Cholestatic and Autoimmune Liver Diseases

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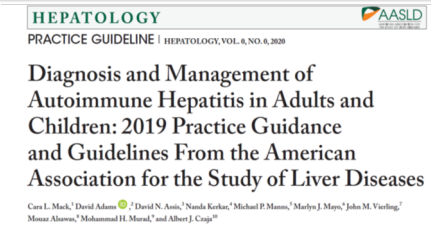
Topics

- Autoimmune Hepatitis (AIH)
- Primary Biliary Cholangitis (PBC)
- Overlap Syndromes/AMA Negative PBC
- Primary Sclerosing Cholangitis (PSC)
- IgG4-Sclerosing Cholangiopathy

Practice Guidelines

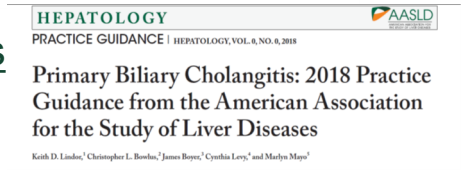
- Autoimmune Hepatitis


HEPATOLOGY

PRACTICE GUIDELINE | HEPATOLOGY, VOL. 0, NO. 0, 2020

Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases

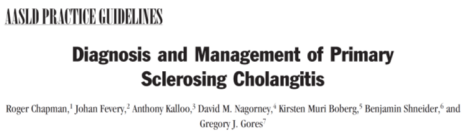
- Primary Biliary Cholangitis


HEPATOLOGY

PRACTICE GUIDANCE | HEPATOLOGY, VOL. 0, NO. 0, 2018

Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases

- Primary Sclerosing Cholangitis


AASLD PRACTICE GUIDELINES

Diagnosis and Management of Primary Sclerosing Cholangitis

Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065 Online ahead of print. Lindor KD, et al. *Hepatology*. 2019 Jan;69(1):394-419. Chapman R, et al. *Hepatology*. 2010 Feb;51(2):660-678.

Autoimmune Hepatitis (AIH)-Introduction

- Wide spectrum of presentation
  - Asymptomatic
  - Symptomatic/Acute severe hepatitis
  - Acute liver failure
- Female predominance (71-95% adults, 60-76% children)
- 28-33% have cirrhosis on presentation
- Concurrent autoimmune diseases common
  - Autoimmune thyroid disease, celiac disease (2.8-3.5%)

Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065

AIH-Pathophysiology

- Break in self-tolerance to hepatocyte autoantigens:
  1) Thymic nTregs incapable of response to autoantigens
  2) APC present autogenic peptides
  3) Costimulation
  4) Cytokine secretion by CD4+ Th cells
  5) Failure of CD4+ and CD8+ Tregs and Bregs to control effector mechanisms
  6) Generation of complex portal inflammatory infiltrates of effector cells leading to cytotoxicity

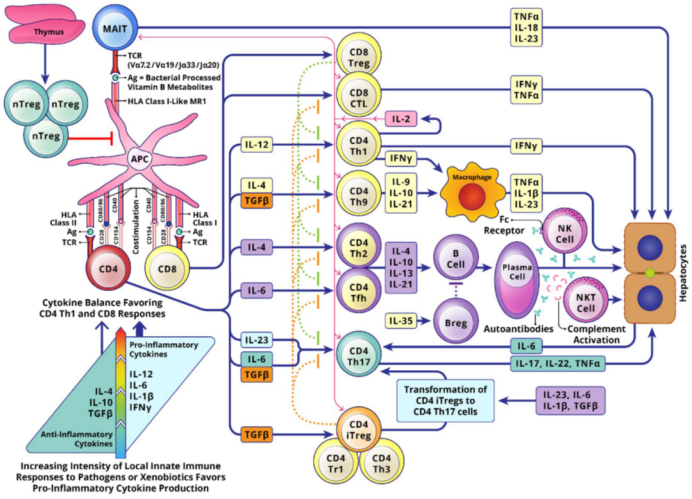


Image from: Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065

AIH-Classification

	Type 1	Type 2
Autoantibodies	ANA/SMA/Anti-Actin	Anti-LKM1
Population	96% US Adults	9-12% US Children
Cirrhosis on Presentation	28-33% adults Children <33%	Rare
Overlap Features	PBC-Adults PSC-Children (p-ANCA pos)	PBC-Not reported PSC-Rare (p-ANCA neg)
Concurrent AI diseases	Autoimmune Thyroiditis	Type 1 DM, Vitiligo
Remission after drug withdrawal	Possible	Rare, long term treatment

