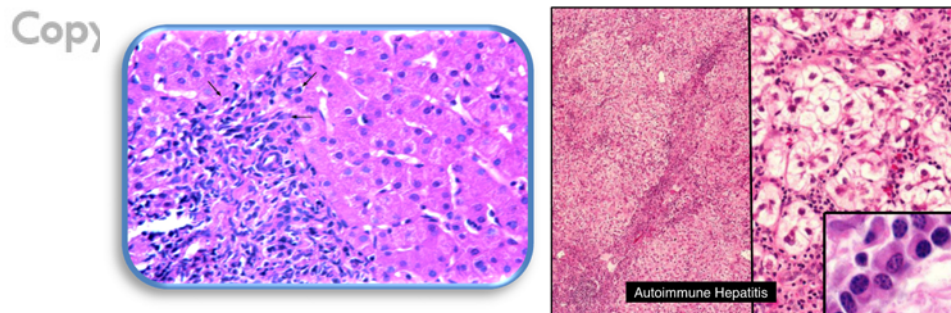


Auto-Immune Hepatitis (AIH)

- Types (10% do not fit into Type I/II/III w/ Bx clinching Dx)
 - AA have more severe dz

	Type I aka Lupoid Hepatitis b/c looks like SLE	Type II
Geography	USA	Europe
Pt	10-20/40-70yo 7F:1M	2-15yo women
Ab	anti-Smooth Muscle Antibody (ASMA) (very specific) and ANA (very sens) therefore check BOTH ASMA and ANA Other: atypical (perinuclear vs cytoplasmic staining) pANCA anti-Soluble Liver Antigen / Liver Pancreas (anti-SLA/SLP) = associated w/ more severe dz and high r/o relapse after Tx	anti-Liver Kidney Microsomal 1 (anti-LKM1) anti-Liver Cytosol 1 (anti-LC1)
Ag	In some cases there is a clear environmental Ag (below) but in most there is some unknown environmental antigen (asialoglycoprotein?) in a genetically susceptible person (DRB1*0301/0401)) <ul style="list-style-type: none"> Drugs (three classic "M's" Methyldopa, Minocycline, Macrobid, other: diclofenac, IFN, atorvastatin) Infections (Acute HAV, Acute HCV, HSV, CMV, Measles) 	The primary Ag is the Cytochrome P450-2D6 in a genetically susceptible person (B14, DR3, C4A) NB associated with more severe disease and less responsive to steroids NB can be associated w/ Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED)

- Presentation
 - 1/3 dx when chronic asymptomatic increased LFTs are investigated (70% eventually develop symptoms)
 - 1/3 acute hepatitis (the most common S/S is fatigue and hepatomegaly)
 - 1/3 cirrhosis ± HCC
- Diagnostic Criteria (various detailed scoring systems generally involve the 4 criteria below)
 - (1) Autoimmune Serology
 - 80% sensitive
 - anti-actin is a very specific subgroup of ASMA
 - titers fluctuate over time and change in pattern and may even disappear
 - + if >1:40-80
 - Titers do not correlate w/ dz activity or prognosis
 - Ab negative AIH does exist!!! and should be considered in cryptogenic cirrhosis and acute liver failure esp if young female w/ other autoimmune diseases**
 - (2) Hypergammaglobulinemia Subtype G (IgG)
 - (3) Liver Bx
 - Interface Hepatitis aka Piecemeal Necrosis (old term)** (1° plasmocytic 2° mononuclear inflammation extending out from portal triad across "limiting plate" which is the first set of hepatocytes)



- NB as the dz gets worse there is the development of scarring**
 - NB bile ducts are spared which is important in distinguishing AIH from PBC/PSC**
 - NB check Bx at presentation and after biochemical/clinical remission during Tx generally after 3-6mo of Tx**
- (4) Exclusion of other causes of hepatitis specifically no Viral, Wilson's, A1AD, Hemochromatosis, DILI which can cause similar autoantibodies and histology
 - NB some pts have both viral hepatitis and autoimmune hepatitis or a viral hepatitis that has some autoimmune features = Tx is directed against the predominant disorder
 - 1° AIH: Auto-Ab >1:320, many other auto-Abs, interface hepatitis, plasma cells
 - 1° Viral: Auto-Ab <1:320, few other auto-Abs, steatosis, lymphocytes

