Overview of Autoimmune Liver Diseases

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Disclosures

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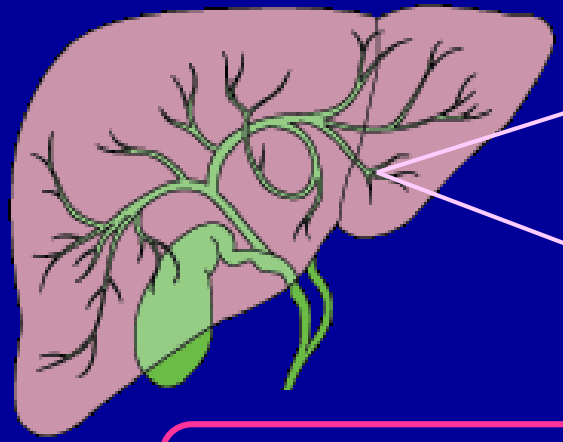
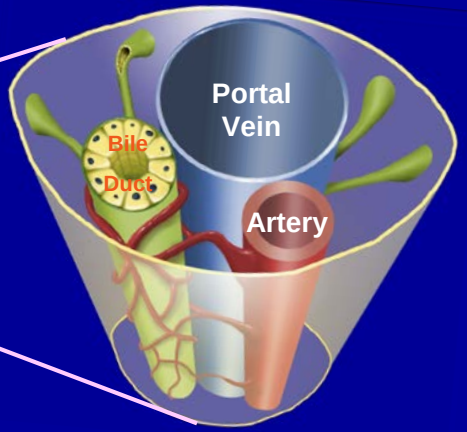
Research Grants: Arena, CymaBay, Enanta, Genfit, Genkyotex, Gilead, Intercept, Lilly, NGM Biopharmaceuticals, Novartis, Roche-Genentech

Scientific Advisor: Arena, Gilead, Lilly, Intercept, Novartis, Roche Genentech

Off-Label Use of Drugs: Discussion of off-label use of FDA-approved medications as therapies based on published data and recommendations of current Practice Guidelines.

Primary Biliary Cholangitis
Diagnostic Criteria





2 of 3 → Diagnostic

- Cholestatic pattern of liver tests (Alk Phos, ggt)
- AMA-Positive
- Compatible liver histology
- Absence of biliary tract dilation on imaging

Primary Biliary Cholangitis

PBC-Specific Autoantibodies: AMA and ANA

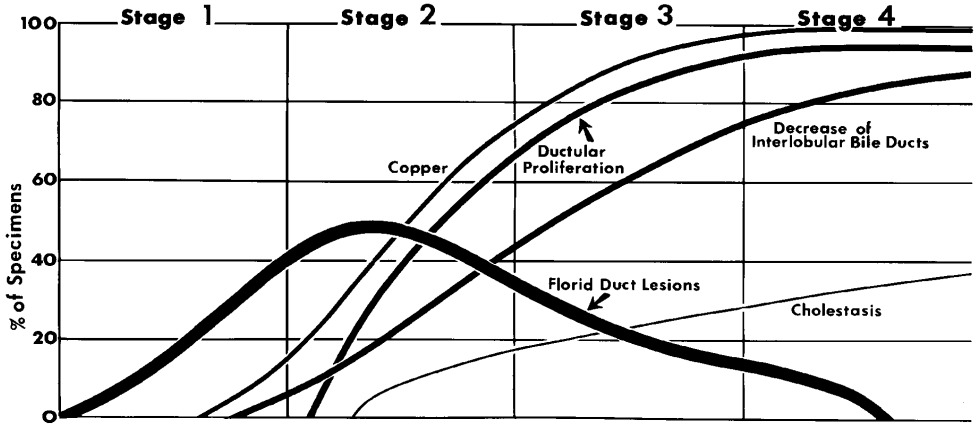
Autoantibody	Frequency (%)
▪ AMA	95-98
▪ ANA	5-54
- gp210	26
- Promyelocytic leukemia protein	19
- Sp100	21
- Lamin B receptor	1
- p62	25
- SOX13	10-15
- sp140	15%
• SMA	26-49
• RF	24-60
• Thyroid	15-26

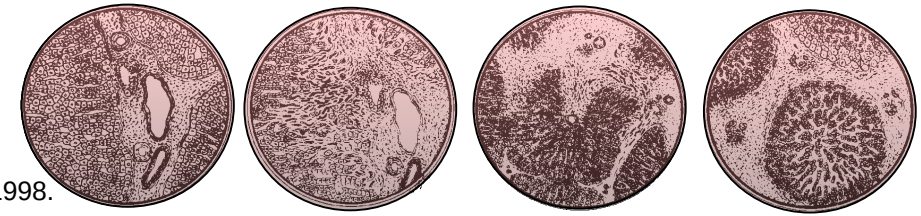
Primary Biliary Cholangitis
Clinicopathological Progression