- 20% AIH patients negative for ANA/SMA/Anti-LKM1; 49% with 1 autoantibody: ANA/SMA/Anti-LKM1
- ANA/SMA nonspecific and common in other diseases-PSC (29%/6%); hepatitis C (26%/6%); hepatitis B (ANA-32%); NAFLD (34%/4%); alcohol (ANA-21%)
- Anti-SLA sole autoantibody + in 14-20% (Predictor of severe disease & relapse)

Adapted from: Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065

AIH-Diagnosis

- Compatible histological findings
- Elevated serum aminotransferase levels
- Elevated serum IgG level
- Presence of one or more autoantibodies
- Exclusion of other diseases
  - Viral hepatitis
  - Drug-induced injury
  - Other chronic metabolic, cholestatic, or hereditary liver disease

Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065

AIH Scoring Systems

Revised scoring system for diagnosis of autoimmune hepatitis

Parameters/Features	Score	Notes*
Female sex	+ 2	
ALP:AST (or ALT) ratio:		
<1.5	+ 2	1
1.5–3.0	0	
> 3.0	−2	
Serum globulins *or* IgG above normal		
>2.0	+3	
1.5–2.0	+2	
1.0–1.5	+1	
<1.0	0	
ANA, SMA or LKM-1		
>1:80	+3	2
1:80	+2	
1:40	+1	
<1:40	0	
AMA positive	−4	
Hepatitis viral markers:		
Positive	−3	3
Negative	+3	
Drug history:		
Positive	−4	4
Negative	+1	
Average alcohol intake		
<25 g/day	+2	
>60 g/day	−2	
Liver histology:		
Interface hepatitis	+3	
Predominantly lymphoplasmacytic infiltrate	+1	
Rosetting of liver cells	+1	
None of the above	−5	
Biliary changes	−3	5
Other changes	−3	6
Other autoimmune disease(s)	+2	7
Optional additional parameters:		8
Seropositivity for other *defined* autoantibodies	+2	9
HLA DR3 or DR4	+1	10
Response to therapy:		
Complete	+2	11
Relapse	+3	
Interpretation of aggregate scores:		
Pre-treatment:		
Definite AIH	>15	
Probable AIH	10–15	
Post-treatment:		
Definite AIH	>17	12
Probable AIH	12–17	

Table 2. Simplified Diagnostic Criteria for Autoimmune Hepatitis

Variable	Cutoff	Points
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	
or LKM	≥1:40	2*
or SLA	Positive	
IgG	>Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
		≥6: probable AIH
		≥7: definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points).

Alvarez F, et al. *J Hepatol* 1999;31:929-938.
Hennes EM, et al. *Hepatology*. 2008 Jul;48(1):169-176.

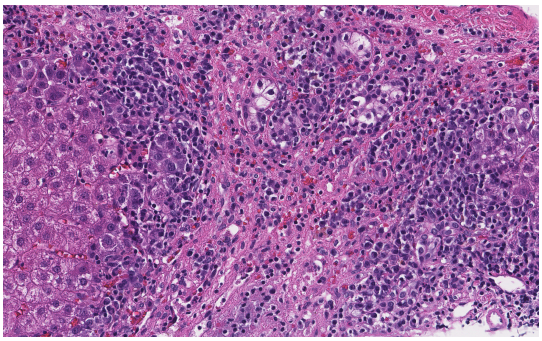
Drug Induced AIH-Like Liver Injury

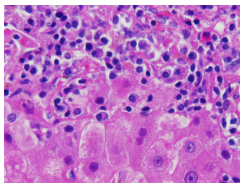
- Commonly Implicated Agents:
  - Minocycline
  - Nitrofurantoin
  - Infliximab
  - Alpha-methyldopa
  - Adalimumab
  - Halothane
- Checkpoint Inhibitor toxicity
  - Lack laboratory and histological features of AIH
  - Majority respond to glucocorticoid therapy

Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065

AIH-Histopathology

- Interface hepatitis
- Plasma cell infiltration (66%)
- Lobular hepatitis (47%)
- Centrilobular necrosis (29%)
- Emperipolesis (65%)
- Hepatocyte rosettes (33%)





- NASH features seen in 17-30%
- IgG4+ plasma cells can be present

Images courtesy of Maura O'Neil
Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065

AIH-Acute Liver Failure/OLT

- Acute Liver Failure
  - Histopathology
    - Central perivenulitis (65%)
    - Plasma cell infiltrate (63%)
    - Hepatic necrosis (42%)
    - Lymphoid follicles (32%)
  - Eval for OLT if no improvement after corticosteroids for 1-2 weeks
- OLT
  - 5% of OLT recipients in US due to AIH
  - AIH recurrence
    - 6-12% within 1 yr after OLT
    - 36%-68% after 5 yrs
  - Gradual withdrawal of glucocorticoids can be considered
- De Novo AIH
  - Criteria:
    - Indication for OLT other than AIH
    - >6 months after OLT
    - Exclude plasma cell rich rejection/hepatitis
  - Histology: Interface hepatitis features with lymphoplasmacytic infiltrates
  - Treatment: Similar to AIH

Stravitz RT, et al. *Hepatology*. 2011 Feb;53(2):517-526.
Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065

AIH-Treatment

- First line
  - Steroids
    - Prednisone -or-
      - Adults: 20-40 mg/d
      - Peds: 1-2 mg/kg/d
    - Budesonide 9 mg/d
  - Azathioprine (AZA) 50-150 mg/d
    - Check TPMT activity prior to start
- Second Line
  - MMF
  - Tacrolimus/Cyclosporine
- Salvage Therapies
  - Anti-TNF
  - Anti-CD20

- AIH Cirrhosis: Do not use budesonide-risk for PV thrombosis
- Acute Severe AIH: Prednisone 60 mg/d or IV steroids
- Do not use AZA in decompensated cirrhosis or acute severe AIH

Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065

AIH-Treatment Withdrawal

- Treatment withdrawal option after biochemical remission ~2 years (normal ALT, IgG levels)
- Liver biopsy may not be mandated in all adults
- Prewithdrawal liver biopsy advised in children
- Relapse in 50-87% of adults, 60-80% children

Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065

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Primary Biliary Cholangitis (PBC)-Introduction

- 9:1 Female:Male predominance
- 15% become decompensated over 5 years
- Etiology due to genetic and environmental triggers
- Loss of humoral tolerance (AMA) and increase of (CD)4+CD8+ pyruvate dehydrogenase complex (PDC-E2) specific T-cells in the liver
- Specific environmental agents (xenobiotics) may lead to loss of tolerance to PDC-E2
  - 2-octynoic acid – Cosmetics
  - 6,8-bis- (acetlythio) octanoic acid – Acetaminophen metabolite

Lindor KD, et al. *Hepatology*. 2019 Jan;69(1):394-419.

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PBC-Diagnosis

- Biochemical cholestasis
  - Alkaline phosphatase elevation
  - Can have mild AST/ALT elevations
- Antimitochondrial Antibody (AMA)-Targets lipoic acid present on the 2-oxo-aciddehydrogenase complexes on the inner mitochondrial membrane
  - Found in 95% of PBC patients
  - 0.5% population AMA positive
  - AMA+ 17% 5 year incidence of PBC
- Increased serum IgM
- ~50% may have + ANA or SMA
- Biopsy not required for diagnosis

Lindor KD, et al. *Hepatology*. 2019 Jan;69(1):394-419.