- NEVER GIVE BOTH AT THE SAME TIME b/c IFN can worsen AIH and steroids can worsen Viral Hepatitis
- Other
 - Extra-Hepatic Disease: 1° Autoimmune Thyroid, TTP, DM, PA, GN, UC 2° Celiac Sprue, Hemolytic Anemia
 - Always exclude Celiac Disease!!!
 - Other Syndromes (consider when other auto-Abs are present, different LFT pattern, concurrent UC, non-response to Tx below but more responsive to URSO)
 - “Overlap Syndrome” when two or more syndromes exist = AIH + Autoimmune Cholangitis (7%), PBS (5%), PSC (1%)
 - NB ~20% of AIH pts have +AMA but don’t call it overlap w/ PBC unless cholestasis is present
 - Tx what the Bx looks most like!!!
 - “Outlier Syndrome” when criteria do not meet any one syndrome
- Tx
 - Prednisone ± Azathioprine
 - Strategy: both approaches are equally effective in inducing clinical/biochemical/histologic remission but the **combination** regimen is associated w/ fewer drug-related SEs and thus is the preferred Tx approach where **prednisone alone is reserved for specific pts (pregnant, cancer, cytopenias)**
 - Indications
 - Absolute Indications: incapacitating symptoms OR bridging/multinodular necrosis OR AST >10xULN or AST >5xULN + IgG >2xULN
 - Relative Indications: mild symptoms OR interface hepatitis OR AST >3-10xULN or AST >5xULN+IgG<2xULN or AST<5xULN+IgG>2xULN
 - Not Indicated: no symptoms AND inactive cirrhosis or portal hepatitis or decompensated cirrhosis AND AST <3xULN (Tx is individualized in these pts)
 - Poor Prognostic Factors: African American, Type II/III, MELD >12
 - Response
 - Drug Toxicity (15%) = lower dose or stop Tx or different med (Cyclosporine or Mycophenolate)
 - Failure (10%) = higher dose or liver transplant (consider other syndromes)
 - Incomplete Response (15%) = indefinite lower dose (consider other syndromes)
 - Remission (60%) = taper Tx
 - Endpoint: No Sx AND AST<2xULN+IgG-NL AND NI Bx or Inactive Cirrhosis
 - What to tell pts: Sx improve in a few weeks (some say if no improvement then consider another dx), labs improve in several weeks, histology improves after several months
 - 50/85% relapse at 6mo/3yrs = reTx but continue indefinite lower dose
 - ESLD on Tx failure requires liver transplant however 15% have recurrence in the orthotopic liver but usually mild (when AIH occurs following transplant for other indications it is called “de novo AIH” and occurs at a rate of 5%)
 - Address underlying trigger if present
 - NB Budesonide has recently been studied and found to be more effective and less side effects than Prednisone
 - Other: cyclosporine, tacrolimus, methotrexate, IVIG, etc

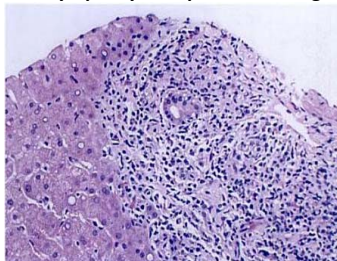
	Approach #1	Approach #2
	Prednisone	Prednisone + Azathioprine
Week 1	60mg QD	30mg + 1mg/kg QD
Week 2	40mg QD	20mg + 1mg/kg QD
Week 3	30mg QD	15mg + 1mg/kg QD
Week 4	30mg QD	15mg + 1mg/kg QD
Maintenance Until Endpoint then Taper Very Slowly over 8-20wks but some need lifelong Tx	20mg QD	10mg + 1mg/kg QD

Autoimmune Sclerosing Cholangiopathy

- Similar to PSC but some key differences:
 - + IgG4 in serum and on IHC
 - ~60yo Japanese Male
 - unlike PSC which have focal bead like strictures the strictures of in this dz are long and segmental
 - Responds to steroids unlike in PSC
 - Bx the ampulla
 - No IBD association
 - Other organ involvement is present
 - Part of the AIP spectrum

Primary Biliary Cirrhosis (PBC)

