Primary Biliary Cirrhosis

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- A T-cell mediated inflammatory destruction of intralobular bile ducts progressively leading to cholestasis and cirrhosis
- 9:1 F to M ratio
- Mostly diagnosed between 30-60 years of age
- Considered an autoimmune disease with a genetic susceptibility factor and environmental trigger (eg, infection)

- Anti-Mitochondrial Antibody (AMA): serologic marker found in 90-95% of patients

  - Targets of AMA are family of enzymes in the inner mitochondrial membrane that catalyze oxidative decarboxylation of keto-acid substrates

  - Pts will have polyclonal elevation of IgM, despite the AMA being of the IgG class

  - ~50% of patients will have ANA

  - ~5% of pts will have AMA negative PBC

- Symptomatic disease

  - Fatigue (21-85% frequency)- does not correlate with severity
  - Pruritus (19-55)- can occur at any point of the disease, us. worse at night
  - Hyperpigmentation(25)
  - Hepatomegaly (25)
  - Splenomegaly (15)
  - Xanthelasma (10)
  - Jaundice (3-10)- occurs late in the disease course
  - RUQ pain (8)

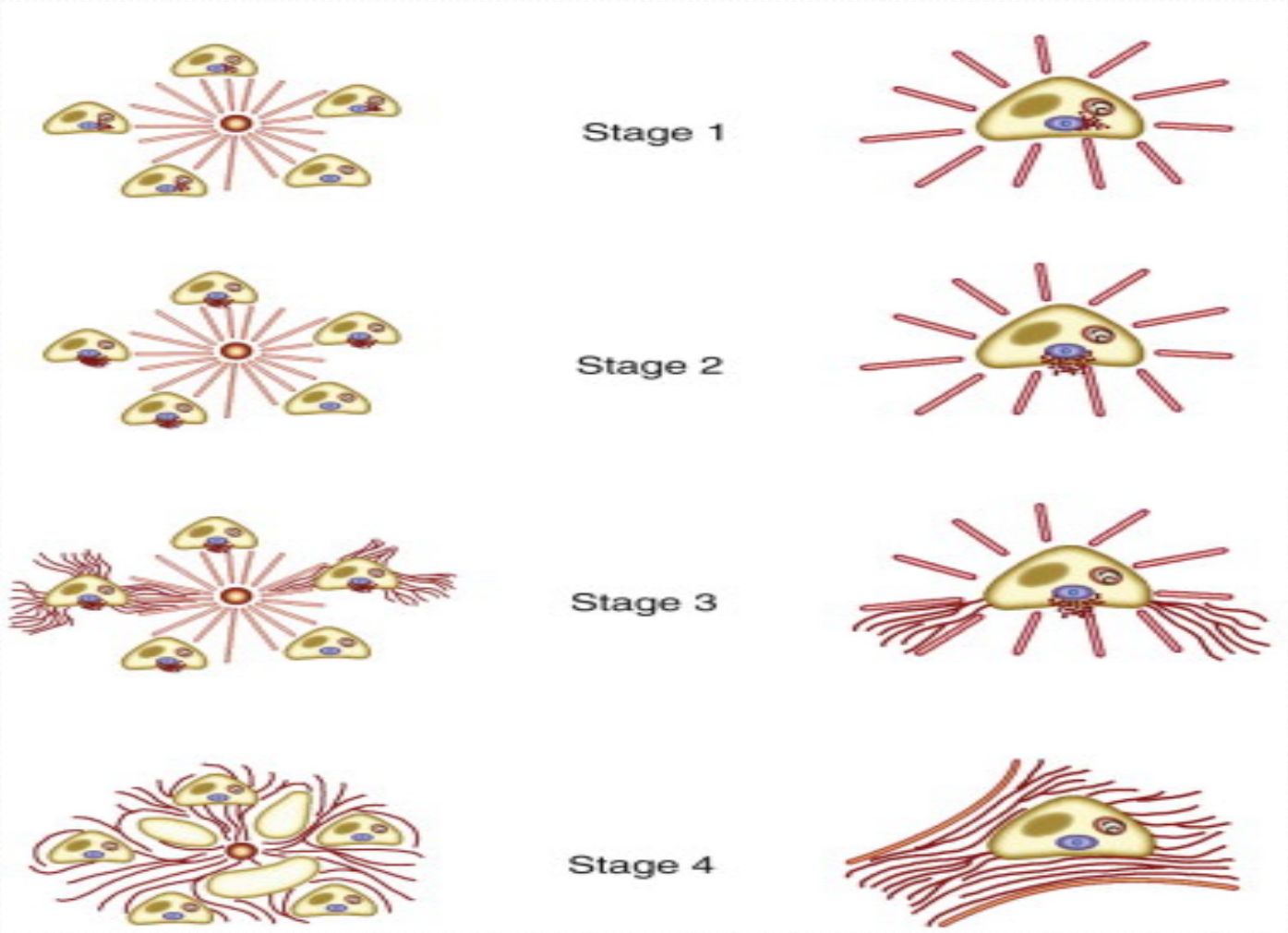
- Lab tests
  - Alkaline phosphatase 3-4x ULN
  - Elevated GGT
  - AST and ALT usually <3x ULN (if higher, suggests AIH overlap or concomitant viral hepatitis)
  - Elevated IgM
  - Elevated serum bile acids
  - Elevated total cholesterol

