Interactive Case Presentation #2: Autoimmune Liver and Biliary Diseases

Moderator:
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The Patient: T.H. (June 10, 2016)

HPI: 52 yo Caucasian female w/ history of elevated liver enzymes, first noted April 2016.

- 5/12/16: AST/ALT 100s-200s, ALP 180, Tbili 0.9, Albumin 4.4, Plts 280
- 6/4/16: AST/ALT in the 1000s, ALP 380, Tbili 1.1, Albumin 3.4, Plts 299
- VS: 145/92, 75, 16, 97.6, Weight: 154, BMI 28

Meds:

- ASA 81 mg, Multi vit, Lipitor 20 mg, levothyroxine 100 mcg
- Took nitrofurantoin x 12 weeks for recurrent UTIs last fall

The Patient: T.H.

PMH/PSH:

- Hyperlipidemia
- UTIs
- Anxiety
- HTN
- Hypothyroidism
- Prediabetes

FMH:

- M-hypothyroidism, Sjogren syndrome
- D-Alzheimer's, HTN
- Denies family history of liver disease

Social:

- Married
- Non smoker
- ETOH: 2-4 per week with dinner
- Illicit Drugs: Denies
- Blood transfusion before 1992: Denies
- Tattoos: 1 from tattoo parlor 10 years ago

The Patient: T.H.

ROS:

- +anxiety
- +vague RUQ discomfort
- +fatigue
- +mild pruritus
- +arthralgia

PE:

- +central adiposity, otherwise unremarkable
- Unable to elicit abd tenderness
- No hepatosplenomegaly
- No signs of decompensated liver disease

Differential Diagnosis

- NAFLD
  + Metabolic syndrome features: overweight, central adiposity, prediabetes, hyperlipidemia, HTN
  - Liver enzymes too elevated for NAFLD
- Hepatitis C
  + Tail end of Baby Boomer generation, greatest risk of having HCV, tattoo
  - No other risk factors
- Autoimmune Hepatitis (AIH)
  + Personal hx hypothyroidism, family hx autoimmune disease, took meds believed to be possible triggers for AIH, often see very high AST/ALT
  - Usually ALP is not elevated
- Primary Biliary Cholangitis (PBC) or Primary Sclerosing Cholangitis (PSC)
  + Middle aged female, fatigue, ALP is elevated, pruritus
- Drug Induced Liver Injury (DILI)
  + Nitrofurantoin known to cause DILI

Work up Recommendation

Labs

- CBC, CMP, pt/INR, GGT
- Immunoglobulins A, G, M
- Viral serologies, acute and chronic: Hep C Ab, Hep B and Hep A, EBV, HSV
- Genetic liver diseases: ceruloplasmin, iron %, alpha 1 antitrypsin
- Autoimmune: AMA M2, ASMA, ANA

Imaging and Staging Liver Disease

- Abdominal US
- Elastography or Fibroscan

Hold off on liver biopsy at this time until lab results are in.

An Overview of Primary Biliary Cholangitis & Primary Sclerosing Cholangitis

Emma Pham, MPAS, PA-C
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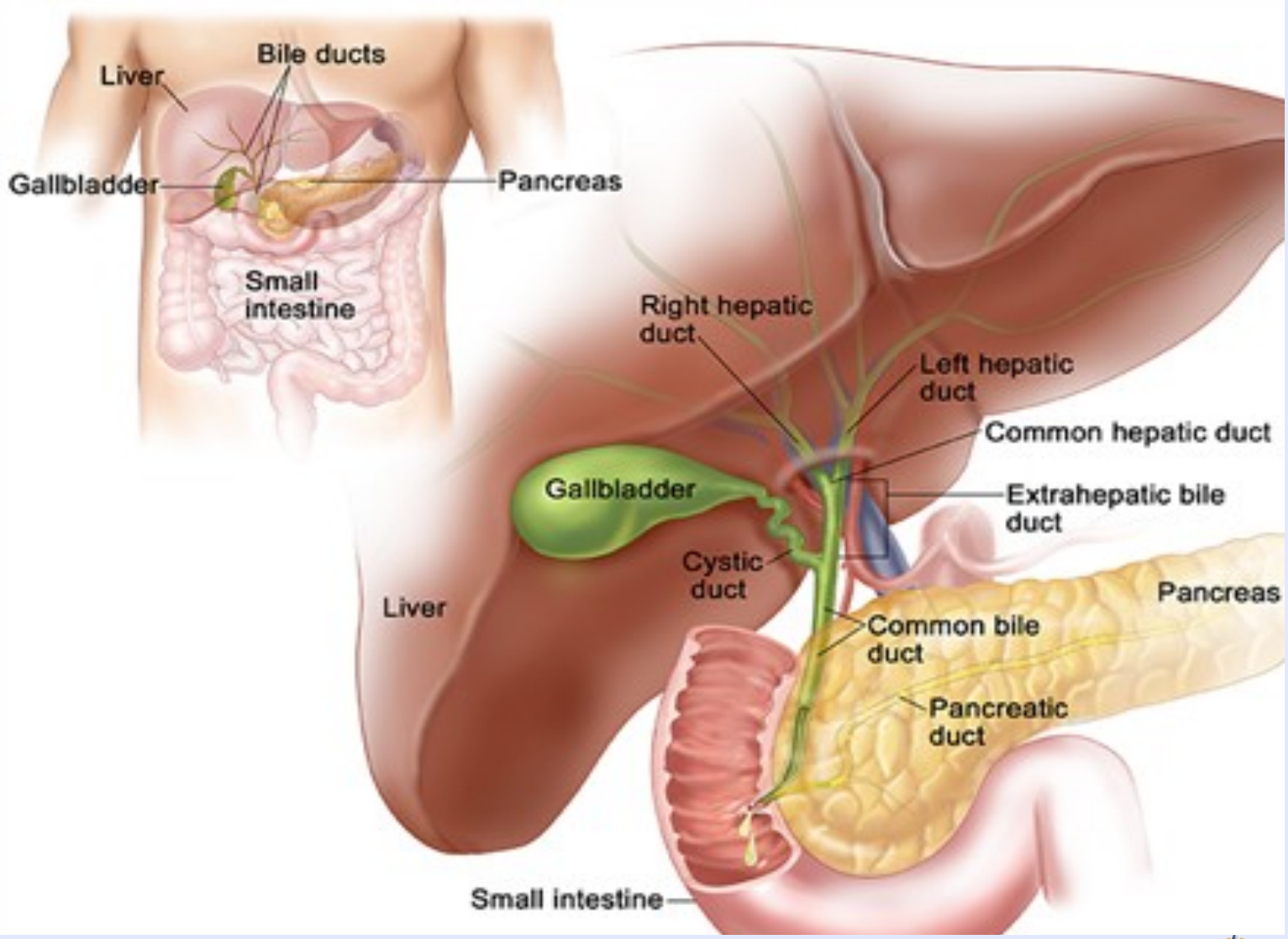
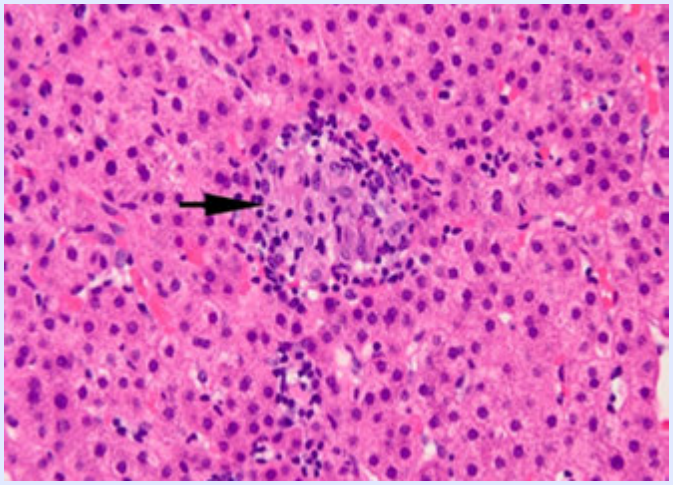
Normal Hepatobiliary Anatomy