Asymptomatic →

Symptomatic →

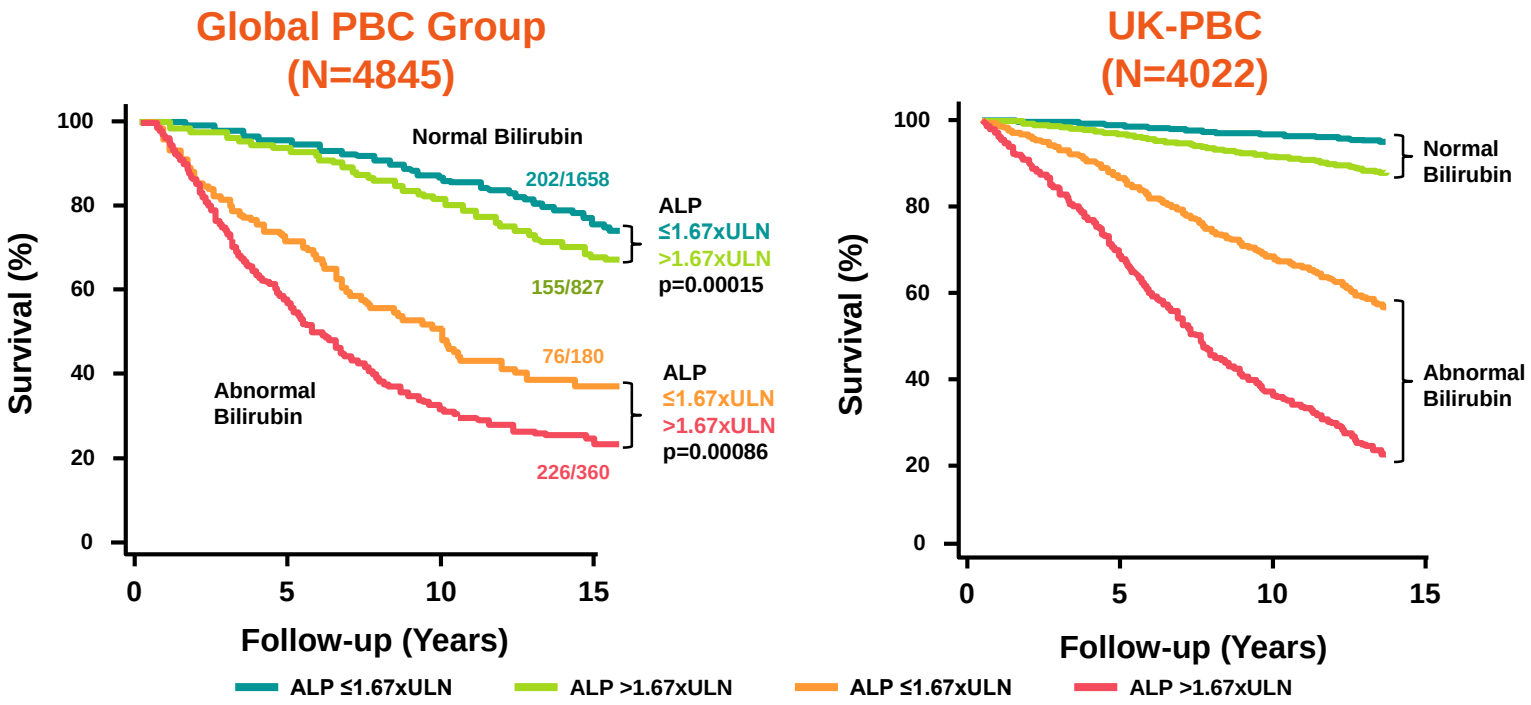
Preclinical	Clinical	
- AMA +	- AMA +	Compensated ↘
- ALP, ggt WNL	- ↑ ALP, ALT/AST with later ↑ Bilirubin	Decompensated





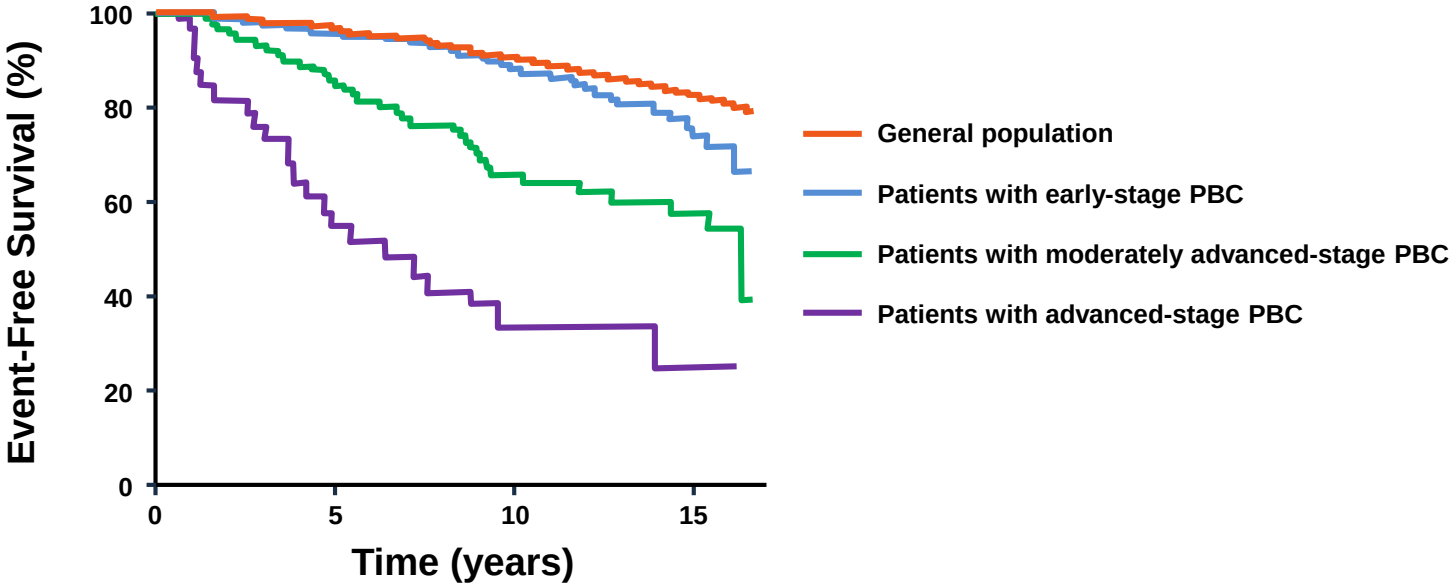
Adapted from Dickson R. Prog Liver Dis, 1998.

Primary Biliary Cholangitis:
Predictive Significance of ALP and Bilirubin in UDCA Era



Courtesy of Global PBC Study Group and UK-PBC

Efficacy of UDCA Treatment of PBC: Better Event-Free Survival in Earlier Stages of Disease



Survival on UDCA is inversely related to stage of PBC when treatment initiated:

- Survival of patients with early-stage PBC comparable to survival of the general population (p=.254)
- Survival in advanced-stage PBC significantly worse (p<0.001)

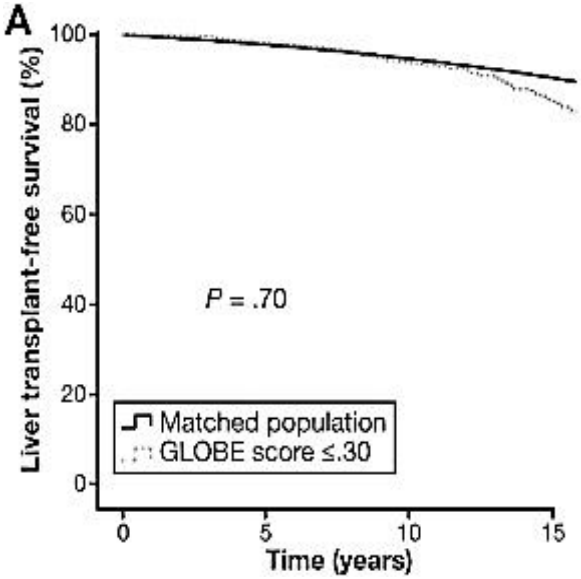
Kuiper EMM, et al. Gastroenterology. 2009;136(4):1281-1287.