- Mechanism
 - Idiopathic vs Secondary
 - Aberrant recognition of mitochondrial self antigens
- Epidemiology
 - ~50yo 9F:1M
 - Olmsted Incidence: 1/100,000
 - Other Autoimmune Conditions: Sjogren's (50%), RA (20%), Hypothyroidism (20%), GN (20%)
 - Other Non-Autoimmune Conditions: **Osteoporosis, RTA, Breast Cancer, PUD** (make sure these are being followed)
- S/S (takes ~5yrs to go from stage to stage, various prognostic models have been developed esp by Mayo to predict who will progress)
 - **Stage I: Asymptomatic and Normal Labs but +AMA/Bx**
 - **Stage II: Asymptomatic but Abnormal Labs and +AMA/Bx**
 - **Stage III: Symptomatic and Abnormal Labs and +AMA/Bx**
 - 1° **Fatigue** (most disabling Sx, worsens as the dz worsens)
 - 2° **Nocturnal Pruritus** (interestingly improves as the dz worsens)
 - Other Cholestatic Complications
 - RUQ ab pain, anorexia, etc
 - hypercholesterolemia specifically w/ high HDL!!! and not LDL but as the dz progresses HDL decreases and LDL increases nevertheless pts are NOT at increased r/o atherosclerotic dz hence you don't need to routinely give lipid lowering agents unless they get significant xanthomas and xanthelasmas, as the pt develops cirrhosis their TC begins to improve
 - fat soluble vitamin deficiency
 - steatorrhea
 - **Stage IV: Cirrhosis (rare)**
- Labs
 - Very high AlkPhos and GGT but otherwise only mild hyperbilirubinemia or increased aminotransferases
 - Ab: Anti-Mitochondrial Antibody (AMA)
 - + if >1:40 w/ a sensitivity of 95% and specificity of 95%
 - false + w/ high ANA
 - titers do not correlate w/ severity
 - 9 Subtypes of AMA
 - M2 subtype targeting pyruvate dehydrogenase complex on inner mitochondrial membrane antigens is the most sensitive/specific but you don't need to check subtypes b/c overall AMA is very sensitive and specific
 - New: Anti-gp120
 - Other: ANA (20%), ASMA (20%), RF, Anti-Thyroid Abs, IgM
- Complications
 - recurrent cholangitis (up to 15% of pts)
 - cirrhosis
 - HCC
- Dx (2/3 of the following criteria)
 - (1) Labs: high AP >6mo
 - (2) Ab: AMA
 - (2) Bx: Ludwig Classification (only needed if the other two criteria are not met)
 - **Stage I "Florid Duct Lesion" = PORTAL TRIAD and SMALL bile duct destruction w/ adjacent granuloma formation and interface lymphocytic hepatitis/cholangitis**



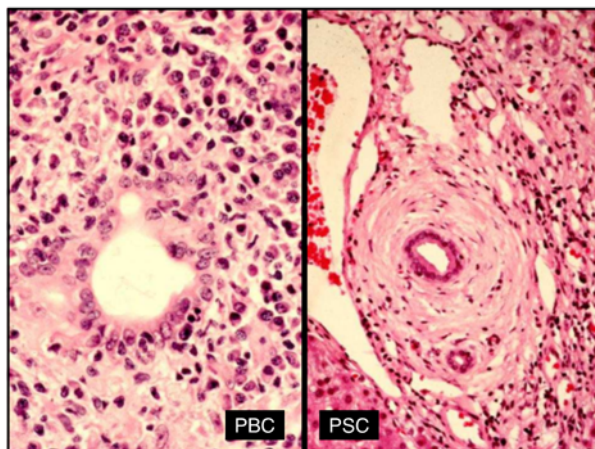
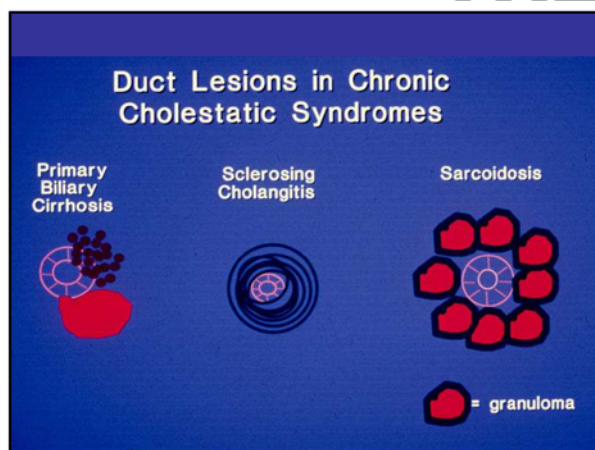
- **Stage II Bile Duct Proliferation**
- **Stage III in b/t II/IV but now some scarring (F1-3)**
- **Stage IV "ductopenia" AND burned out inflammation aka not-present AND Cirrhosis (F4)**

