver disease manage by drug therapy

80% of patients will have histologic remission within 3 years





Steroids (Prednisone vs budesonide)	•EASL guidelines 0.5-1 mg/kg •Taper once remission has been achieved (< 2 x ULN)
Prednisone + Azathioprine	•Preferred to avoid steroids side effects •Avoid in poorly control diabetics and severe cytopenias
Other options	•MMF •Tacrolimus

J Hepatol 2015;63:971–1004
HEPATOLOGY, VOL. 72, NO. 2, 2020

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Effects of immunosuppression on COVID 19 patients with AIH

- Not well establish but an Italian case series showed that COVID-19 in patients with AIH treated with immunosuppression appears to have a disease course presumptively similar to the general population
  - Start prednisone or azathioprine if patient have/does not have COVID 19 infection
- Reducing IS dose may cause a relapse in a patient with AIH
  - No change in medication should be done unless there is a sound clinical indication
- AIH patients taking immunosuppression having active COVID 19 infection
  - Consider to reduce the prednisone dose but do not discontinue completely due to increased risk for adrenal insufficiency
  - Consider to reduce azathioprine or mycophenolate mofetil if patient has lymphopenia, fever of worsening pulmonary function due to COVID 19 infection

Hepatol Commun 2020, 4: 1257-1262.

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When to stop treatment?

Liver enzymes and IgG have been normal for at least 2 years

EASL guidelines recommend liver biopsy prior to considering treatment withdrawal

Liver biopsy shows no inflammation

- Histology lags biochemistries by up to 8 months

*Only about 1/20 patients will achieve long term remission after discontinuing therapy

J Hepatol 2015;63:971–1004

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Who are more likely to relapse?

- Younger age
- Higher MELD at presentation
- Acute presentation with high bilirubin level
- Type 2 AIH (LKM-1, LC-1 Ab)
- Failure to obtained remission
- Abnormal liver biopsy after treatment
- SLA antibodies

Clin Gastro Hepatol 13 (12)2088–2108

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Case

- 44-year-old man presented with worsening jaundice of 4 weeks' duration. He had a history of ulcerative colitis for 20 years, which was currently in remission. He was well until 4 weeks before he sought treatment from his local physician because he had noticed increasing jaundice and pruritus. He has had no fevers or chills. He has noticed a 10- to 15-pound weight loss over the past 2-3 months. His appetite had been good. Examination revealed the patient to be moderately built and in no acute distress. He was icteric. His abdomen was soft with no ascites or splenomegaly. The left lobe of the liver was palpable 3-4 cm below the left costal margin.

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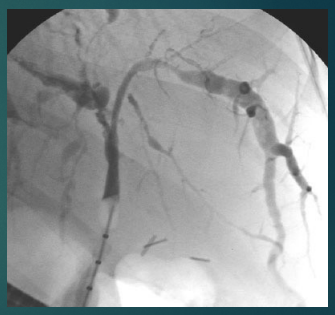
PSC Case

- Hemoglobin was 11.3 g/dL, platelet count 265 10^9/L, and international normalized ratio (INR) 1.0. The liver enzymes were elevated, with aspartate aminotransferase106 U/L (normal 10-31 U/L), alanine aminotransferase 205 U/L (normal 10-45 U/L), and alkaline phosphatase 855 U/L (normal 45-115 U/L). The total bilirubin was 14.6 mg/dL (normal 0.1-1.0 mg/dL) with a direct bilirubin of 10.4 mg/dL. The carbohydrate antigen19-9 (CA 19-9) was elevated at 320 U/mL (normal 55 U/mL). HIV was negative and IgG4 was normal. A computed tomographic scan of the liver revealed a few dilated bile ducts in both lobes of the liver. No mass lesion was seen in the hilar region. Endoscopic retrograde cholangiography revealed diffuse intra- and extrahepatic primary sclerosing cholangitis with a stricture at the bifurcation of the common hepatic duct.



Liver Transplantation 2006;12:S14

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PSC Epidemiology

- PSC affects both sexes and all age groups but is more commonly found in men close to 40 years of age
- Incidence rates range from 0 to 1.3 per 100,000 inhabitants per year
- Prevalence rates range from 0 to 16.2 per 100,000 inhabitants
- Up to 75% of patients with PSC have associated inflammatory bowel disease, usually ulcerative colitis
- Increased risk for cholangiocarcinoma, gallbladder cancer, and colorectal cancer
- At least half of the patients will require a liver transplantation
  - The median time from diagnosis to PSC-related death or transplant is approximately 21 years

Hepatol. 2012;56(5):1181–8

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PSC Pathophysiology

- Perplexing disease characterized by chronic biliary inflammation and fibrosis with eventual destruction of intrahepatic and/or extrahepatic bile ducts
- Mechanism still unclear