Primary Biliary Cholangitis:
GLOBE Score: Survival Benefit of UDCA Treatment

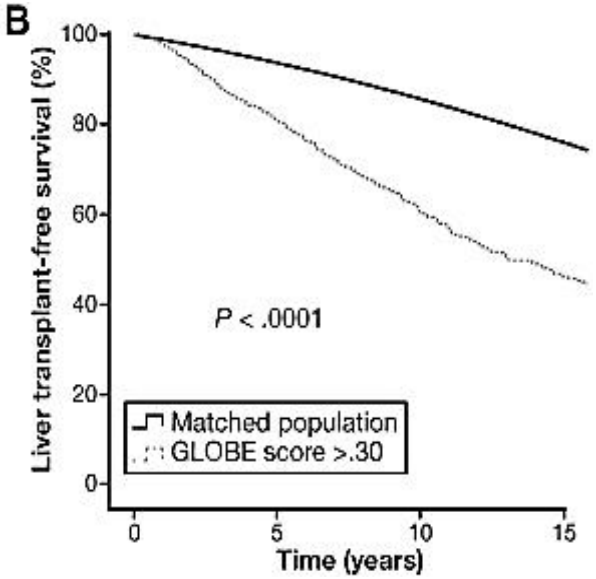
GLOBE Score Calculation:

0.44378 X age at *start of UDCA*
+
0.93982 X Ln(Bili X ULN at 1 yr F/U)
+
0.335648 X Ln(ALP X ULN at 1 yr F/U)
–
2.266708 Alb X LLN at 1 yr F/U
–
0.002581 X Plts/10^9/L at 1 yr F/U