PBC-Histopathology

- Chronic non-suppurative cholangitis
- Florid duct lesion
  - Inflammatory changes and periductular necrosis
- Epithelioid granulomas (early stage)
- Portal venules compressed / occluded
- Ductopenia

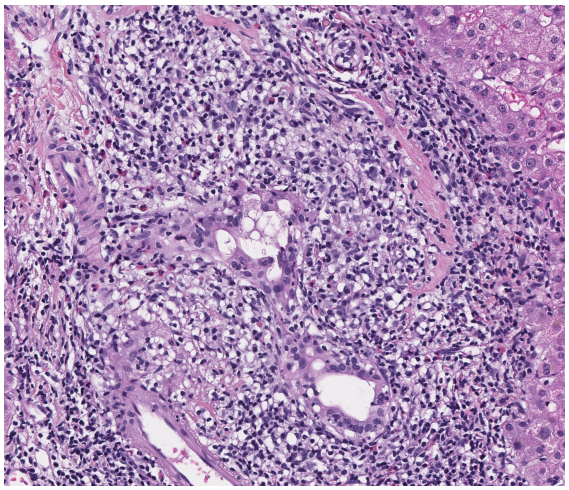


Image courtesy of Maura O'Neil

Lindor KD, et al. *Hepatology*. 2019 Jan;69(1):394-419.

PBC-Clinical Features

- Symptoms: Fatigue 50-80%, Pruritis 20-70%, RUQ abdominal pain 17%, *Sicca syndrome*
- Concomitant autoimmune conditions: Sjogren syndrome, CREST, scleroderma, Raynaud disease
  - Possible: Autoimmune thyroid, celiac disease
- Exam findings: Excoriations, xanthelasma, xanthoma, hepatomegaly

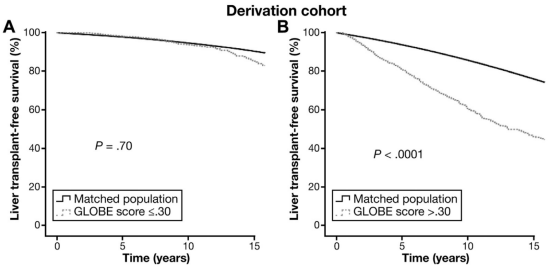
Lindor KD, et al. *Hepatology*. 2019 Jan;69(1):394-419.

PBC-Prognostic Models

Prognostic Models:

- GLOBE score:
  - Bilirubin
  - Albumin
  - Alk phos
  - Platelet count

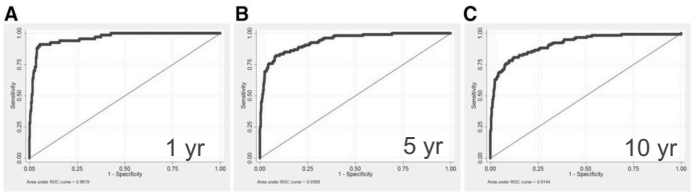
  } At 1 year
  - Age at treatment start
  - https://www.globalpbc.com/globe



- UK-PBC score:
  - Alk phos
  - AST/ALT
  - Bilirubin

  } At 1 year
  - Albumin
  - Platelet

  } Baseline



Lammers WJ, et al. *Gastroenterology*. 2015 Dec;149(7):1804-1812.e4.
Carbone, et al. *Hepatology*. 2016;63:930-950.

PBC-Treatment

Ursodeoxycholic Acid (UDCA)

- Dosed 13-15 mg/kg/d
- Mechanism: Choleretic, cytoprotective, anti-inflammatory, immunomodulatory
- Improved biochemistries, survival, reduced need for OLT
- Cholestyramine may affect absorption
- 40% inadequate response to treatment
  - Defined as Alk phos >1.67 ULN after 6-12 months
- Side effects: Diarrhea, thinning of hair
- Rebound pruritis and ↑ in ALP, AST/ALT with withdrawal/discontinuation of UDCA