http://hb.surgery.ucsf.edu/media/2907208/UCSF045_ExtrahepaticBileDuctAnatomy

Primary Biliary Cholangitis (PBC)

- Formerly Primary Biliary Cirrhosis
- Autoimmune progressive, cholestatic disease which may extend over many decades
- Combination of genetic predisposition and environmental triggers
- Destruction of intrahepatic bile ducts



Presence of lymphocytes, plasma cells, macrophages, polymorphonuclear cells

1. Carey EJ, et al. *Lancet.* 2015;386(10003):1565-1575.
2. Primary biliary cirrhosis (PBC). PathPedia website. http://www.pathpedia.com/education/eatlas/histopathology/liver_and_bile_ducts/primary_biliary_cirrhosis_(pbc).aspx. Accessed February 17, 2016.
3. 1. Kumagi T, Heathcote EJ. *Orphanet J Rare Dis*. 2008;3:1.

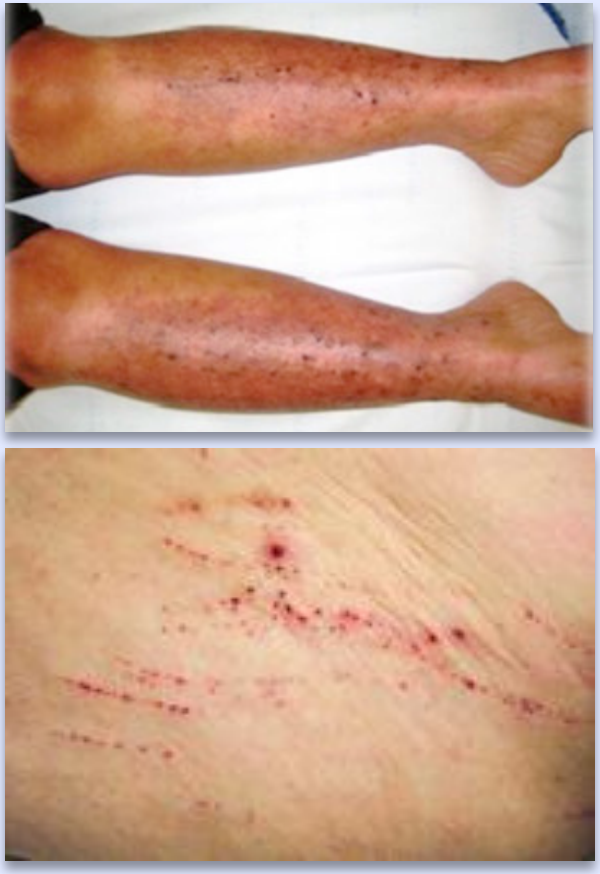
Important Tidbits to Remember

- 95% affected are women
- After HCV, second most common reason for transplant in women
- Elevated alkaline phosphatase is main lab feature
- Symptoms may be absent early in disease
- Untreated, most will progress to advanced disease over 15 years

Clinical Presentation

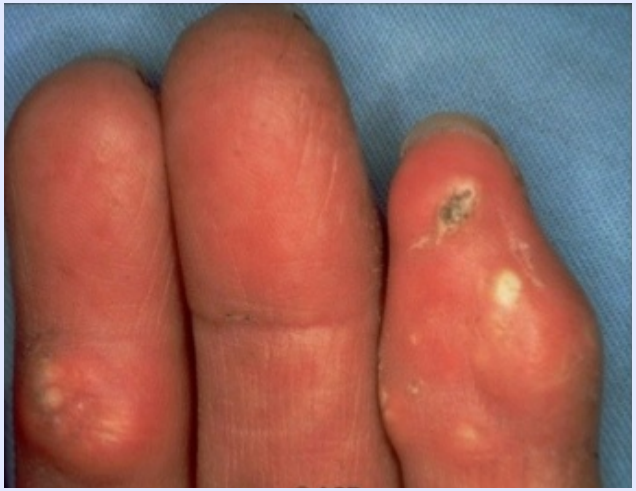
- Most common symptoms
  - Fatigue
  - Pruritus
- SICCA syndrome (dry eyes and/or dry mouth)
- CREST syndrome

Symptoms have no correlation with the natural history of disease

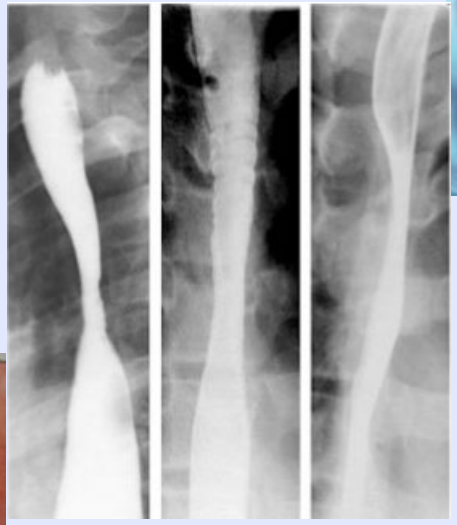


Pinheiro NC, et al. *BMJ Case Rep.* 2013. https://thebileflow.wordpress.com/2011/10/19/pathology-pruritus/.