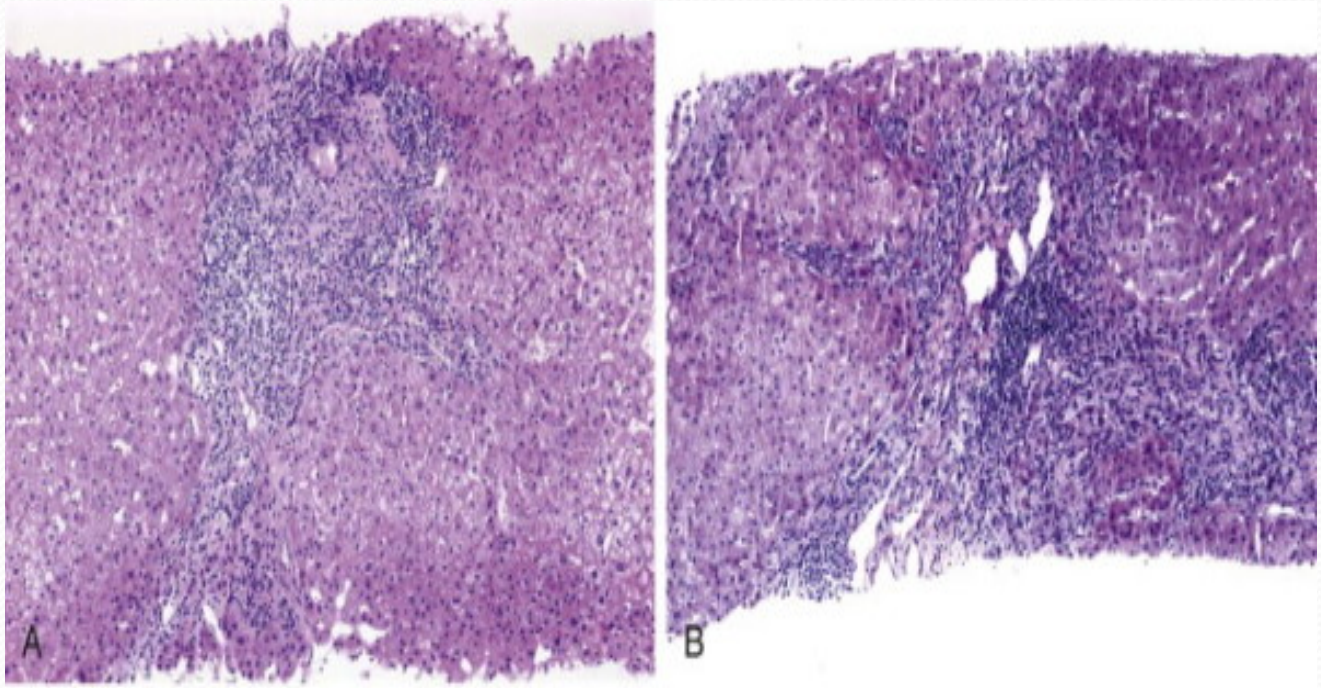
- Serology
  - Indirect immunofluorescence detects AMA (90-95% of patients)
  - RF (70%)
  - ASMA (66%)
  - ANA (50%)
  - Antithryoid (41%)

- Pathology
  - Initial lesion is chronic, nonsuppurative inflammation of the epithelial cells of small bile ducts (interlobular and septal ducts)
  - Ductopenia is the most significant diagnostic finding and is the absence of interlobular bile ducts in >50% of portal tracts
  - Florid duct lesion– segmental degeneration of the interlobular and segmental bile ducts with noncaseating epithelioid granulomas (diagnostic but seen in few cases)
  - The inflammatory infiltrate includes lymphocytes and mononuclear cells at the basal membrane of cholangiocytes undergoing necrosis as well as plasma cells, macrophages and polymorphonuclear cells

- Histologic staging
  - 1: inflammatory destruction of the 100um diameter intrahepatic septal and interlobular bile ducts– the florid duct lesion
  - 2:inflammation extends from the portal tract to the hepatic parencyhma (interface hepatitis)
  - 3:scarring, fibrosis (without regenerative nodules), and lymphocytes in the portal, periportal, and parenchyma
  - 4: cirrhosis with fibrosis and regenerative nodules

Histologic Stages





A: Stage 2 PBC:Mononuclear cells expand the portal tracts, no fibrosis
B: Stage 4 PBC: cirrhosis with fibrosis surrounding the parenchyma, still mononuclear infiltrate in the portal tract