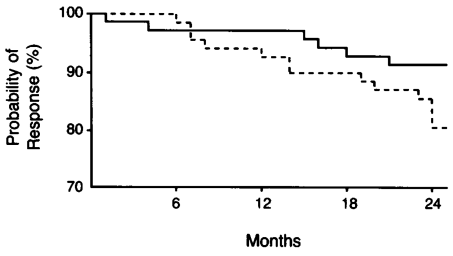


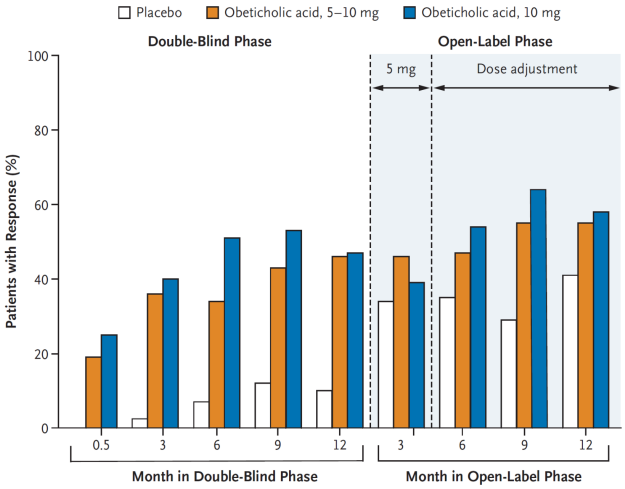
Figure 1. Probability of Responding to Treatment with Ursodiol (Solid Line) or Placebo (Dotted Line).

Poupon RE, et al. *N Engl J Med*. 1991;324:1548-1554
Lindor KD, et al. *Hepatology*. 2019 Jan;69(1):394-419.

PBC-Treatment

Obeticholic Acid (OCA)

- Dosed 5-10 mg/day
- Indication: Inadequate response to UDCA (alk phos >1.67 ULN) or intolerance of UDCA
- Mechanism: Farnesoid X receptor agonist
- 21-25% reduction in ALP
- Side effects: Pruritis, abdominal pain, hyperlipidemia
- Use discouraged in decompensated patients (CTP-B/CTP-C)
  - Reduced dosing in CTP-B/CTP-C population (5 mg/week)
  - FDA Box Warning issued 2/2018



Nevens F, et al. *N Eng J Med*. 2016;375:631-643.
Lindor KD, et al. *Hepatology*. 2019 Jan;69(1):394-419.

PBC-Symptom/Complication Management

- Fatigue
  - Check TSH, consider depression, OSA, anemia
  - Fluoxetine, Ondansetron, Modafanil all no benefit in studies
- Pruritis
  - Anion-exchange resins/Bile acid sequestrants
  - Rifampicin 150-300 mg/d
  - Opiate Antagonists-Naltrexone 50 mg/d
  - SSRI-Sertraline 75-100 mg/d
  - Phenobarbital
  - Antihistamines
- Sicca Syndrome
  - Keratoconjunctivitis Sicca-Artificial tears, Pilocarpine/Cevimeline
  - Xerostomia
- Portal hypertension can develop without cirrhosis
- Esophageal varices
  - EGD at diagnosis if suspected cirrhosis
- Osteopenia/Osteoporosis
  - Calcium 1000-1500 mg/d
  - Vitamin D 1000 IU/d
  - Monitor bone density
  - Alendronate can be used
- Hyperlipidemia
  - Potential ↑ risk for CV disease
  - UDCA lowers LDL
- Fat-Soluble vitamin deficiencies
  - Vitamin A, D, E, K

Lindor KD, et al. *Hepatology*. 2019 Jan;69(1):394-419.

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PBC-Liver Transplant

- Excellent outcomes with OLT
- Graft survival: 1 yr-85%, 3 yr-80%, 10 yr-72%
- Patient survival: 1 yr-90.2%, 3-yr-86.7%, 10 yr-79%
- Recurrent disease in 20-30% over 10 yrs, 50% at 20 yrs
- ? Reduced incidence of recurrence with CSA
- UDCA may lower recurrence rates (21% vs. 62%)

Bosch A, et al. *J Hepatol*. 2015;63:1449-1458.
Lindor KD, et al. *Hepatology*. 2019 Jan;69(1):394-419.