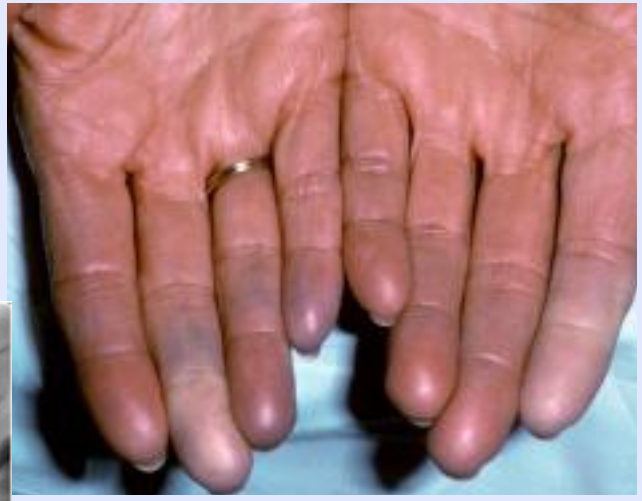
CREST



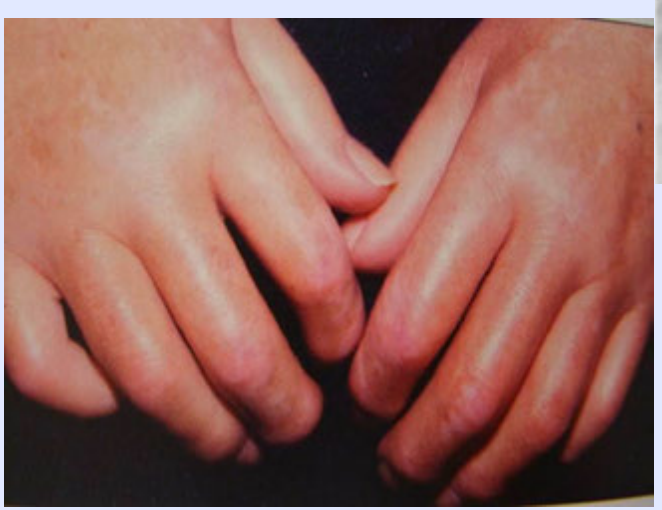
Calcinosis



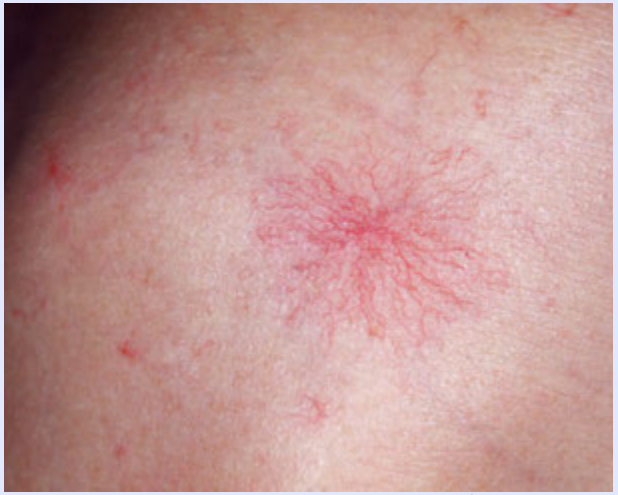
Esophageal dysmotility



Raynaud's



Sclerodactyly



Telangiectasias

Many Patients with PBC Also Suffer from Cholestasis and/or Cirrhosis

	% of Patients Affected
Complications of chronic cholestasis[1]	
Osteoporosis	20%-44%
Hyperlipidemia	75%-95%
Vitamin deficiency	8%-33%
Complications related to cirrhosis	
Varices associated with portal hypertension	6% (with early-stage disease)[1] ~31% (with late-stage disease)[2]
Hepatocellular carcinoma	1%-6% of patients per year[1]

1. Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575; 2. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308.

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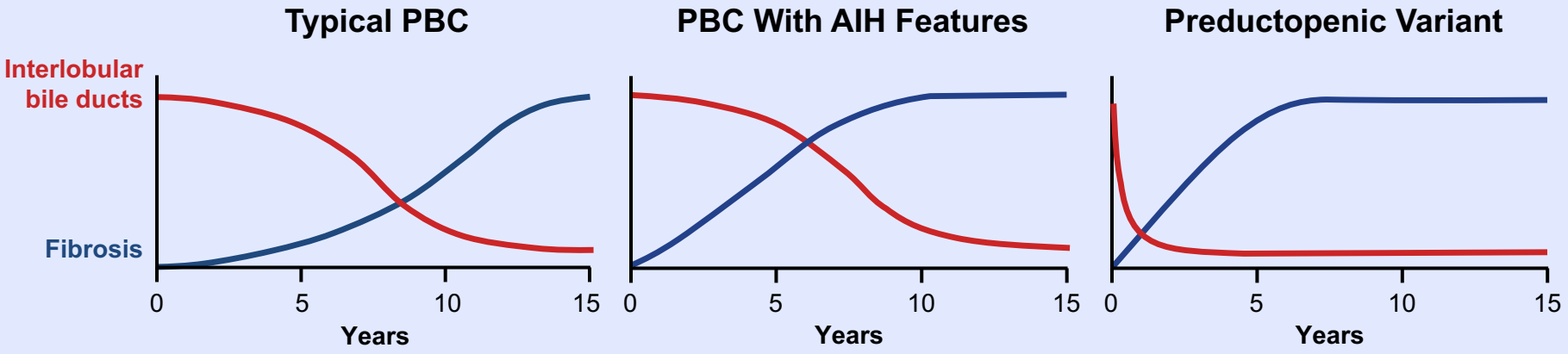
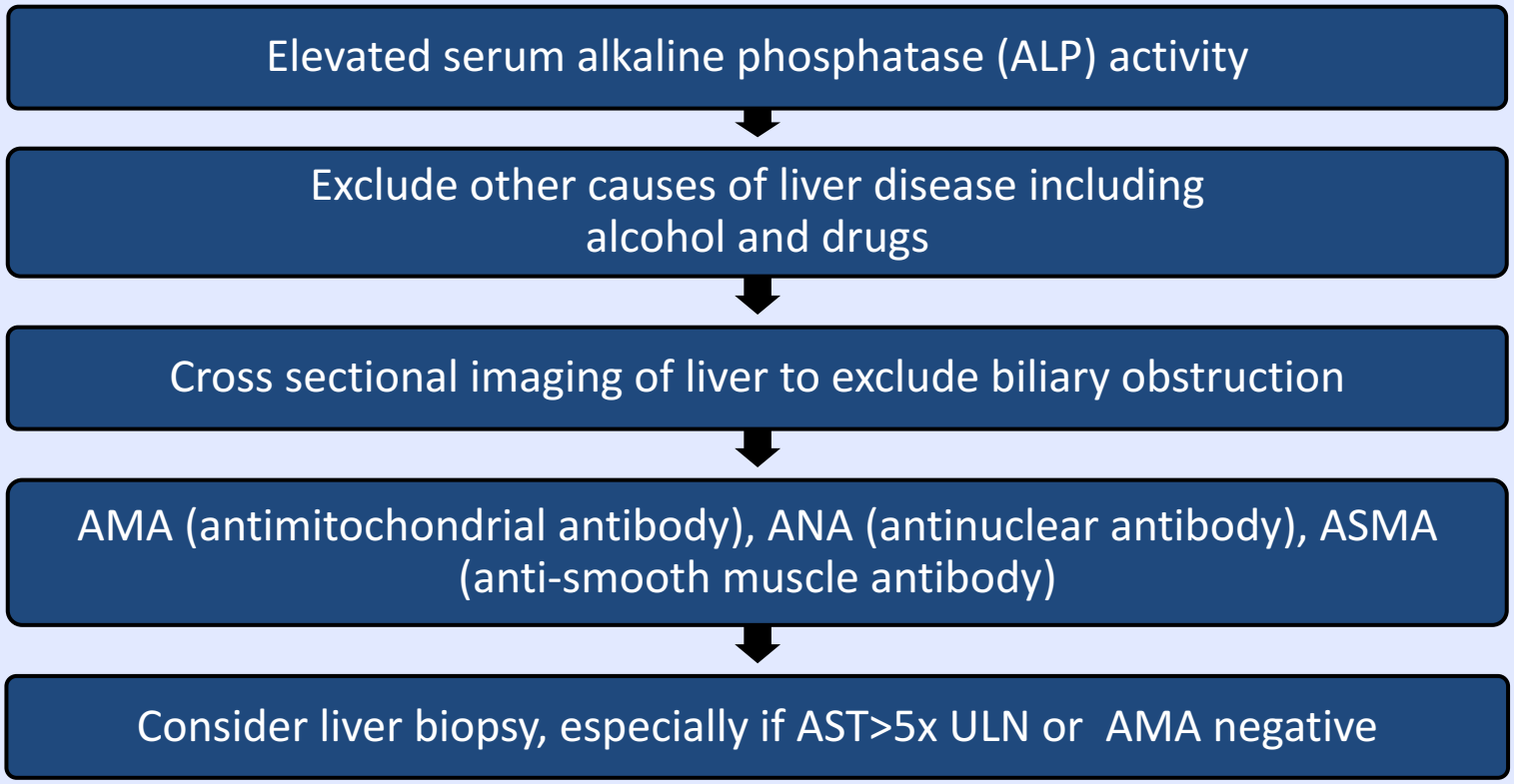
Forms of PBC[1]