Associated diseases

- Sjogren's syndrome (sicca): 72-100%
- RTA: 50-60
- Arthritis: 4-42
- Gallstones: 33
- Autoimmune thyroiditis:15-20
- Scleroderma and variants: 15-19
  - Raynaud's, CREST
- Cutaneous disorders:11
- HCC: 1-2
- Celiac and pulmonary fibrosis: Rare

- To biopsy or not?
  - Pt with + AMA, alkaline phosphatase >1.5xULN, and AST< 5x ULN→ 98.2% PP value
- To image or not?
  - Useful to rule-out biliary obstruction, otherwise is not helpful in diagnosis

- AASLD diagnostic guide: 2 of 3
  - Lab evidence of cholestasis primarily on basis of elevated AP
  - Presence of AMA
  - Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts

- Asymptomatic disease
  - ~5.6 years from positive AMA to lab abnormalities
  - Less advanced disease
  - Eventually will have progressive disease

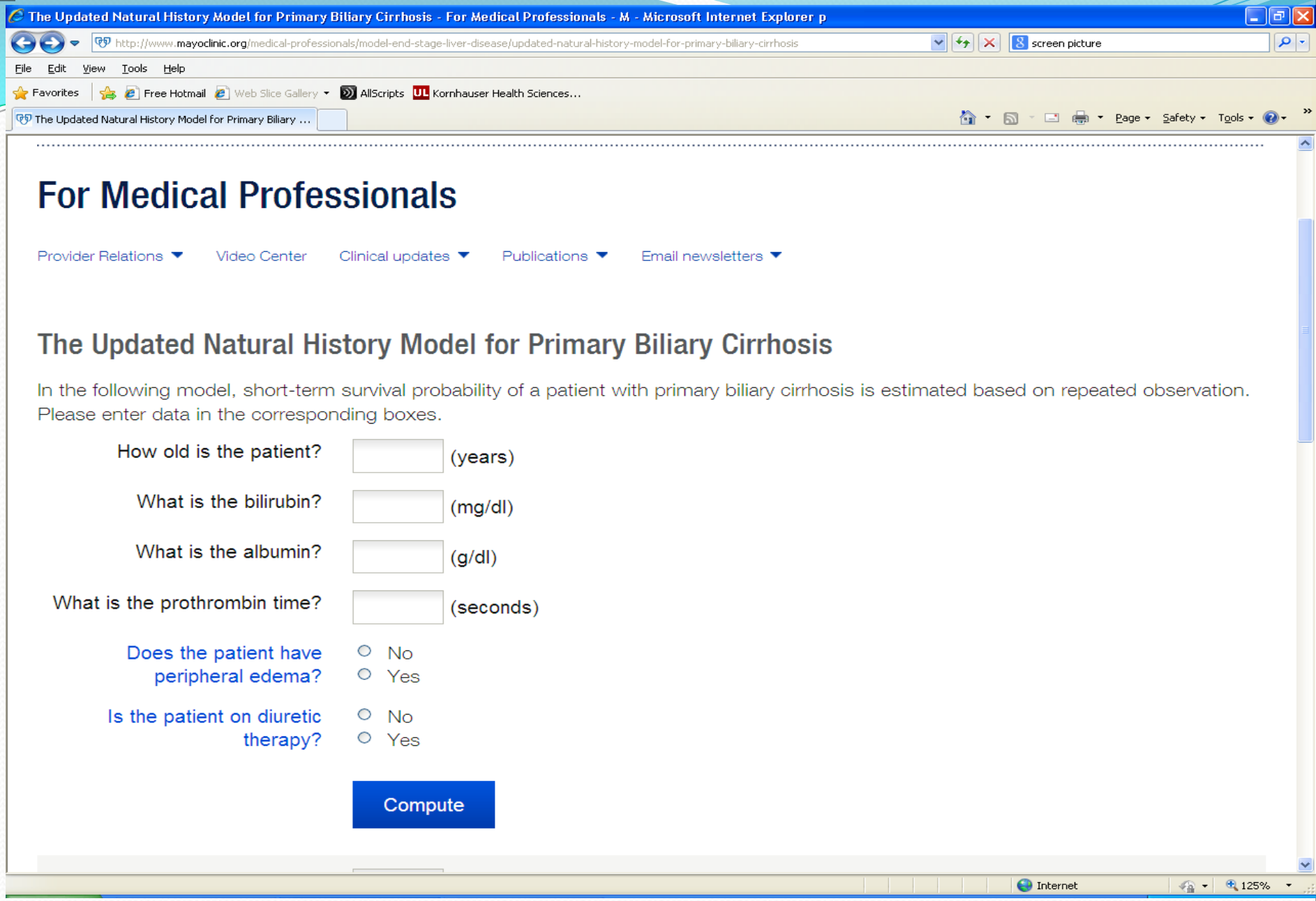
Symptomatic disease

- Fatigue: no correlation to dz severity, stage, or duration (r/o hypothyroidism which occurs in 20% of pts)
  - Rx: modafanil
- Pruritus: unknown causes(? bile components, opiodergic neurotransmission)
  - Rx: cholestyramine, rifampicin, naltrexone, SSRIs
- Sicca syndrome: dry eyes and dry mouth
  - Rx: methylcellulose ggts
- Bone disease: 1/3 will have osteoporosis, due to “low turnover” with decreased bone formation and normal resorption (vitamin D levels are usual nl unless advanced disease
  - Rx: Vitamin D, bisphosphonates (sp. Alendronate)
- Hyperlipidemia: both LDL and HDL elevations, no increased atherosclerotic risk