GLOBE Score ≤ 0.30

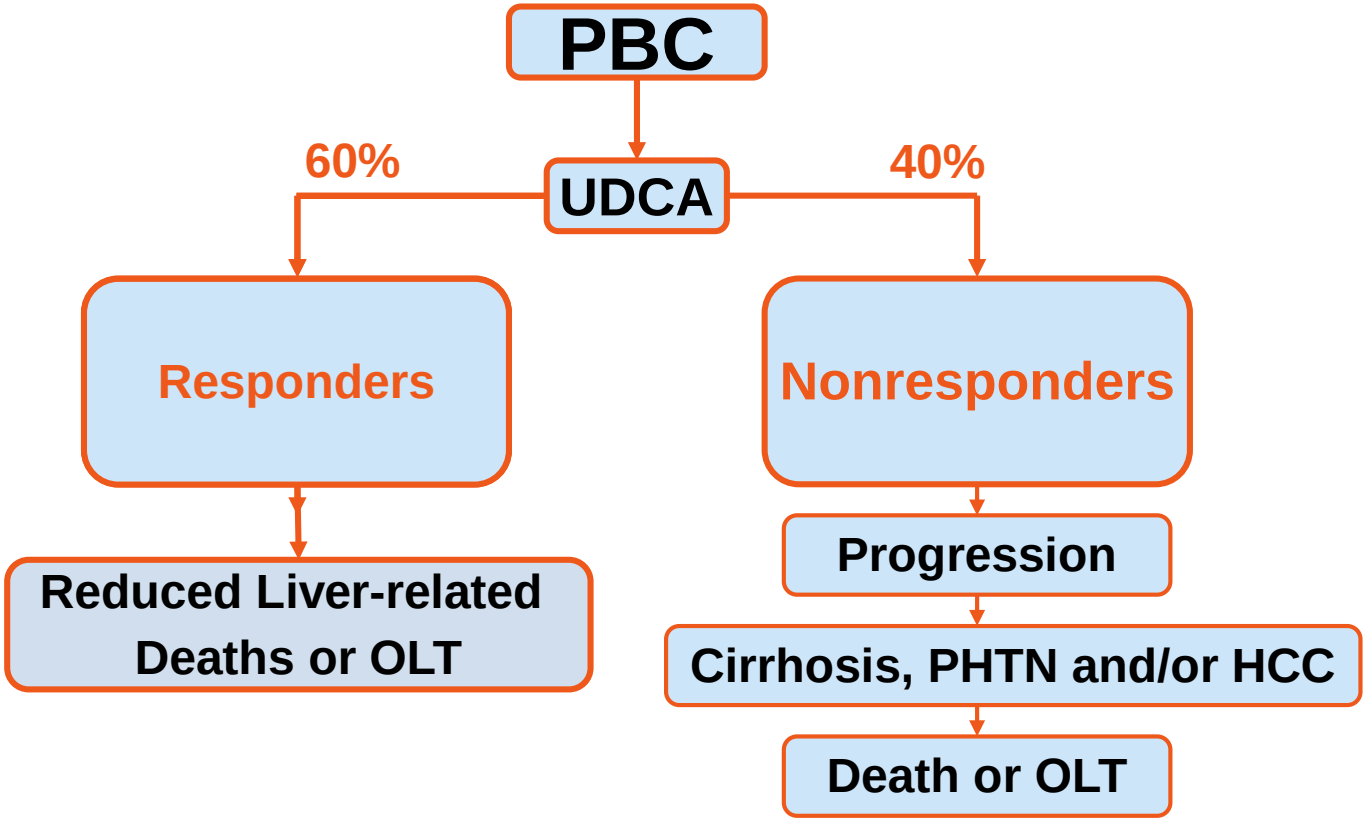


GLOBE Score > 0.30

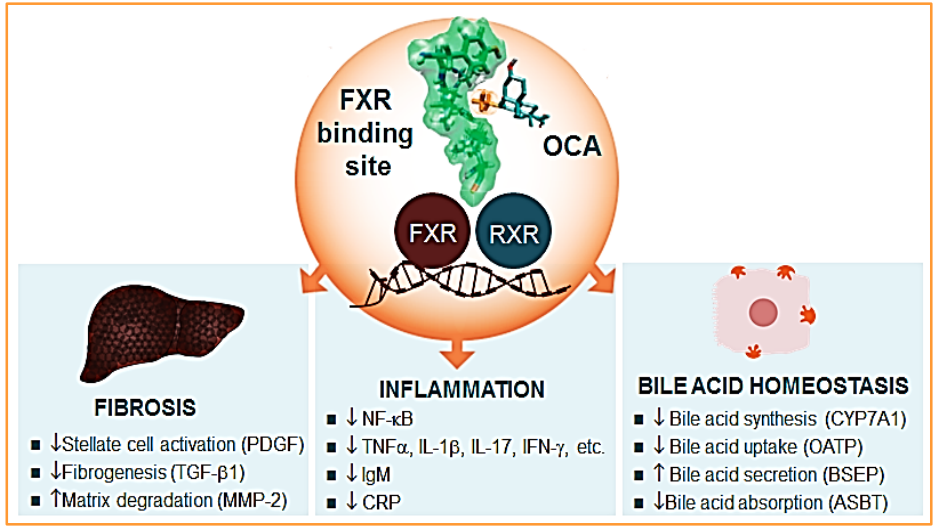


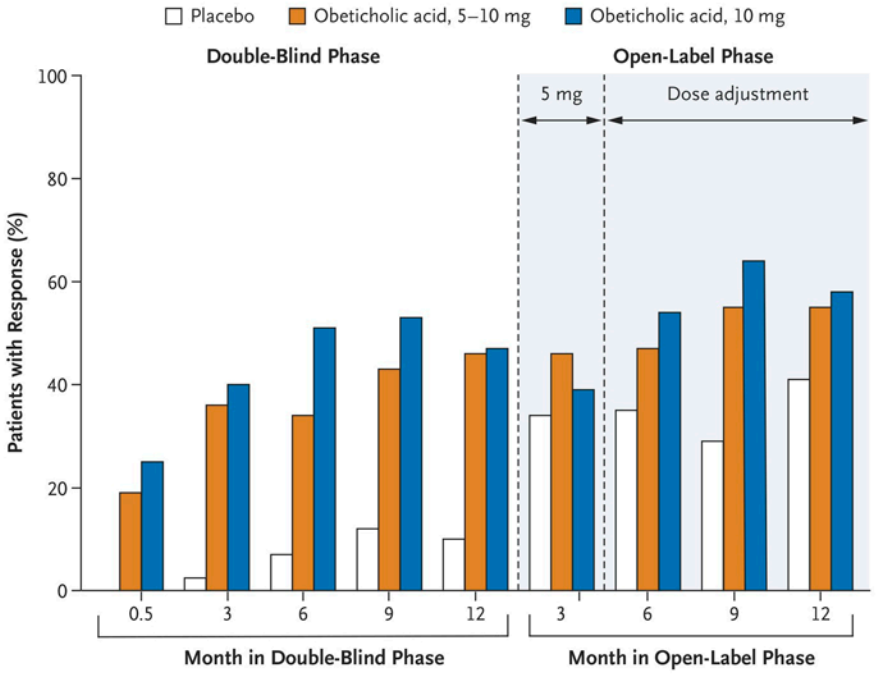
Lammers WJ, et al. Gastroenterology. 2015; 149: 1804-12

Primary Biliary Cholangitis:
Response to UDCA Reveals Magnitude of Unmet Need



Obeticholic Acid
Modified Bile Acid and Potent FXR Agonist





No. of Patients									
Placebo	73	73	73	73	73	64	60	59	59
Obeticholic acid, 5–10 mg	70	70	70	70	70	63	62	62	60
Obeticholic acid, 10 mg	73	73	73	73	73	64	59	61	59

- FXR= Farnesoid X Nuclear Receptor
- Natural ligand chenodeoxycholic acid
- OCA 100X greater FXR agonist

Nevens F, et al. N Engl J Med 2016; 375: 631-43

Primary Biliary Cholangitis: POISE RCT
Adverse Events of Obeticholic Acid (OCA) Therapy

Adverse Events Occurring in ≥10% of Subjects

Event	Double-Blind Phase			Open-Label Extension
	Placebo (N=73)	Obeticholic Acid, 5–10 mg (N=70)	Obeticholic Acid, 10 mg (N=73)	Total Obeticholic Acid (N=193)
	number of patients (percent)			
Pruritus	28 (38)	39 (56)	50 (68)	138 (72)
Nasopharyngitis	13 (18)	17 (24)	13 (18)	45 (23)
Headache	13 (18)	12 (17)	6 (8)	36 (19)
Fatigue	10 (14)	11 (16)	17 (23)	50 (26)
Nausea	9 (12)	4 (6)	8 (11)	28 (15)
Diarrhea	8 (11)	2 (3)	8 (11)	17 (9)
Back pain	8 (11)	4 (6)	4 (5)	24 (12)
Upper respiratory tract infection	8 (11)	4 (6)	4 (5)	20 (10)
Urinary tract infection	8 (11)	4 (6)	4 (5)	31 (16)
Dyspepsia	8 (11)	4 (6)	0	10 (5)
Arthralgia	3 (4)	4 (6)	7 (10)	32 (17)
Serious adverse event	3 (4)	11 (16)	8 (11)	27 (14)

Nevens F, et al. N Engl J Med 2016; 375: 631-43

Obeticholic Acid for Decompensated Cirrhosis
FDA Boxed Warning for OCA (OCALIVA)

Staging / Classification	Non-Cirrhotic or Compensated Child-Pugh Class A	Child-Pugh Class B or C or Patients with a Prior Decompensation Event[a]
Starting OCALIVA Dosage for first 3 months	**5 mg once daily**	**5 mg once weekly**
OCALIVA Dosage Titration after first 3 months, for patients who have not achieved an adequate reduction in ALP and/or total bilirubin and who are tolerating OCALIVA[b]	**10 mg once daily**	**5 mg twice weekly** (at least 3 days apart) **Titrate to 10 mg twice weekly** (at least 3 days apart) based on response and tolerability
Maximum OCALIVA Dosage	**10 mg once daily**	**10 mg twice weekly** (at least 3 days apart)

[a] Gastroesophageal variceal bleeding, new or worsening jaundice, spontaneous bacterial peritonitis, etc.