- Up to 30% may have a severe, progressive form of PBC resulting in early development of liver fibrosis and liver failure[1]
- Some patients progress through histological stages in less than a decade[2]

1. Poupon R. *J Hepatol*. 2010;52(5):745-758; 2. Al-Harthy N, Kumagi T. *Hepat Med*. 2012;4:61-71.

AASLD Suggested Diagnostic Algorithm for Patients With Suspected PBC



Additional Useful Tests

- IgM elevation
- M2 antibody

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Ursodeoxycholic Acid (UDCA)

- Orally administered nontoxic bile acid
- Balances the bile acid ratio normally produced by the liver, some of which are more toxic to the liver
- UDCA in a dose of 13-15 mg/kg/day
- UDCA is initiated gradually and given BID

AASLD Guidance Document

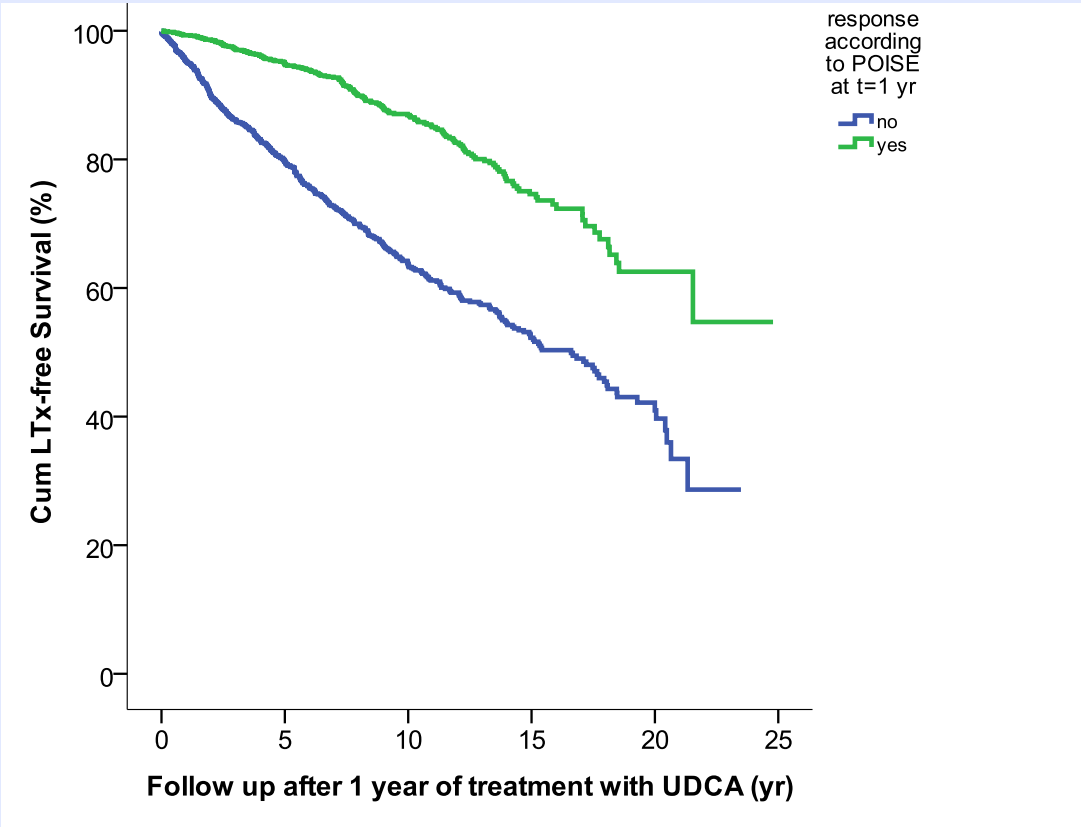
Ursodeoxycholic Acid (UDCA)

- Improvement in liver tests will be seen within a few weeks and 90% of the improvement usually occurs within 6-9 months
- Safe, may improve clinical symptoms, delay progression of disease and survival, and improve QOL
- However, up to 40% of PBC patients treated with UDCA have a suboptimal response

Pares A, *Gastroenterology*, 2006; Marschall HU, *Gastroenterology*, 2005.