Treatment (only 1 FDA approved)

- Ursodeoxycholic Acid (UDCA)– occurs naturally in small quantities in human bile (<4%)
  - Proposed mechanisms: inhibiting absorption of toxic endogenous bile salts, stabilizing hepatocyte membranes against the toxic bile salts, replacing the toxic bile salts with less toxic ones, and reducing expression of MHC I and II antigens
  - UDCA increases to 30-60% of the total bile acids

- Dose is 13-15mg/kg/day once daily or divided into BID dosing
  - Rapidly improves lab values, decreases histologic severity of interface hepatitis, inflammation, cholestasis, decreases risk of GE varices, ascites, and delays progression of cirrhosis
- 90% improvement seen in 6-9 months
- 20% will normalize liver chemistry by 2 yrs, 15-35% more by 5 years
- Treatment affect assessed by decline of AP or Mayo risk score
- Does not impact the symptoms (pruritus, fatigue)


The Updated Natural History Model for Primary Biliary Cirrhosis - For Medical Professionals - M - Microsoft Internet Explorer p
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The Updated Natural History Model for Primary Biliary ...
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For Medical Professionals
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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
Internet
125%

- Other therapies: corticosteroids, azathioprine, methotrexate, mycophenolate, etc. have not shown to be of benefit as either solo or add-on therapy

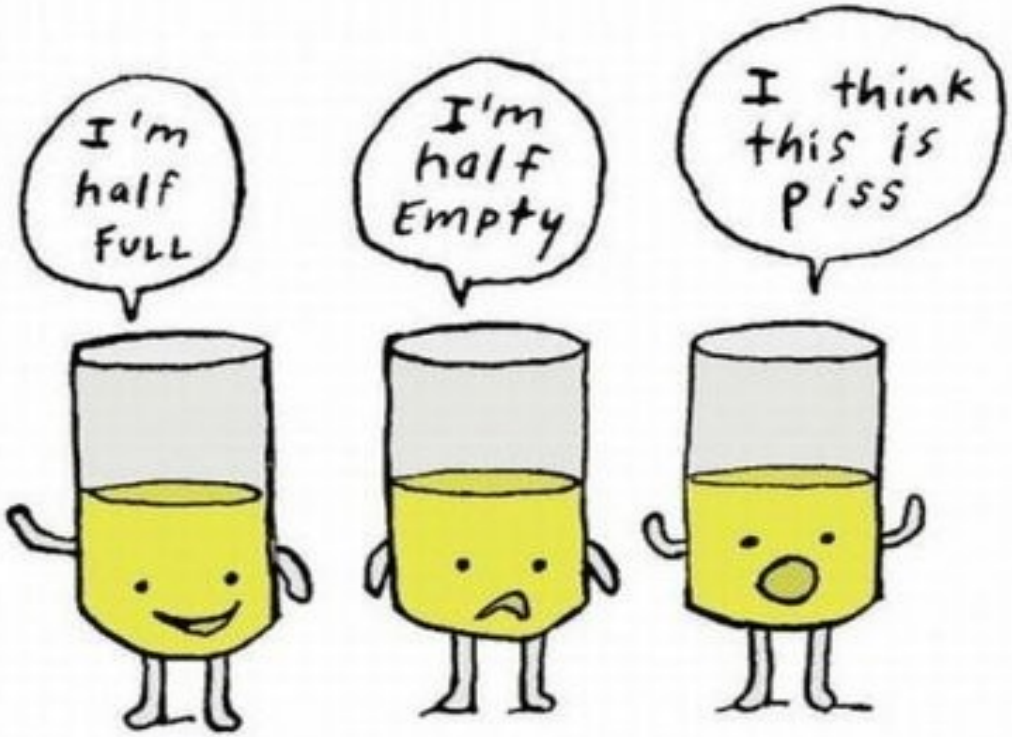
- There is questionable benefit to budesonide, still evolving

- UDCA is continued indefinitely
- Liver chemistries q 3-6 months
- Yearly TSH
- Pts with cirrhosis:
  - Assess for varices q 2 years
  - Assess bone density q 2-4 years
  - Assess fat soluble vitamins yearly
  - USN q 6 months for HCC surveillance

Transplant

- The number of patients requiring transplant has declined by 20% in the past 25 years
- Best treatment for end stage PBC
- Referral indications are same as for other pts with chronic ESLD; but also include complications due to cholestasis, poor QOL from fatigue, intractable pruritus, severe muscle wasting, and increasing bilirubin without evidence of malignancy