[b] Prior to dosage adjustment, re-calculate the Child-Pugh classification

https://www.fda.gov/drugs/drugsafety/ucm594941.htm (accessed 27 FEB 2018)

Primary Biliary Cholangitis
Management of Cholestatic Pruritus

General Recommendations[1]	▪ Skin moisturizer ▪ Wet, cooling, or moist wraps ▪ Topical agents with symptomatic relief (eg, camphor, menthol) ▪ Relaxation techniques ▪ Training to stop the cycle of itch, scratch, itch
First-line[2-4]	▪ Bile acid sequestrants: - Cholestyramine - Colestipol, colesevelam
The following agents may be used for pruritus refractory to bile acid sequestrants:	
Second-line[2-4]	▪ Rifampicin
Third-line[2-4]	▪ Oral opioid antagonists: - Naltrexone - Nalmefene
Fourth-line[2-4]	▪ Selective serotonin reuptake inhibitors: - Sertraline

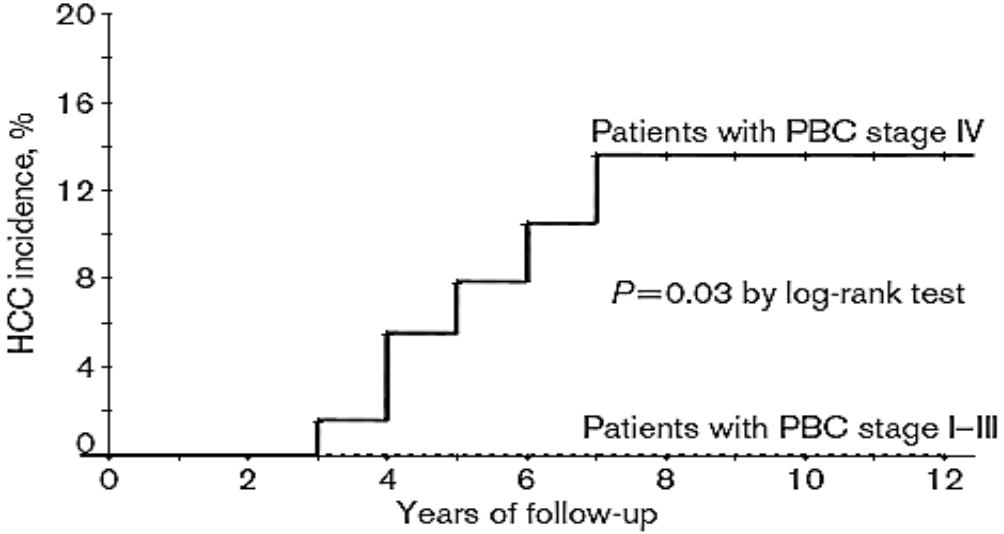
1. Weisshaar E, et al. *Acta Derm Venereol*. 2012;92(5):563-581. European Association for the Study of the Liver. *J Hepatol*. 2009;51(2):237-267.
2. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308. 4. Hohenester S, et al. *Semin Immunopathol*. 2009;31(3):283-307.

Primary Biliary Cholangitis
Management of Complications of Cholestasis/Cirrhosis

Complications of Cholestasis or Cirrhosis	Proportion of Patients Affected
Osteoporosis → Vitamin D, Ca^{++}, Alendronate	20%-44%
Hyperlipidemia → Statin	75%-95%
Vitamin deficiency → Water soluble Vit A, D, E, K	8%-33%
Gastroesophageal varices associated w/ PVHTN ▪ EGD surveillance ▪ β-blocker ▪ EVBL	6% (with early-stage disease) ~31% (with late-stage disease)
Hepatocellular carcinoma → Surveillance imaging + AFP q 6 months	1.5% of patients per year

Primary Biliary Cholangitis:
Hepatocellular Carcinoma

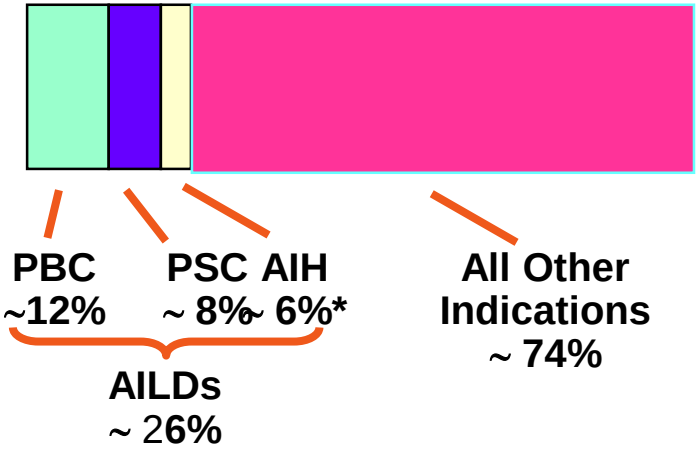
Incidence: ~1.5%/year in Cirrhotic Patients → Surveillance imaging + AFP q 6 mos



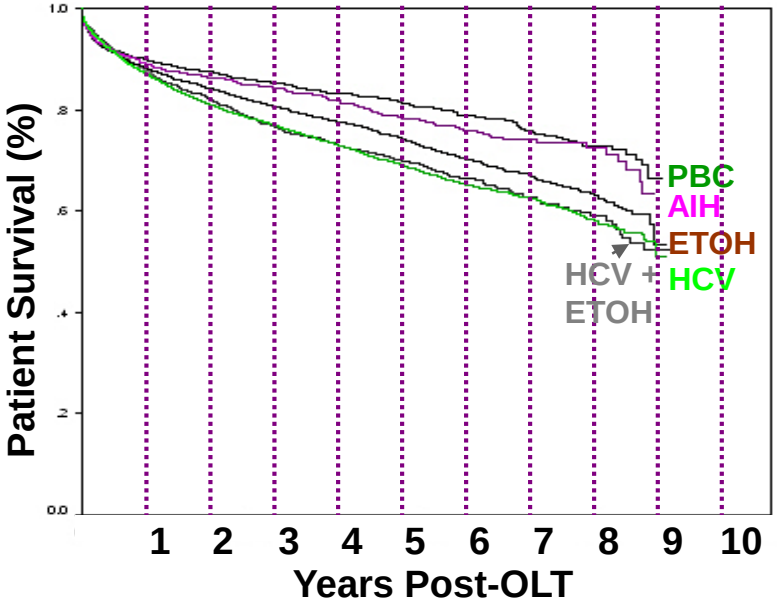
Cumulative incidence of hepatocellular carcinoma (HCC) in 149 patients with primary biliary cirrhosis (PBC) in relation to their histologic stage [stages I–III (n=60) versus stage IV (n=89)].