ALP <1.67 x ULN and Normal Bilirubin after 1 Year of UDCA is Highly Predictive of Outcome

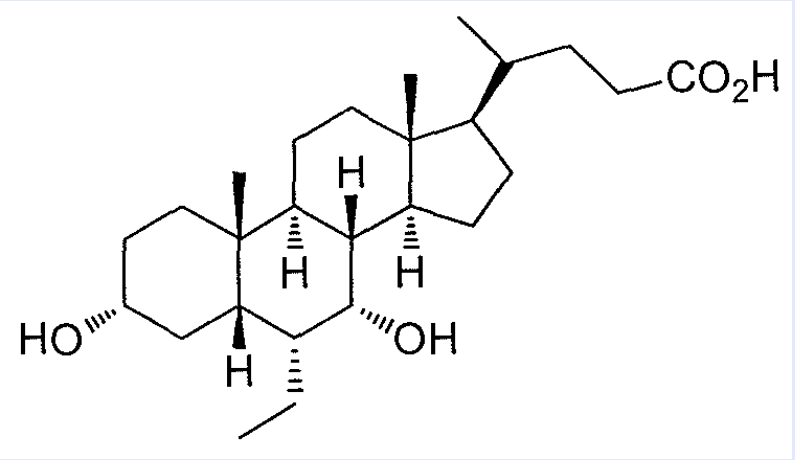
Global PBC Study Group (N=4845)



Lammers, EASL, AASLD. 2013.

Obeticholic Acid (OCA)

- A modified bile acid and FXR agonist
- OCA given to individuals with PBC with an inadequate response to or unable to tolerate UDCA
- Produced a significant clinically meaningful improvement in liver biochemistry
- Approved by FDA on May 27, 2016 (Ocaliva)



Long-term Management of Patients with PBC (AASLD Guidance)

- Liver tests every 3-6 months
- Thyroid status (TSH) annually
- Bone mineral densitometry every 2-4 years
- Vitamins A, D, K annually if bilirubin >2.0
- Upper endoscopy every 1-3 years if cirrhotic or Mayo risk score >4.1
- Ultrasound ± AFP every 6 months in patients with known or suspected cirrhosis

PBC Prognosis Using Mayo Risk Score

The Updated Natural History Model for Primary Biliary Cirrhosis

In the following model, short-term survival probability of a patient with primary biliary cirrhosis is estimated based on repeated observation. Please enter data in the corresponding boxes.

How old is the patient? ____ (years)

What is the bilirubin? ____ (mg/dl)

What is the albumin? ____ (g/dl)

What is the prothrombin time? ____ (seconds)

Does the patient have peripheral edema? ○ No ○ Yes

Is the patient on diuretic therapy? ○ No ○ Yes

Compute

Risk score: ____

Estimated Probability of Survival (%)

Time 0	3 Mos.	6 Mos.	9 Mos.	12 Mos.	15 Mos.	18 Mos.	24 Mos.
100							

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PBC Prognosis Using Mayo Risk Score

How old is the patient?	50	(years)
What is the bilirubin?	3	(mg/dl)
What is the albumin?	3	(g/dl)
What is the prothrombin time?	15	(seconds)
Does the patient have peripheral edema?	○ No ◉ Yes	
Is the patient on diuretic therapy?	○ No ◉ Yes	

Compute

Risk score: 8.38137

Estimated Probability of Survival (%)

Time 0	3 Mos.	6 Mos.	9 Mos.	12 Mos.	15 Mos.	18 Mos.	24 Mos.
100	96	93	92	90	87	82	81

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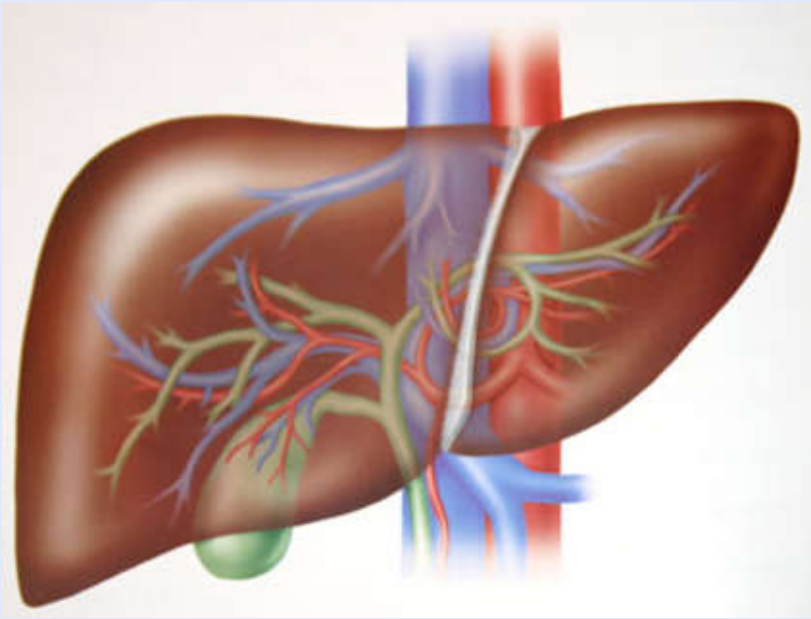
Liver transplantation (LT)

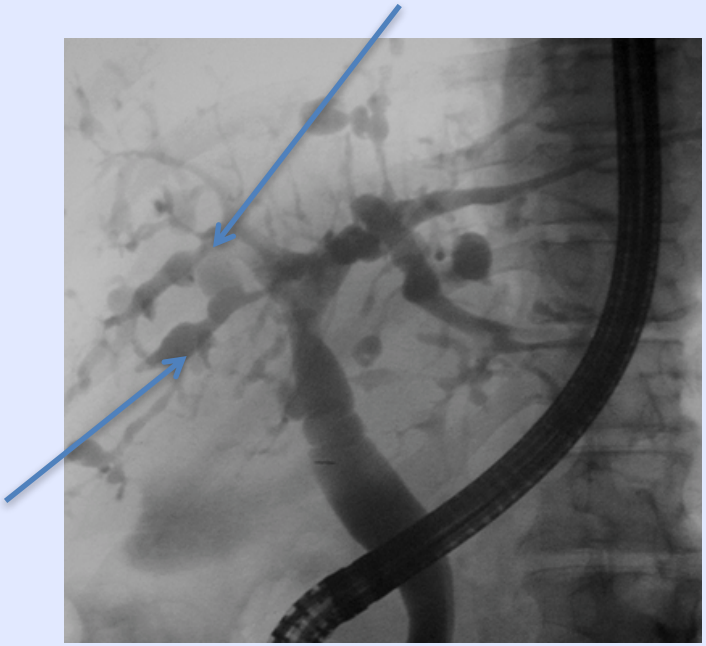
- Indicated for
  - Patients progressing to decompensated cirrhosis
    - Patients with late diagnosis
    - No response to UDCA (30-40%)
    - MELD $\geq$ 15
    - HCC meeting transplant criteria
  - Patients with intractable pruritus