- Other = Imaging: (M/ERCP, PTC) normal or just smooth narrowing w/o ductal irregularities

- Tx
 - Liver Transplant (in the past transplantation was indicated if the Mayo Risk Score indicated <95% survival at 1yr but now the MELD Score is used, recurrent PBC occurs in 15-30% of pts at 10yrs, evaluate if Stage IV or intractable Sx)

- Ursodeoxycholic Acid
 - RDBPCT (Poupon, NEJM, 1994) and several more
 - only drug that has been shown to slow progression of the disease w/ decreased r/o death and need for LTx, improve biochemical test, decrease Sx, reduce inflammation on Bx, decrease the r/o varices, improve survival free of liver transplantation
 - more effective the earlier the stage
 - works as a cholerrhetic agent increasing bile flow, immune modulator by reducing MHC Ags and attenuates the effect and percentages of hepatotoxic endogenous hydrophobic bile acids by diluting them
- Anti-Pruritics
- Fat Soluble Vitamin Deficiency
 - 2/2 reduced intestinal [conjugated bile acid]
 - Always test annually
 - So-called "hepatic osteodystrophy" characterized by the combination of osteomalacia (2/2 vitD deficiency) and osteoporosis (pathogenesis unknown b/c even if VitD is supplemented OP still occurs) some say screen Q3yrs, Ca 1g – VitD 1000IU QD if -penia, bisphosphonates if -porosis
 - low fat diet 50g/d decreases Sx of steatorrhea without compromising total energy intake
 - vit E deficiency is rare
- Steatorrhea
 - Rule out concurrent exocrine pancreatic insufficiency and celiac dz
- colchicines/methotrexate (emerging data that these agents in combination w/ URSO is effective)
- combivir, obeticholic acid, fibrates, prednisone is effective but wrought w/ SEs hence studies have been looking at budesonide
- Prognosis
 - No change in mortality if asymptomatic but if symptomatic then 50% mortality in 10yrs if not transplanted

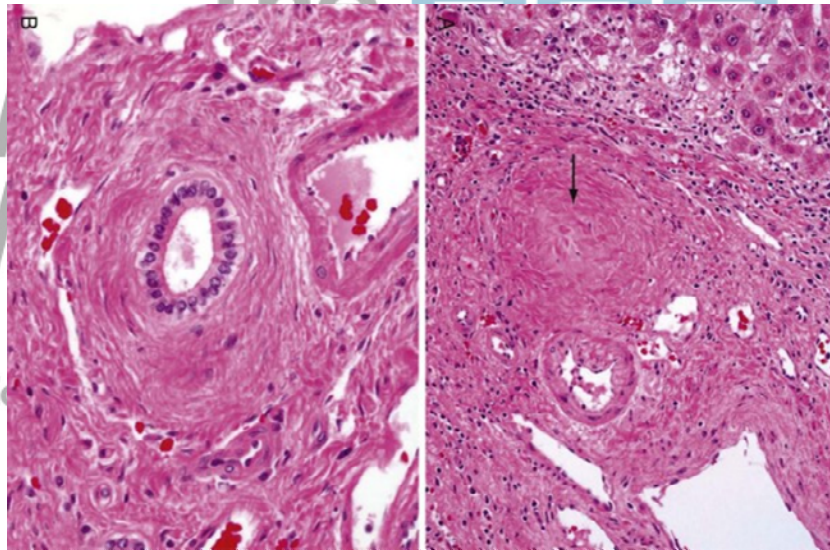
PBC (severe inflammation w/ duct destruction followed by proliferation) vs PSC (little to no inflammation w/ no duct destruction or proliferation just fibrosis)



Primary Sclerosing Cholangitis (PSC)