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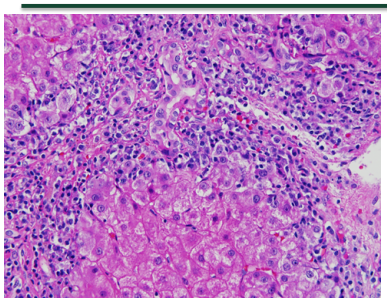
AMA Negative PBC

- Should not utilize nomenclature 'Autoimmune cholangitis' interchangeably
- ↑ prevalence of ANA, SMA; lower IgM levels
- Presence of PBC-specific antinuclear antibodies
  - 30% with sp100 and gp210 by direct immunofluorescence
  - 35% anti-kelch-like 12
  - 22% anti-hexokinase 1
- Similar PBC histology with less portal inflammation

Chasca DM, Lindor KD. *Clin Liv Dis*. 2018; 22(3):589-601.
Ozaslan E, et al. *Clin Res Hepatol Gastroenterol*. 2016 40(5):553-561.
Lindor KD, et al. *Hepatology*. 2019 Jan;69(1):394-419.

AIH/PBC Overlap



- Clinical description
- Non validated pathologic entity
- May help predict nonresponse to conventional treatment
- ↑ risk of treatment failure, death, or need for OLT
- Treatment: Pred + AZA + Urso

- Paris Criteria-AIH/PBC Overlap
  - 2 of 3 PBC criteria must be met:
    - Alk phos >2 fold ULN or GGT > 5 fold ULN
    - AMA positive
    - Florid duct lesions on histopathology
  - 2 of 3 AIH Criteria must be met:
    - Interface hepatitis (Mandatory)
    - ALT >5 fold ULN
    - IgG >2 fold ULN or SMA positive

Image courtesy of Maura O'Neil
Chazouilleres O. et al. *Hepatology*. 1998;28:296-307.
Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065

AIH/PSC Overlap

- Autoimmune Sclerosing Cholangitis (ASC) in children
- Presence of UC
  - AIH adults-16%
  - AIH children-20%

- Criteria:
  - Typical AIH features
  - Absence of AMA
  - PSC features:
    - Evidence of large duct PSC on ERCP or MRCP

    -OR-
    - Small duct PSC features on histology

Mack CL, et al. *Hepatology*. 2019 Dec 21. doi: 10.1002/hep.31065

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Primary Sclerosing Cholangitis (PSC)-Introduction

- Highly variable natural history
- Diagnosis of exclusion
- No associated autoantibody profile
  - ANA, SMA may be seen in >50% of cases
  - Presence of IgG4+ in PSC (10%) may predict a more aggressive course
- 60-70% male
- Age at diagnosis: ~30-40 yrs

Lindor KD, et al. *Am J Gastroenterol.* 2015 May;110(5):646-659
Chapman R, et al. *Hepatology*. 2010 Feb;51(2):660-678.

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PSC-Diagnosis

- Characteristic multifocal biliary strictures with segmental dilatations
  - Seen on ERCP, MRCP or percutaneous transhepatic cholangiography
- Cholestatic biochemical profile
- Secondary causes of biliary injury excluded
- Small duct PSC: Clinical, biochemical and histological features of PSC with normal cholangiogram
  - Biopsy required for diagnosis
  - 12% can progress to large duct PSC

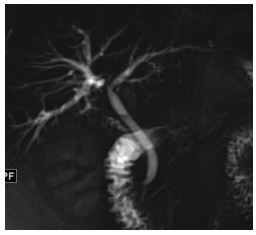


Image courtesy of Ryan Ash

Chapman R, et al. *Hepatology*. 2010 Feb;51(2):660-678.
Bjornsson E, et al. *Gut*. 2002 Nov; 51(5):731-735.