PBC Summary

- PBC is chronic cholestatic disease resulting in destruction of intrahepatic bile ducts
- Most common symptoms of PBC is fatigue and profound pruritus
- Elevated ALP with positive AMA is highly disease-specific
- Majority of patients respond to UDCA
- OCA can be used as adjunct therapy for patients that are non-responder or partial responders to UDCA
- Liver transplantation is an option for patients who are decompensated or have refractory pruritus

What is PSC?: Primary Sclerosing Cholangitis



Bile duct stricturing= “chain of lakes”

- Chronic progressive inflammatory disease than affects extra and/or intrahepatic bile ducts
  - biliary stricturing and fibrosis
  - “chain of lakes” on cholangiogram

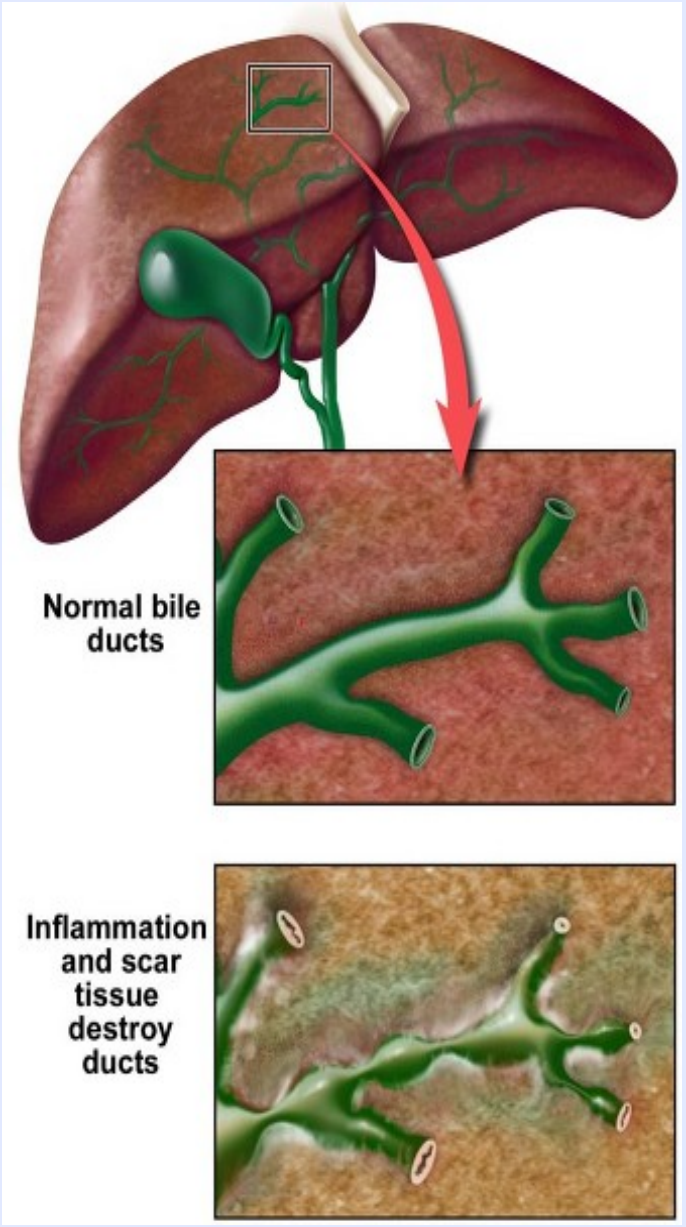
ERCP: endoscopic retrograde cholangio-pancreatography

Epidemiology, Natural History & Prognosis

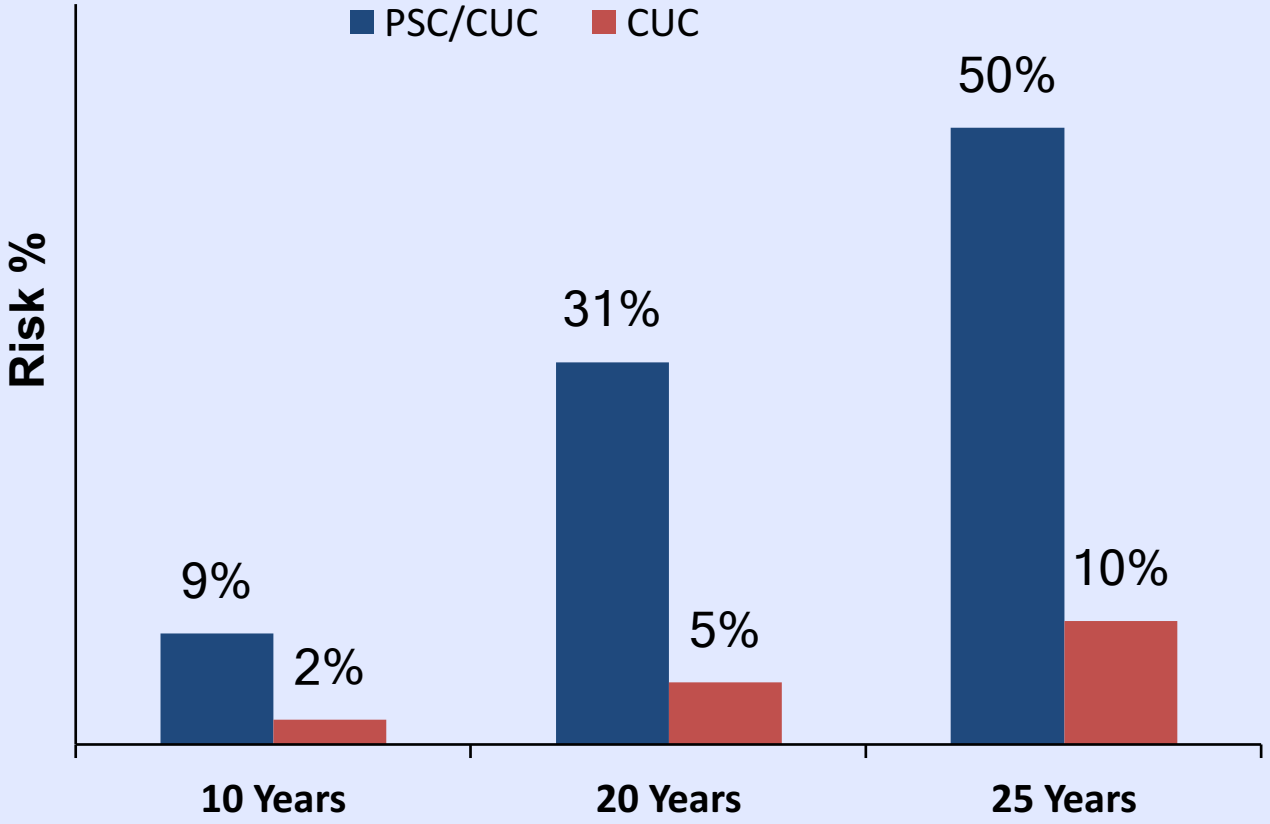
- Prevalence 6-8/100,000
- Usually diagnosed in 20s and 30s
- Male predominance~3:1
- 80% have IBD- usually ulcerative colitis (UC) 90%
  - 4% with UC get PSC
- ~44% asymptomatic at diagnosis
- Median survival ~12 years
- 4th leading diagnosis leading to LT in North America
- Associated with cancer
  - Cholangiocarcinoma
  - HCC (with cirrhosis)
  - Colon Cancer (if IBD present)