- 1 year post transplant survival >90%, 5 year >80%
- 20-25% will have recurrence of disease over 10 years
  - Immunosuppression with cyclosporine reduces this (tacrolimus has a higher incidence)
- Recurrence does not appear to significantly impact survival
- AMA may persist
- Improves fatigue and pruritus, bone disease will worsen then improve, Sicca syndrome unchanged


I'm half FULL
I'm half Empty
I think this is piss
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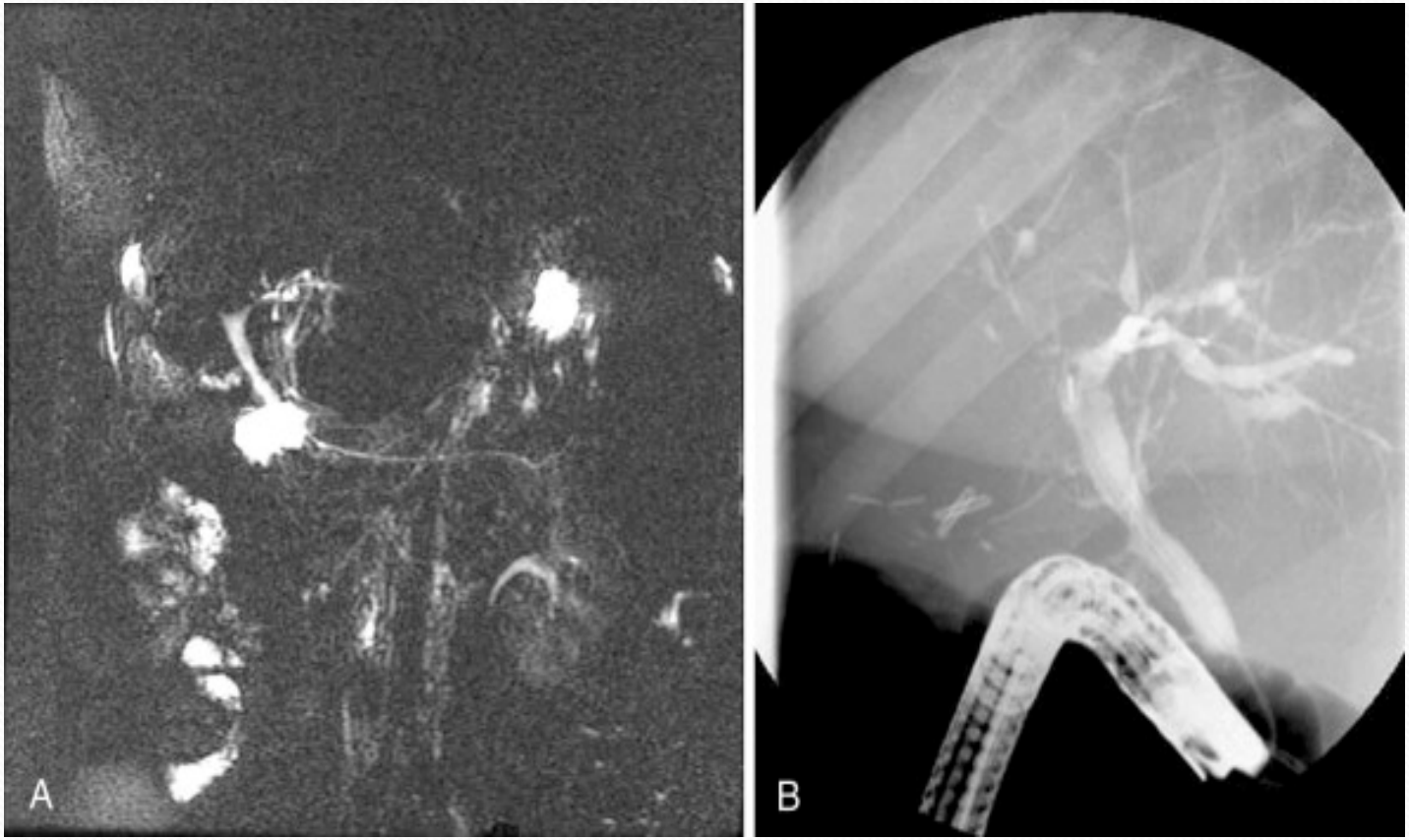
Primary Sclerosing Cholangitis

- Cholestatic liver disease with inflammation and fibrosis of intra- and extra-hepatic bile ducts culminating in multifocal bile duct strictures
  - Idiopathic, IBD association but also associated with a number of autoimmune, infiltrative, or fibrotic disorders