Secondary Causes of Sclerosing Cholangitis

- AIDS Cholangiopathy
- Cholangiocarcinoma
- Choledocholithiasis
- Diffuse intrahepatic metastasis
- Eosinophilic cholangitis
- Hepatic inflammatory pseudotumor
- Histiocytosis X
- Intra-arterial chemotherapy
- IgG4-associated cholangitis
- Ischemic cholangitis
- Mast cell cholangiopathy
- Portal hypertensive biliopathy
- Recurrent pancreatitis
- Recurrent pyogenic cholangitis
- Surgical biliary trauma

Adapted from: Chapman R, et al. *Hepatology*. 2010 Feb;51(2):660-678.

PSC-Liver Biopsy/Histological Features

- Biopsy may be needed for diagnosis if ERCP/MRCP negative-evaluate for small duct PSC or overlap syndromes
- Histology findings nonspecific
- Periductal concentric fibrosis ("Onion-skin")
  - Infrequently seen
  - Not pathognomonic

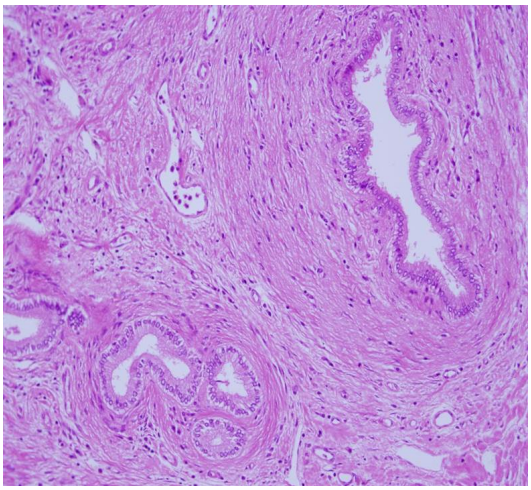


Image courtesy of Maura O'Neil
Chapman R, et al. *Hepatology*. 2010 Feb;51(2):660-678.

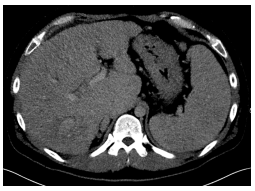
PSC-Treatment

- No specific approved pharmacotherapy
- Symptom directed management
- UDCA
  - Not recommended
  - Trials of high dose UDCA (28-30 mg/kg/d) ↑ risk of death/OLT
  - Improvement in biochemistries at <20 mg/kg dosing, possible improvement in patients who normalize biochemistries
- No benefit: Corticosteroids, AZA, CSA, TAC, MTX, MMF

Lindor KD, et al. *Hepatology* 2009 Sep;50(3):808-814.
Lindor KD, et al. *Am J Gastroenterol.* 2015 May;110(5):646-659
Chapman R, et al. *Hepatology*. 2010 Feb;51(2):660-678.

PSC-Complications

- Dominant Strictures ~50% of PSC patients
  - Biliary sphincterotomy, endoscopic dilatation +/- stent, brushings
  - Percutaneous cholangiography
- Cholangitis
  - Recurrent episodes→Prophylactic antibiotics, eval for OLT
- Cholangiocarcinoma
  - 10-15% of PSC patients
  - Screen with US/CT/MRI +/- CA 19-9 every 6-12 months
- Gallbladder disease
  - Cholecystectomy recommended for any GB mass lesion/polyp
- Metabolic bone disease
- Portal hypertension



Images courtesy of Shaun Best

Chapman R, et al. *Hepatology*. 2010 Feb;51(2):660-678.
Lindor KD, et al. *Am J Gastroenterol.* 2015 May;110(5):646-659.
Bowlus CL, et al. Clin Gastroenterol Hepatol. 2019 Nov;17(12):2416-2422

PSC and IBD

- Concomitant IBD common: 60-80% UC>>Crohn's
  - 5-10% of IBD patients have PSC
- Full colonoscopy with biopsies recommended at diagnosis
- Endoscopic findings in PSC/UC:
  - Rectal sparing, backwash ileitis, mild/quiescent course, ↑ risk of pouchitis, ↑ peristomal varices
- Increased risk for colon cancer before and after OLT:
  - Colonoscopy every 1-2 years in UC/PSC patients
  - Colonoscopy annually following OLT in UC/PSC patients

Chapman MH, et al. *Gut* 2019;68:1356-1378
Lindor KD, et al. *Am J Gastroenterol*. 2015 May;110(5):646-659
Chapman R, et al. *Hepatology*. 2010 Feb;51(2):660-678.