Clinical Presentation

- Ranges from asymptomatic to pruritus, fatigue or even jaundice
- May have recurrent bouts of cholangitis with fevers/chills and bacteremia



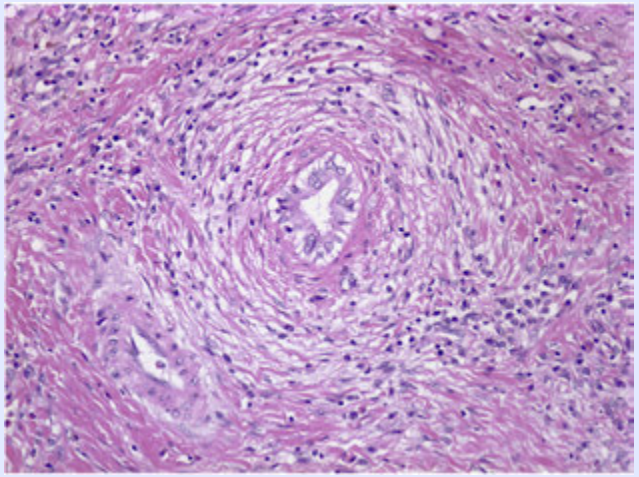
Colon Cancer Risk with IBD/PSC



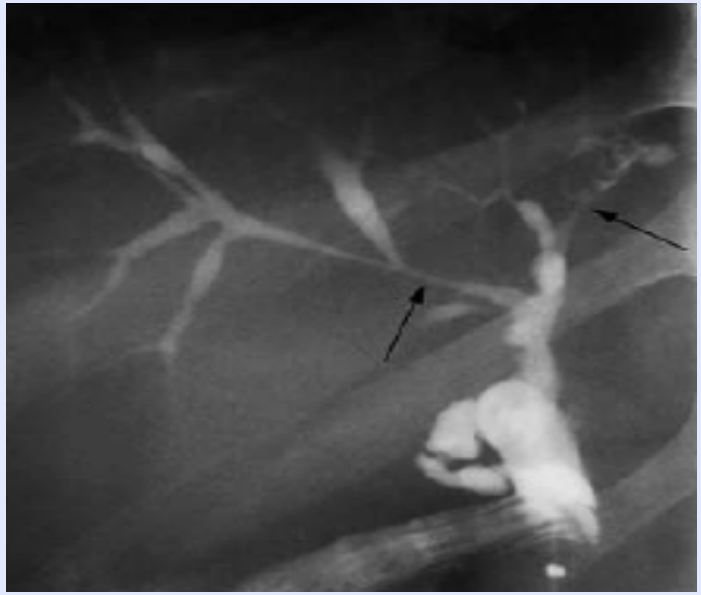
Broome U, Lofberg R, Veress B, et al. Primary sclerosing cholangitis and ulcerative colitis: Evidence for increased neoplastic potential. *Hepatology*. 1995;22(5):1404-8

Diagnosis of PSC

- Cholestatic Liver Tests (elevated ALP and GGT)
- Cholangiography (MRCP or ERCP)
- Exclusion of secondary sclerosing cholangitis
- 95% at least one autoantibody
  - 85% + pANCA
  - 50% + ANA
  - 25% + SMA



Histologic Features of PSC



pANCA is perinuclear antineutrophil cytoplasmic antibody

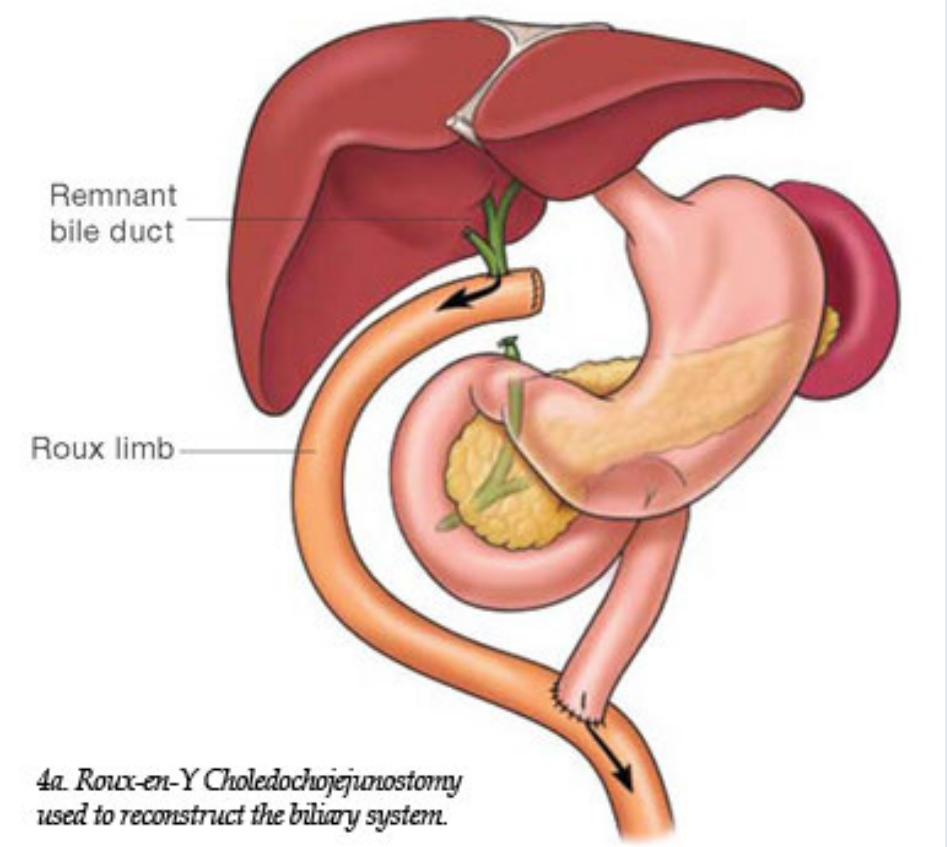
Eaton JE, Talwalkar JA, Lazaridis KN, et al. Pathogenesis of Primary Sclerosing Cholangitis and Advances in Diagnosis and Management. *Gastroenterology*. 2013;145:521-536.