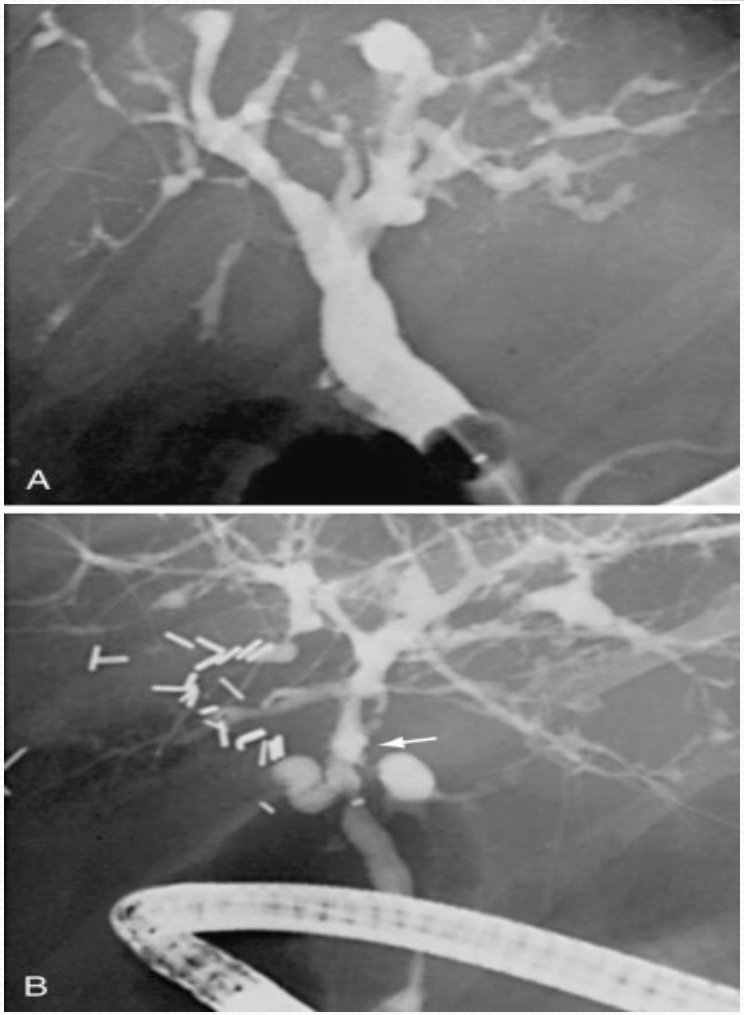
- Secondary sclerosing cholangitis: has a known cause (AIP, biliary parasites, infection, choledocholithiasis, toxins, ischemia, neoplasia)
  - AIDS cholangiopathy
  - Cholangiocarcinoma
  - Choledocholithiasis
  - Diffuse intrahepatic metastasis
  - Eosinophilic cholangitis
  - Hepatic inflammatory pseudotumor
  - Histocytosis X
  - IgG4-associated cholangitis
  - Intra-arterial chemotherapy
  - Ischemic cholangitis
  - Mast cell cholangiopathy
  - Portal hypertensive biliopathy
  - Recurrent pancreatitis
  - Recurrent pyogenic cholangitis
  - Surgical biliary trauma

- Most pt's diagnosed between 25-45yo, 70% M (but lower in pts with PSC without IBD)

- Diagnosed by characteristic cholangiographic findings (multifocal strictures and biliary tree ectasia) and clinical, serological, lab and histology findings
  - Small-duct PSC (variant) involves intra-hepatic ducts without extrahepatic abnormalities and may have a normal cholangiogram
- Must exclude SSC and AIDS cholangiopathy (assoc. with crypto, micro, cmv, and other organisms)
- Up to 41% will have gallbladder abnormalities (including tumor)
- ERCP, MRCP to evaluate the ducts– demonstrates the "beads on a string" image of multifocal short strictures in between normal or slightly dilated segments



A: MRCP
B: ERCP (same pt)
(atrophy of R sided ducts and dilation on the left)


A
B

- PSC and PBC share similar histologic findings
  - PBC affects more middle-aged women, has no IBD association, has high AMA titers, no strictures on cholangiogram
- Autoimmune pancreatitis-sclerosing cholangitis (AIP-SC)
  - Stricturing of the pancreatic duct, enlargement of pancreas, elevated IgG4 levels, and lymphoplasmacytic infiltrate on biopsy
  - Similar appearance to PSC
  - Steroid responsive (PSC is not)

IBD association

- ~80% of PSC pts have IBD
  - 85-95% of those pts have UC
- Recommended that all newly diagnosed PSC pts undergo colonoscopy with random biopsies
- 5.5% prevalance of PSC in those with pancolitis as opposed to 0.5% with distal colitis (ie, more colon involved, greater the incidence)
- IBD in PSC has characteristics of extensive colitis, rectal sparing, backwash ileitis, tendency for a milder course, higher risk of pouchitis following proctocolectomy, higher risk of CRC and dysplasia compared to UC alone (need surveillance q 1-2 years)

- Poorly understood etiology and pathogenesis
- Association with specific HLA haplotypes (B8 and DR3 most prevalent)
- Associations with many other autoimmune diseases
  - T1DM and Graves most frequent
  - AIH overlap syndrome