PSC-Liver Transplant

- ~85% 5 year survival rates
- Surgical approach: Roux-en-Y choledochoduodenostomy
- Disease recurrence in 20-25% in 5-10 years
  - ↑ risk with IBD, intact colon, male sex, prior history of CCA, ACR

Chapman R, et al. *Hepatology*. 2010 Feb;51(2):660-678.

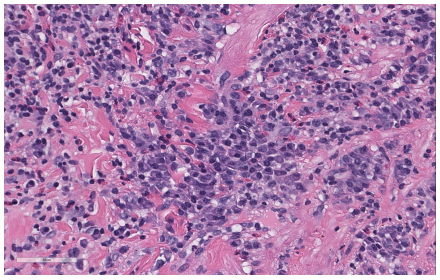
IgG4 Sclerosing Cholangitis

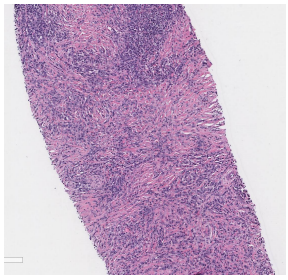
- Part of IgG4-related disease (IgG4-RD); nearly any organ can be involved
- Epithelial organs primary target for IgG4-RD
- Variable presentation: Biliary strictures to mass-like features, mimicking malignancy
- Slight male predominance in US, mean age ~55 yrs
- 6-10% of IgG4-RD with hepatobiliary involvement
- 6-10% IgG4-SC patients have IBD
- Treatment:
  - Initial therapy: Prednisone 40 mg/d for 4 weeks followed by taper
  - Maintenance/Relapse: AZA, Rituximab

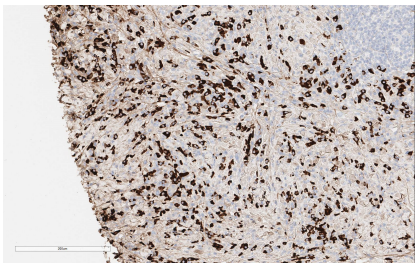
Chen JH, Deshpande V. *Gastroenterol Clin North Am.* 2017 Jun;46:(2):195-216.

IgG4 Sclerosing Cholangitis-Histology

- Diffuse increase in IgG4+ plasma cells
- IgG4:IgG ratio >40%
- Storiform fibrosis
- Obliterative phlebitis
- Lymphoplasmacytic infiltrate







Images courtesy of Maura O'Neil

Chen JH, Deshpande V. *Gastroenterol Clin North Am.* 2017 Jun;46:(2):195-216.

IgG4 Sclerosing Cholangitis vs. PSC

	IgG4 Sclerosing Cholangitis	PSC
Age / Gender	50-70 yrs old / M>F	30-50 yrs old / M>F
Cholangiogram	Long strictures with upstream dilatation	Short strictures with normal caliber duct in between (Beads on string)
Extrahepatic organ involvement/ Disease association	Pancreas, salivary glands, kidneys, periorbital tissues, aorta, lymph nodes, lungs, meninges	IBD
IgG4 Elevation	90%	15%
Histology	Dense IgG+ lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis	Ductopenia, onion-skin periductal fibrosis
Immunohistochemistry >10 IgG4+ cells/HPF	Usually	Occasionally
Response to steroids	Yes	No

Adopted from: Chen JH, Deshpande V. *Gastroenterol Clin North Am.* 2017 Jun;46:(2):195-216.

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GOOD LUCK!!!

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