Hepatology 2010;51:660–78

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PSC Clinical Presentation

- Typical symptoms include RUQ abdominal discomfort, fatigue, pruritus, and weight loss
- Episodes of cholangitis (i.e., fever and chills) are a very uncommon features at presentation
- Physical examination is abnormal in approximately half of symptomatic patients at the time of diagnosis
  - Jaundice, hepatomegaly, and splenomegaly are the most frequent abnormal findings
- Many patients with PSC are asymptomatic
- Approximately 60%-80% of patients with PSC have concomitant IBD, most often ulcerative colitis (UC)

Hepatology 2010;51:660–78

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PSC DIAGNOSIS

- Suspected in the setting of chronic cholestasis
- Confirmed with a cholangiography (MRC, ERC, or PTC) showing multifocal strictures and segmental dilatations of bile ducts
- Secondary causes of sclerosing cholangitis have been excluded

Secondary Sclerosing Cholangitis Causes	
AIDS cholangiopathy	IgG4-associated cholangitis
Cholangiocarcinoma	Intra-arterial chemotherapy
Choledocholithiasis	Ischemic cholangitis
Diffuse intrahepatic metastasis	Mast cell cholangiopathy
Eosinophilic cholangitis	Recurrent pancreatitis
Hepatic inflammatory pseudotumor	Recurrent pyogenic cholangitis
Histiocytosis X	Surgical biliary trauma

Hepatology 2010;51:660–78

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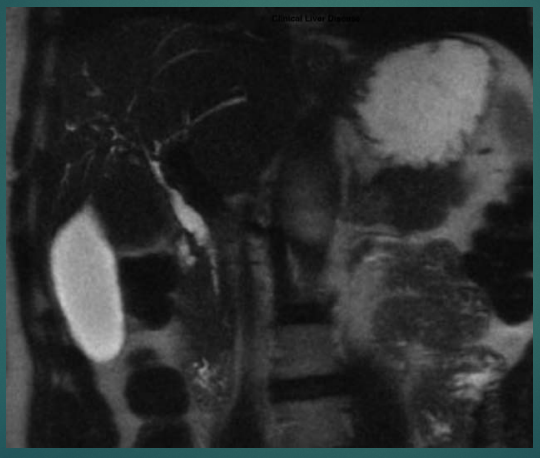
MRCP



Clinical Liver Disease 2013; 2(5)

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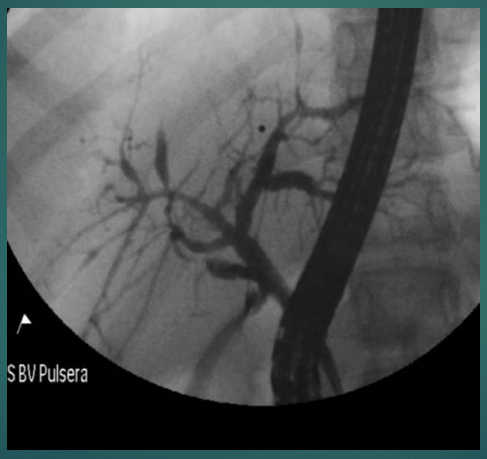
ERCP



Clinical Liver Disease 2013; 2(5)

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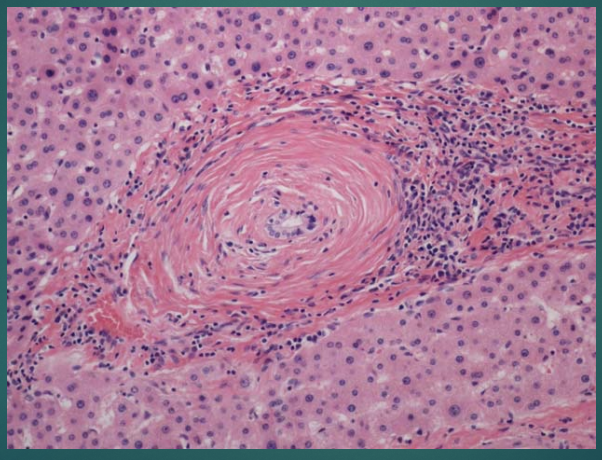
PSC Liver Biopsy



Clinical Liver Disease 2013; 2(5)

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PSC Management

- No specific treatment for it
- UDCA use is controversial
- Dilation of dominant strictures with ERCP
  - Prophylactic antibiotics
  - Avoid stenting
  - Brush cytology and spyglass for tissue diagnosis
- Screen for IBD and manage accordingly
- Annual CCA screening
  - MRI/MRCP
  - CA19-9
- Bone density

Hepatology 2010;51:660–78

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