- Pathogenesis
 - Unclear but likely similar postulated pathogenesis to IBD in which an immunogenetically susceptible person (esp HLA-DR3*0101 haplotype) is exposed to environmental trigger leading to inflammation
- Epidemiology
 - incidence (1/100,000) and prevalence (1/10,000)
 - 25-45yo w/ mean 40yo
 - 2.3Male:1Female
 - NB however in the small subset w/o IBD there is a female predominance and an older mean age
- Mechanism
 - Primary: idiopathic condition that can be associated w/ 1° IBD (85% UC vs 15% CD), 2° autoimmune (eg. Scleroderma, MCTD = different than those seen in PBC)
 - Colonic IBD
 - Why the association? unknown but likely there exists a common epitope b/t colonic and biliary epithelium and antibodies directed against this epitope has been suggested to be the link b/t PSC and Colonic IBD
 - ~75% of PSC have Colonic IBD (such that if pt has PSC a colonoscopy w/ Bx is necessary to r/o subclinical UC) but only ~5% of Colonic IBD have PSC
 - PSC can occur before / during / after (most) active IBD and even after colectomy
 - RFs: colon (the more colon involved the higher the risk of PSC and thus PSC is seen in pancolitis UC), rectal sparing, backwash ileitis
 - despite association b/t UC and PSC the diseases progress independently of the other in that one does not portend a different history for the other and the Tx of one does not change the course of the other
 - Complications
 - increased r/o CRC beyond the risk conferred by IBD of the colon alone (it is recommended that surveillance colonoscopy be done Q1-2yrs)
 - increased r/o pouchitis after IPAA
 - increased r/o peristomal varices after ileostomy
 - Secondary: clinical and radiographic syndrome that looks like PSC but develops as a consequence of a known direct injury to the bile ducts (refer to general notes)
 - NB since PSC can lead to stone formation and cancer and since stone formation and cancer can cause sclerosing cholangitis it can sometimes be difficult to determine the chicken and the egg
- Variants
 - Small Duct PSC
 - Occurs when pt clinically/biochemically/serologically has PSC but the cholangiogram is normal
 - Believed to represent 25% of cases (70% both intra/extra vs 5% extra only)
 - Some studies suggest that 15% of pts progress to classic large duct PSC
 - Better prognosis than large duct PSC
 - Overlap PSC (refer above)
- S/S
 - Four Stages (15-44% present during the first two stages) similar to PBC
 - (1) Asymptomatic: no Sx + normal labs but cholangiographic evidence
 - (2) Biochemical: no Sx but abnormal labs and cholangiographic evidence
 - (3) Symptomatic: Cholestatic/Cholangitis S/S (slowly progressive intermittent **fatigue** (65-75%), jaundice (30-73%), ab pain (24-72%), pruritus (35-69%), hepatomegaly (34-62%), splenomegaly (32-34%), fever (13-45%), weight loss (10-34%))
 - (4) Decompensated: worsening Cholestatic/Cholangitis S/S w/ evidence of ESLD
- Labs
 - Very high AlkPhos (3-5x ULN, however can be nl in 6% of pts) but otherwise only variably mild hyperbilirubinemia/transaminasemia (2-3x ULN, however can be nl in a ?% of pts)
 - Autoimmune Serology (none are specific, no role in routine diagnosis but helpful, none are implicated in pathogenesis, none correlate w/ dz activity/severity/response, typically if + they are at low titers)
 - pANCA (85%)
 - ANA (33%)
 - IgM (25-50%)
 - ASMA (65%)
 - Anti-Endothelial Ab (11-35%)
 - Anti-Cardiolipin Ab (4-66%)
 - Cathepsin G (7-14%)
 - Lactoferrin (2-12%)
 - Thyroperoxidase (7-16%)
 - Thyroglobulin (4-8%)
 - RF (12-15%)
- Dx
 - **Diagnostic Approach**