Treatment

- Medical management
  - Ursodeoxycholic acid (20-25 mg/kg)
    - Uncertain benefit but should not use high dose
  - Pruritus: cholestyramine, rifampicin, opioid antagonist
- Endoscopic therapy
  - Balloon dilation and stenting
    - Dilation recommended due to decreased risk of infection
    - Follow bili and alk phos for treatment improvement
- Cholangiocarcinoma (CCA) and HCC surveillance

Liver Transplantation

- Indicated for
  - Patients progressing to decompensated cirrhosis
    - MELD $\geq$ 15
    - HCC meeting transplant criteria
  - Patients with intractable pruritus, recurrent bacterial cholangitis, or cholangiocarcinoma
- Eventually most patients will require LT as there is no effective treatment



4a. Roux-en-Y Choledochojejunostomy used to reconstruct the biliary system.

PSC Summary

- Chronic progressive inflammatory disease affect extra- and/or intrahepatic bile ducts
- No established therapy, however ursodiol can be used
- Risk of biliary cancers and colon cancer
- Liver transplantation is often the only treatment option

Similarities and Differences

Primary Biliary Cholangitis	Primary Sclerosing Cholangitis
Etiology Unclear	Etiology Unclear
Effects Intrahepatic bile ducts	Can effect extra-intrahepatic bile ducts
Vanishing bile ducts Presence lymphocytes, plasma cells, macrophages, and PMNs on biopsy	Stricturing of bile ducts Absences of inflammatory cells on biopsy
Associated with SICCA or CREST syndrome	Associated with UC
UDCA helps in majority of patients; OCA recently approved	New drug therapies are in clinical development; in general PSC leads to liver transplantation

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Lab/Imaging Results (June 10, 2016)

- Labs:
  - Alb 4.4, Tbili 0.5, Alk Phos 200, AST 91, ALT 110, IgM and IgG elevated, ferritin 444, GGT 72, WBC 5.9, Hgb 13.1, HCT 40.7, Plt 280
  - EBV PCR neg, HSV PCR neg, HAV IgM neg, HBV surface AG neg, HBV core IgM AB neg, HCV AB neg
  - ANA 1:160 (pos), AMA M2 +, SMA +
- Abdominal US
  - Liver: mild fatty liver with no focal lesions, spleen: normal
- Elastography
  - 8.2 kPa
  - Moderate fibrosis?
- Biopsy performed and confirmed PBC and AIH

Autoimmune Hepatitis (AIH)

Christy Rosas, MPAS, PA-C

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San Antonio, Texas

AIH: Clinical Presentation

- 30% present with cirrhosis
- Up to 50% may present with jaundice
- Asymptomatic (35-45%) with abnormal enzymes
  - Often discovered during evaluation for other autoimmune conditions

AIH: Demographics and Epidemiology

- Afflicts ~200,000 in U.S.A.
- Incidence 1.9 per 105 per year
  - Prevalence 16.9 per 105
- Afflicts both children and adults
  - Female to male ratio=4:1
- Bimodal age distribution: 10-20 vs. 45-75 yrs
- 6% liver transplants in US

AIH Pathogenesis

- Genetic factors
  - Antigen presentation/immunocyte activation
  - DRB1 encodes for MHC II antigen binding grooves (antigen presentation to T cells)
- Triggering factors
  - Infections (HCV, HDV)
  - Medications

    -Minocycline, Nitrofurantoin, Methyldopa, Atorvastatin, Diclofenac, Augmentin, Isoniazid, Infliximab

Czaja et al. Hepatology 2002;36:479
Krawitt. N Engl J Med 2006;354:54
Manns et al. Hepatology 2006;14:S132

Diagnosis

- Serology
  - Positive ANA, SMA or LKM
  - Elevated serum IgG to twice normal levels
  - 5% have seronegative disease
- Histology
  - Biopsy required for diagnosis ALWAYS
  - Sometimes atypical features
  - Overlap syndromes (PBC/PSC)

Goals for treatment of AIH

- Normalization of ALT and IgG
- Normalization of histology
- Regression of fibrosis
- Prevention of cirrhosis
- Minimization of side effects

AIH: Criteria for Treatment

- Symptomatic disease and either
  - AST>10-fold normal
  - AST 5-10 fold normal and >2-fold elevation of IgG
- Presence of fibrosis

Combination Therapy

Acute presentation and severe histological activity

↓

Corticosteroids 30-60 mg/day for 1-2 weeks + AZA 50-100 mg/day

↓

Prednisone 10 mg/day + AZA 50-100 mg/d

↓ **Gradual taper off prednisone**

Asymptomatic AIH and mild-moderate histological activity

↓

Corticosteroids 20 mg/day for 1-2 weeks + AZA 50 mg/day

↓ **Gradual reduction 2.5 mg/week+same AZA dose**

Prednisone 5-10 mg/day + AZA 50 mg/day

↓ **Gradual taper off prednisone**

Adjust the AZA dose depending on the biochemical response and tolerance

Modified from Medina, et al. *Aliment Pharmacol Ther*. 2003.

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AIH Treatment Side Effects

- Long term prednisone
  - Osteoporosis and fractures
  - Diabetes
  - Obesity
  - CV disease
- Cytopenias
- AZA-induced pancreatitis
- Long term lymphoma and skin cancer risks

AIH: Take Home Points

- Chronic hepatocellular disease in genetically predisposed patients of unclear trigger
- Diagnosis based upon liver enzymes, serology, gamma globulins, and histology
- Immunosuppressive therapy is the mainstay of treatment and is long term for nearly all patients
- Tailor therapy based upon treatment endpoints

Patient T.H.: Treatment Plan

- PBC
  - Ursodiol
  - Obeticholic acid if no response
- AIH
  - Treat with azathioprine and prednisone, weaning the latter off in few months