Labs

- Alkaline phosphatase chronically 3-5x normal
- AST and ALT rarely > 4-5x ULN
- Bilirubin fluctuates
- Serum antibodies: many present in low titers but none used in diagnosis
  - Anti-neutrophil cytoplasmic Ab (50-80%)
  - ANA
  - ASMA
  - Anti-endothelial cell Ab
  - Anti-cardiolipin Ab
  - Thyroperoxidase
  - Thyroglobulin
  - RF

- Imaging
  - MRCP, ERCP, percutaneous transhepatic cholangiography with findings as noted previously
- Pathology
  - Diffusely thickened and fibrotic extrahepatic bile duct wall with mixed inflammatory infiltrate
  - Concentric fibrosis around medium size ducts– “onion skin”
    - Can lead to fibro-obliterative cholangitis in the smaller ducts
  - Bile duct proliferation
  - Periductal inflammation
  - Ductopenia
  - *Staging as in PBC

- Histologic staging
  - 1: inflammatory destruction of the 100um diameter intrahepatic septal and interlobular bile ducts– the florid duct lesion
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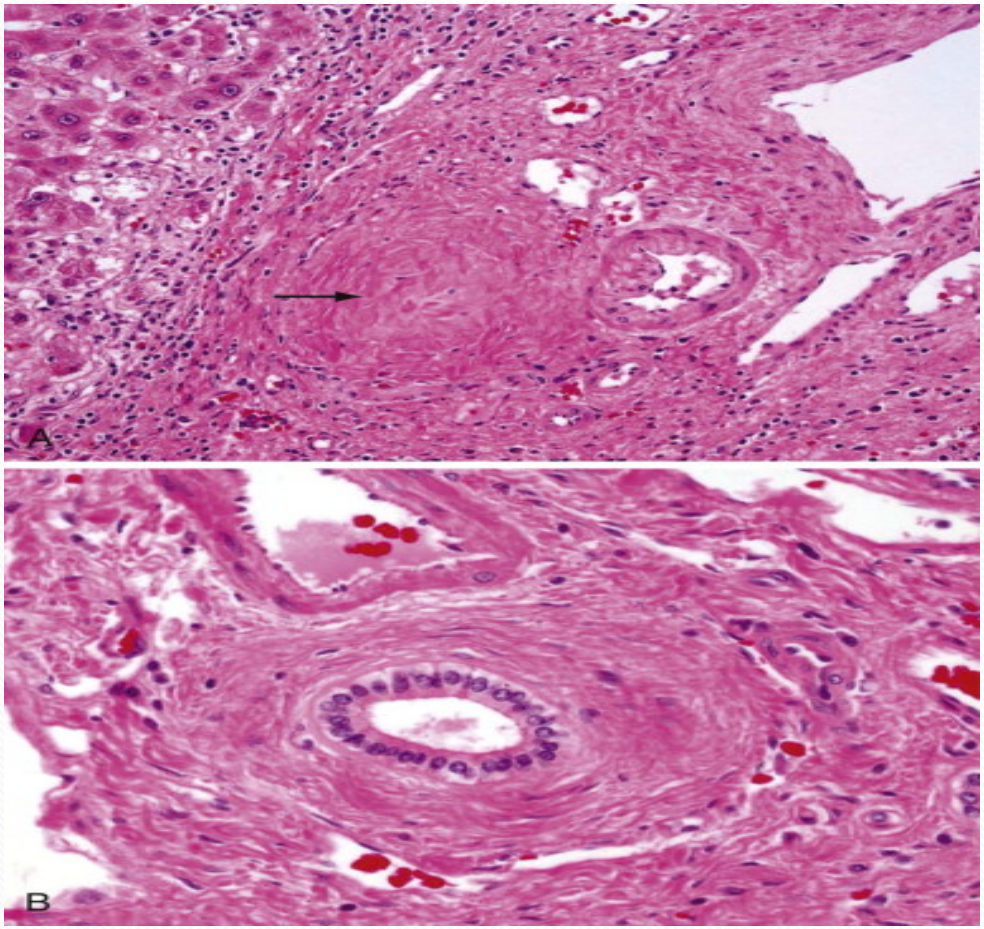


A:Fibro-obliterative cholangitis (bile duct obliterated by fibrosis)
B: Concentric “onion skin” fibrosis

Clinical phases

- 1)Asymptomatic: cholangiographic evidence found incidentally
- 2)Biochemical: no symptoms but elevated AP and variable elevations of transaminases and bili
- 3)Symptomatic: cholestasis and liver injury sx– fatigue, pruritus, cholangitis, jaundice
- 4)Decompensated cirrhosis

- *Pts diagnosed at symptomatic stage have a worse prognosis
- *Small duct PSC usually with better prognosis

Complications

- Cholestasis
- Cholelithiasis and choledocholithiasis (25%)
- Colonic neoplasia: increased risk with UC and PSC as compared to UC alone