Deutsch et al. Eur J Gastroenterol Hepatol 2008; 20:5

Primary Biliary Cholangitis:
Orthotopic Liver Transplantation (OLT)



Post-OLT Patient Survival



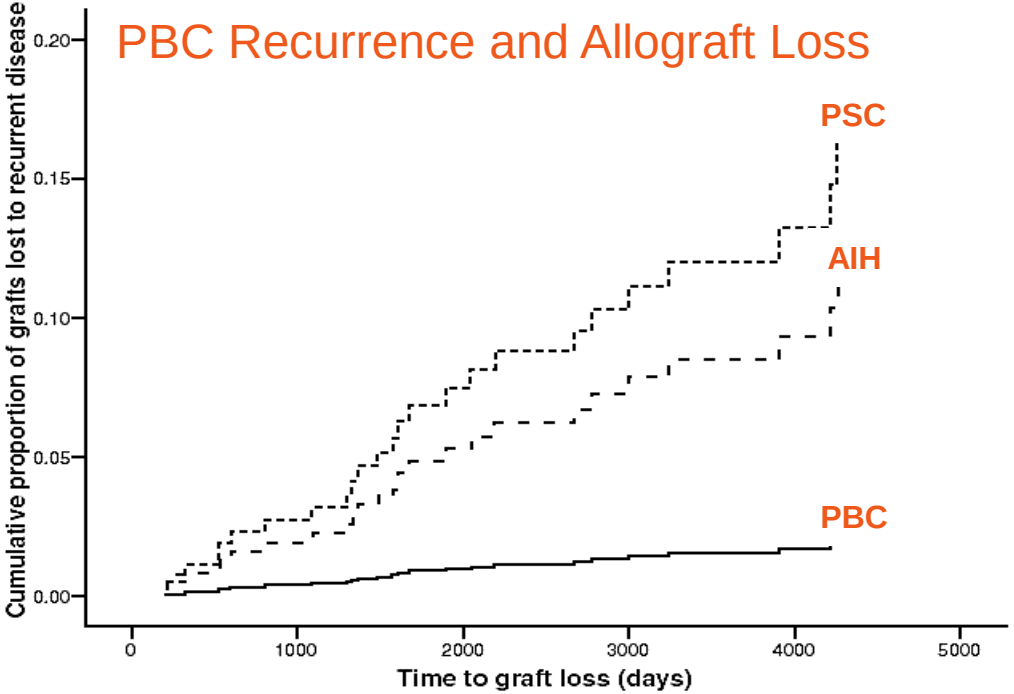
Evaluate for OLT:

- MELD Score ≥ 15
- Life Threatening Complications
- HCC

Ilyas J, O'Mahony C, Vierling. Best Pract Res Clin Gastro; 2011

Primary Biliary Cholangitis
Recurrence of PBC After Liver Transplantation

- PBC Recurrence: 17-46% median of 5 yrs post-OLT
- Diagnostic Criteria:
  - OLT for PBC
  - AMA+
  - ↑ IgM
  - Histology:
    - Lymphocytic cholangitis
    - Granulomas
    - Lymphoid aggregates



Montano-Loza AJ, et al. Aliment Pharmacol Ther. 2017; 45: 485-500

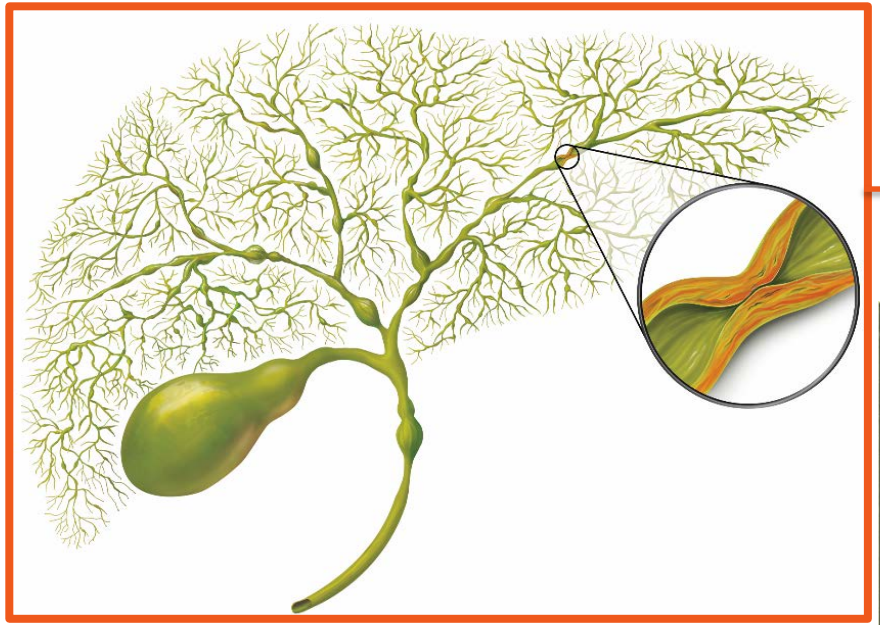
Schreuder et al. Transplant Int. 2009; 22:144

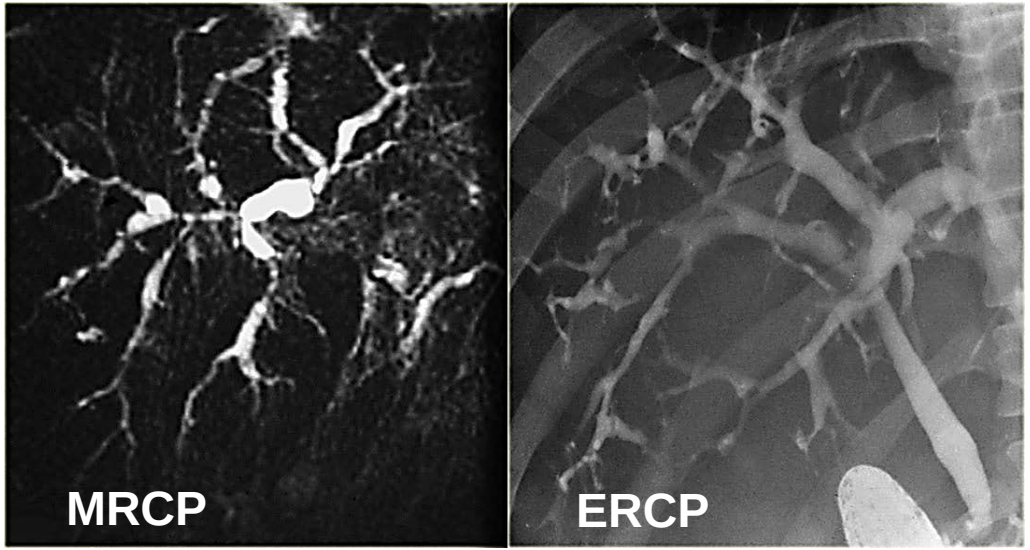
Primary Sclerosing Cholangitis (PSC)