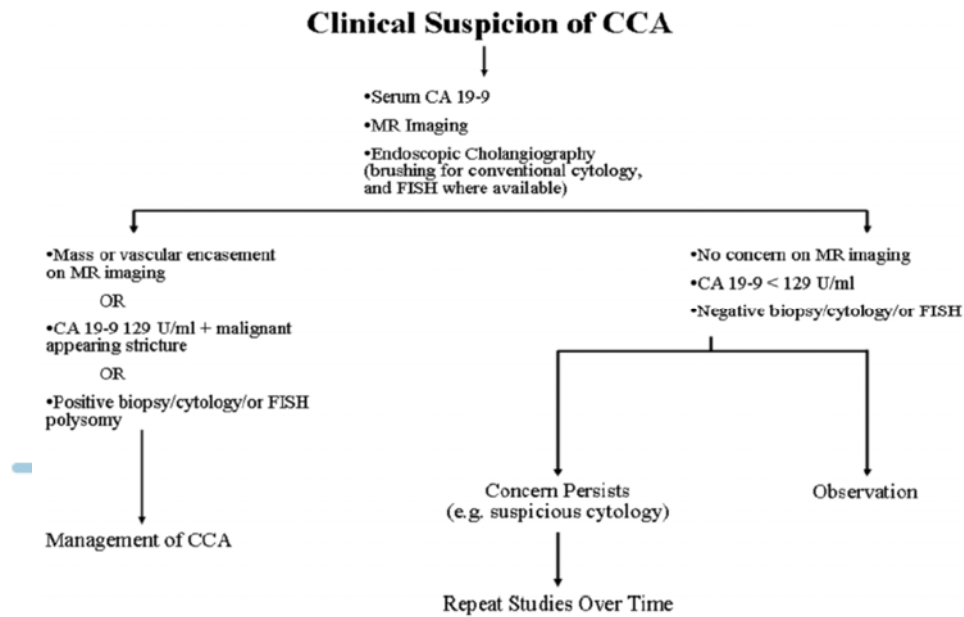
- **1st Cholestatic Biochemical Profile or Clinical Picture**
 - Consider Secondary Causes
 - Check ASMA/IgG4/AMA and if high then get liver Bx to r/o AIH/AC/PBC for overlap syndrome
- **2nd Cholangiography w/ MRCP (this is the first test!!!)**
 - Diagnostic
 - Normal: liver biopsy for small duct PSC
 - Non-Diagnostic: ERCP
- US/CT: normal or show non diagnostic bile duct thickening/dilation, etc
 - NB LAD can be seen in PSC and usually of no concern
- Cholangiography: (M/ERCP, PTC) short multifocal inflammation w/ subsequent extra/intra-hepatic stricturing w/ post-stenotic dilation and areas of normal caliber ducts = “beaded” appearance and rarely confluent
 - ERCP is considered the gold standard and has the added potential for further diagnostic capabilities and therapeutic interventions but it has complications of pancreatitis/cholangitis and adds radiation exposure as such MRCP is now considered the initial diagnostic TOC b/c it provides an alternative non-invasive and in studies comparing the two both had comparable sensitivities however each is highly dependent on technique and institutional expertise, there is some evidence that MRCP unlike ERCP can miss early PSC
- Pathology: First Picture - “onion skin lesion” = LARGE (unlike PBC) bile duct concentric fibrosis w/ mild lymphoplasmacytic inflammation but no actual duct destruction (unlike PBC) → Second Picture - luminal obliteration (“fibrous oblitative cholangitis”, only seen in 10% of cases) and post-stenotic thin walled dilated segments (“cholangiectasia”) → paucity of bile ducts (“ductopenia”) and cirrhosis
 - NB liver biopsy rarely adds useful diagnostic information therefore not needed for Dx but consider if small duct PSC and overlap PSC



- Tx
 - Primary
 - General
 - NO specific Tx except for liver transplant, therefore try to recognize and promptly treat complications, vitamin deficiencies, pruritus and follow pt closely along with cancer surveillance
 - No benefit in colectomy w/ intent of Tx PSC
 - Fatigue
 - Always exclude other often concurrent conditions that impact energy level: hypothyroidism, anemia, adrenal insufficiency, depression
 - Modafenil
 - Cholestatic Complications (just like PBC but less common)
 - Endoscopic/Surgical Therapy