Cholangiocarcinoma

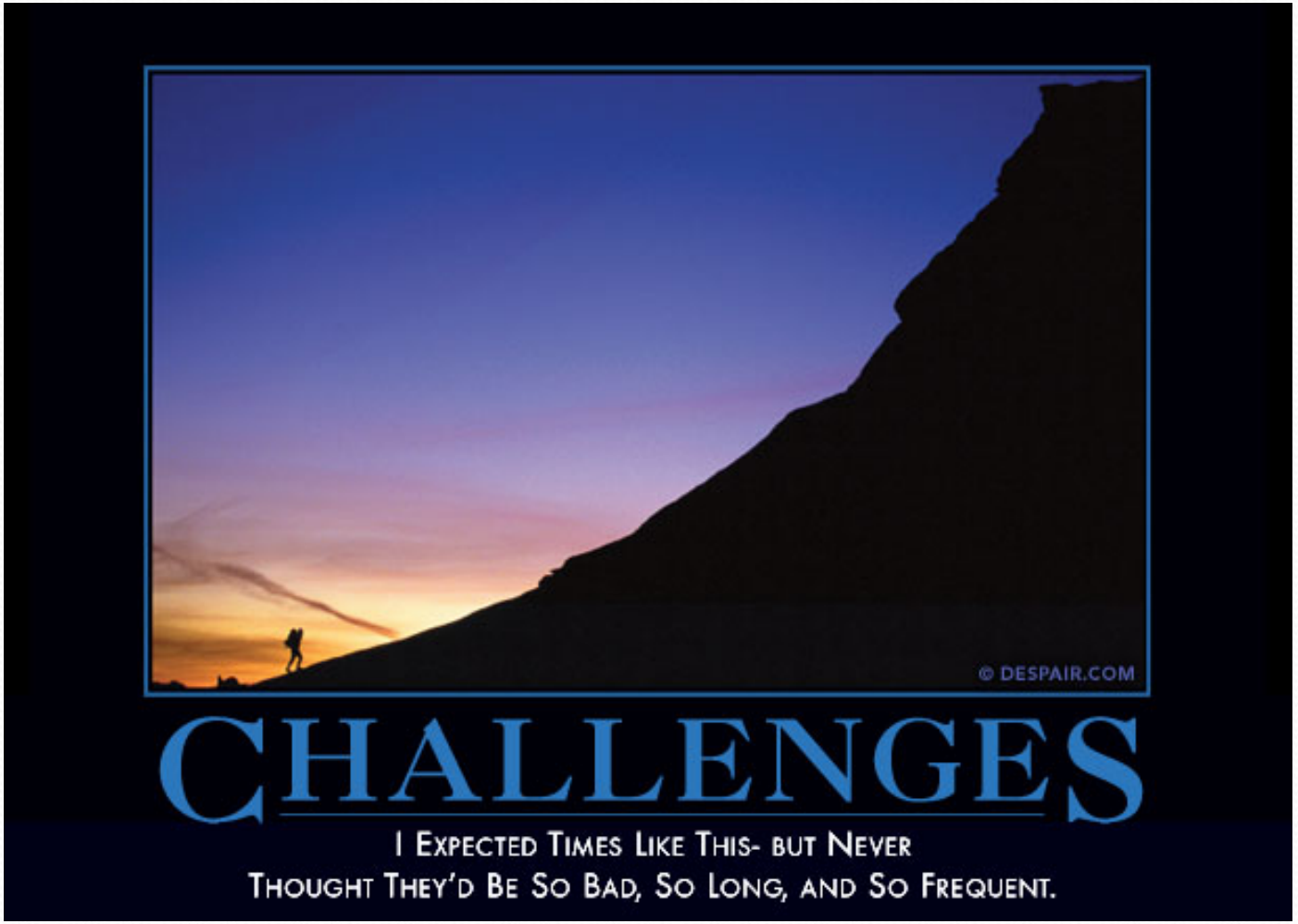
- 7-9% risk over 10 years
- Leading cause of death for PSC patients; PSC is considered a premalignant biliary condition
- Thought due to chronic inflammation
- Suspect in a pt who has rapid clinical deterioration (jaundice, weight loss, and abdominal pain)
- Can be difficult to differentiate from a dominant stricture
- Difficult to image because frequently grows in sheets and not as a mass
  - Samples: ERCP with brush cytology and FNA, EUS with FNA, High-frequency intraductal usn
- ~5 month survival after diagnosis unless transplanted

Treatment

- UDCA has shown to improve labs but not survival, not recommended by AASLD
- Other immunosuppressants have not shown efficacy, unless overlap syndrome
- Dominant Strictures: stenosis of CBD ≤1.5mm or ≤ 1mm of hepatic duct
  - Can be a presentation of cholangiocarcinoma
  - Managed endoscopically or percutaneously to relieve obstruction
    - Brush cytology and biopsy to r/o malignancy prior to intervention
    - Biliary sphincterotomy and balloon dilatation +/- stent placement most efficacious

Transplant

- AASLD recommends as successful treatment
- Indications as for ESLD
- 85% 5 year survival rates
- 20-25% disease recurrence in 5-10 years
- Have increased metabolic bone disease after transplant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CHALLENGES
I Expected Times Like This- but Never
Thought They'd Be So Bad, So Long, and So Frequent.