Demographics and Epidemiology

- Afflicts all ages and races
- Prevalence ~ 40 per million with familial predisposition
  - 0.7% among 1st degree relatives (100-fold ↑)
  - 1.5% among siblings
- Male: Female Ratio: 1.5:1 (60% males)
- Diagnosis < 45 years of age in 67%

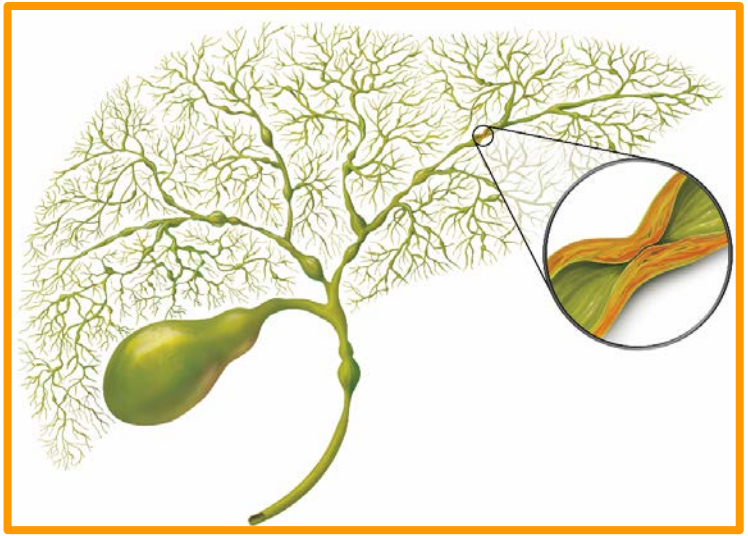
Diagnosis of Primary Sclerosing Cholangitis: Cholestasis + Cholangiography

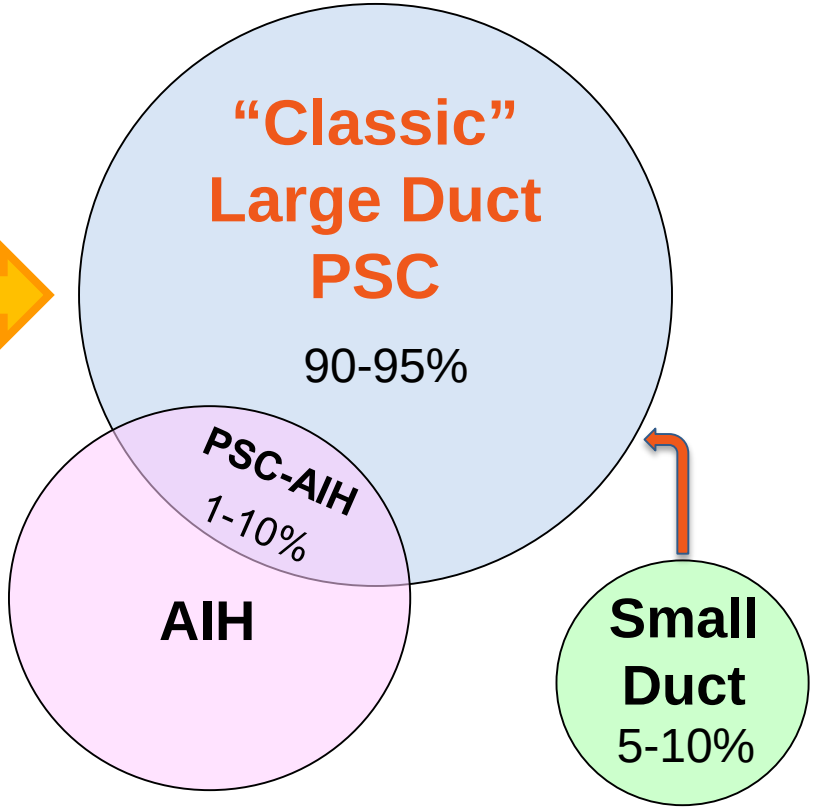




Vierling JM: PSC. Schiff's Liver Diseases, 12th Ed, 2017

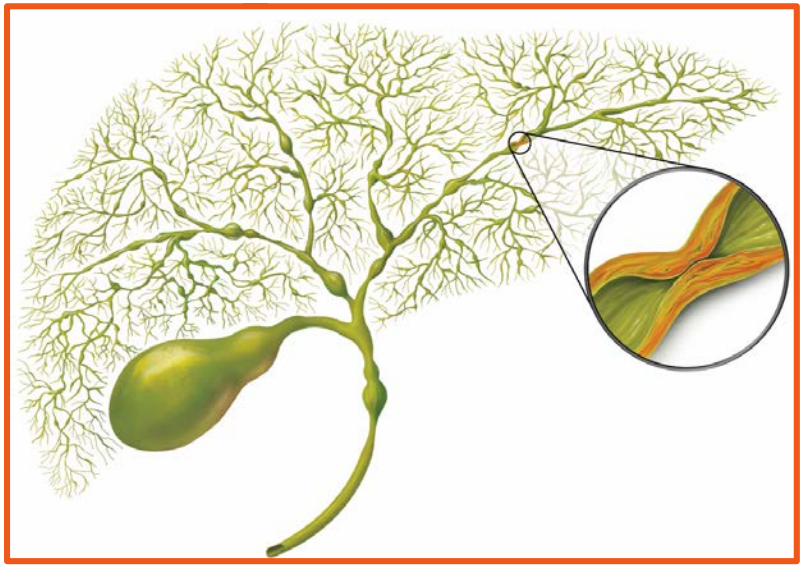
Primary Sclerosing Cholangitis (PSC)
Three Distinct Clinicopathological Entities





Primary Sclerosing Cholangitis (PSC)
Primary vs. Secondary Sclerosing Cholangitis

PSC



SSC

1. IgG4 Sclerosing Cholangitis

2. Infections in Immunocompromised

- Cryptosporidium
- Trichosporon
- CMV
- Cryptococcus
- Visceral protothecosis
- HTLV-1-associated myelopathy
- Sepsis/MOSF/Burns

3. Ischemic

- Arterial injury
- Trauma to biliary tract

4. Toxic/Ischemic

- 5-FU intra-arterial chemotherapy
- Formalin injection of hydatid cyst
- Methotrexate

5. Neoplastic

- Langerhan's histiocytosis X
- Systemic mastocytosis

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Primary Sclerosing Cholangitis (PSC)
Association with Multiple Autoantibodies