- Theory: long-term biliary patency should slow progression of the disease towards biliary cirrhosis (makes sense) however there have not been well designed studies that convincingly demonstrate this
- **What we do know is that pts that benefit the most are those with one or few “dominant” strictures and with acute (not chronic) worsening clinical (esp pruritus) & biochemical (esp bili) indices then clinical/biochemical indices improve but if they are clinically asymptomatic and/or biochemically normal then do NOT stent b/c you are just increasing their r/o infection**
- Abx Prophylaxis if undergoing any biliary tree manipulation: ERCP, surgery, etc, if recurrent some recommend long-term abx rotation prophylaxis (Augmentin/Cipro/Bactrim) in 4wks cycles
- Pharmacologic Therapy
 - Problems: most studies are small/uncontrolled and study endpoints are variable (biochemical/histologic/clinical), dz course is variable w/ spontaneous remission/flare
 - What we can say is that NO pharmacologic Tx has clearly altered the course of PSC
 - Meds: abx, cholestyramine, general immunosuppressants (glucocorticoids, azathioprine, methotrexate, cyclosporine, tacrolimus), antifibrotics (penicillamine, colchicine), anti-TNFs = no improvements in various outcomes measured, however, they may serve a role in overlap PSC where esp steroids are effective in treating AIH/AIP
 - Ursodeoxycholic Acid (UDCA) aka Urso
 - most extensively studied of all drugs w/ well designed RCT
 - initial low dose (10-20mg/kg/d) studies found biochemical improvement BUT NO effect on more important endpoints including Sx/histology and this prompted more recent studies on higher doses (20-30mg/kg/d) but studies showed conflicting results and one study showed increased r/o death, serious adverse events, and need for transplant in the Tx arm
 - currently the AASLD recommend against the use of UDCA
- Liver Transplant
 - liver transplant is the only therapy known to improve the natural history of PSC and is the recommended Tx
 - higher risk of chronic ductopenic rejection and ischemic biliary duct stricturing
 - Outcome: 1/5/10yr survival is 93.7/86.4/69.8%
 - Indications: cirrhosis, intractable pruritus, recurrent cholangitis, carefully selected limited stage cholangiocarcinoma who are on a strict neoadjuvant therapy protocol otherwise cholangiocarcinoma is considered a relative contraindication
 - Complication: Post-Transplant Non-Anastomotic Stricturing
 - DDx: recurrent PSC, ABO incompatibility, hepatic artery thrombosis, CMV infection, chronic rejection, cholangitis, prolonged graft ischemia time
 - Recurrent PSC is defined as stricturing w/in 90d and absence of other RFs, risk is 5.7-21.1% after 5yrs, no medical therapy has been shown to prevent recurrence, RF: active IBD, intact colon, male, OKT3 use, presence of CCA prior to transplant
 - Clinical course of IBD and CRC after liver transplant is variable among studies
- Complications
 - Liver Disease
 - Biliary Cirrhosis (obviously)
 - Colon Disease
 - UC: annual colonoscopy w/ Bx even if normal colon to rule out IBD
 - GB Disease
 - Cholelithiasis (26%)
 - Neoplasm (4%): Q1yr US recommended to detect lesions and cholecystectomy if anything is detected
 - BD Disease
 - Dominant Stricture (20%)
 - Recurrent Cholangitis (15%)
 - can be recurrent requiring prophylactic abx and even transplant
 - Cholangiocarcinoma (100x increased risk and is seen in 10% of PSC pts after 10yr of dz thus ~1% annual risk but screening is not recommended b/c studies show no benefit, ~40% of autopsies have CCA and ~15% of LTx have CCA)
 - RFs (bili, variceal bleeding, proctocolectomy, chronic UC) but NOT duration of PSC
 - Dx: If you suspect CCA based on (1) Clinical: pt who rapidly deteriorates w/ worsening jaundice/weight-loss/ab-pain and (2) ERCP: long dominant stricture then check (A) **CA19-9 >130U/mL** (nl <55U/mL) is 79% sensitive and 98% specific (also seen in bacterial cholangitis), (B) **MRI** (in general US/CT/MRI are non-sensitive unless there is mass but CCA rarely grows in this manner), (C) **Brush/Biopsy w/ FISH** via ERCP
 - If you don't have suspicious clinical/ERCP findings then do not screen!!!
 - brush cytology is 18-40% sensitive (b/c some tumors are very desmoplastic and paucicellular) and poor specificity (b/c chronically inflamed cells may take on a malignant cytologic appearance)

- Px: URSO does not reduce risk
- Tx: very challenging b/c CCA is often multifocal and at an advanced stage at diagnosis often w/ non-identifiable mets and high recurrence rate at biliary enteric anastomosis therefore liver transplantation
- Prognosis: leading cause of death in PSC pts w/ median survival of 9-12mo



- Prognostic Factors
 - Unlike in PBC in PSC even if you are asymptomatic your mortality is lower compared to the general population
 - Multivariate analysis has revealed a number of poor prognostic factors: hepatomegaly, TB, AlkPhos, age, histologic findings, presence on concomitant IBD, pattern of duct involvement
 - different models (eg Mayo) are not always congruent therefore their use is not recommended but they can help aid in the timing of transplant