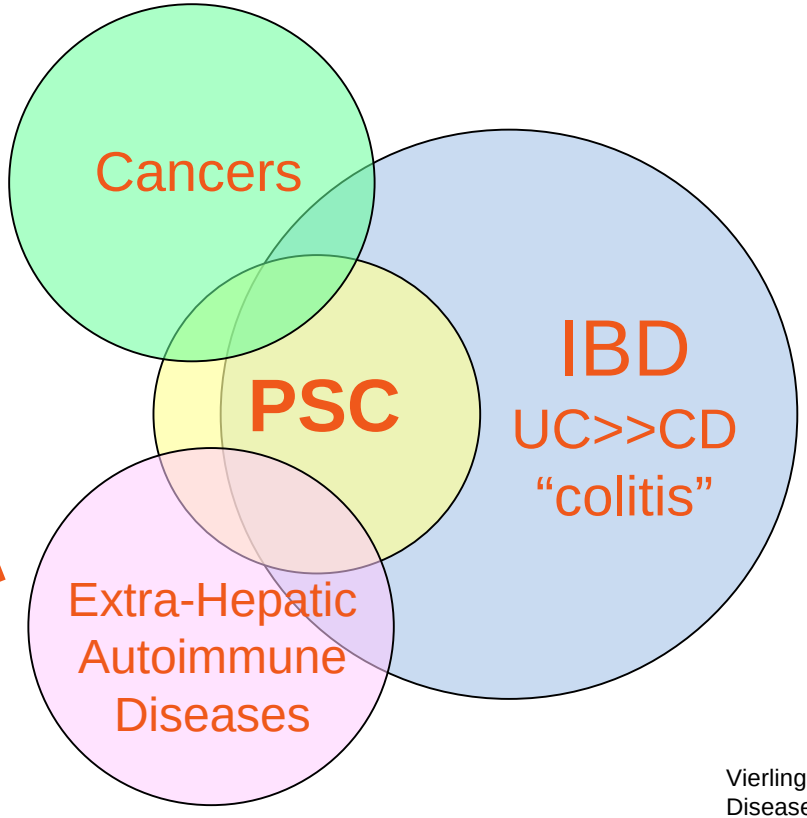
Studies (n=)	Antibody	Prevalence
12	pANCA	33-88% (>65%)
6	ANA	7-77% (35%)
3	SMA	13-20%
3	AMA	0-9%
1	Anti-colon	62%
2	Anti-colon protein (Mr 40kDa)	67%
1	Anti-endothelial cell	35%
6	Miscellaneous	4-66%

Donaldson PT, Norris S. Autoimmunity 2002; 35: 555-64; Neri, et al: Dig Liver Dis 2003;35: 571-6; Sheth S, et al. Hum Genet 2003; 113: 286-92; Terjung B, Worman HJ: Best Pract Res Clin Gastro 2001; 15: 629-642

Primary Sclerosing Cholangitis (PSC)
Strong Disease Associations

Autoimmune Diseases:

- Celiac disease
- Rheumatoid arthritis
- Primary systemic sclerosis
- Sjögren syndrome
- Sclerosing sialoadenitis
- Rapidly progressing glomerulonephritis
- SLE
- AI hemolytic anemia
- Type 1 diabetes mellitus



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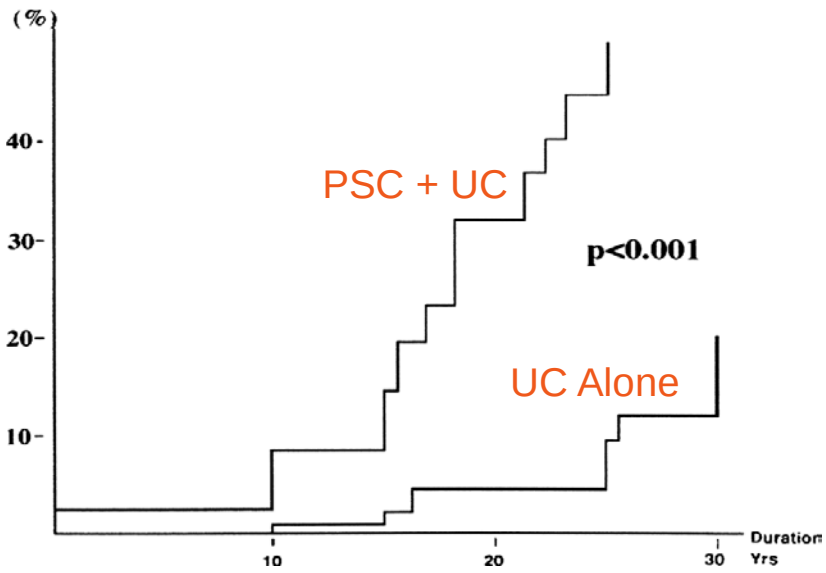
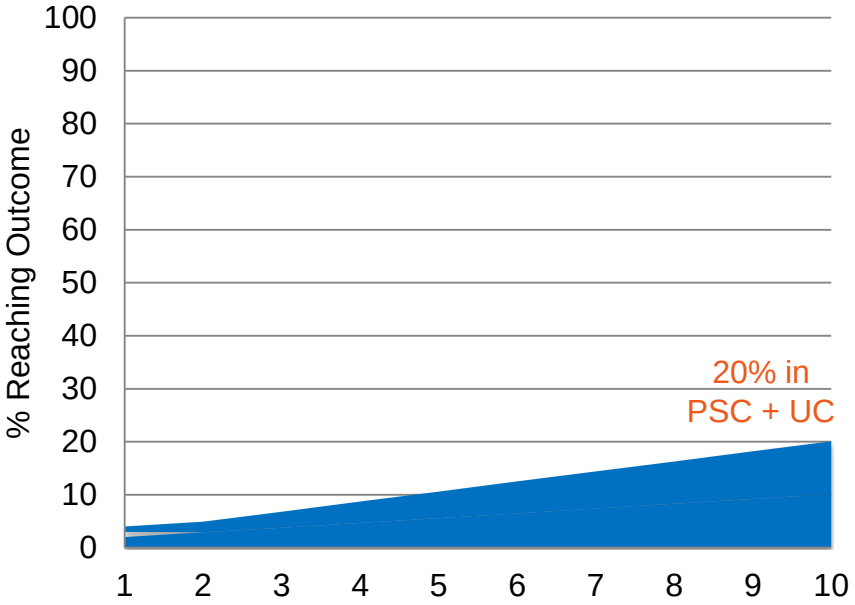
Primary Sclerosing Cholangitis (PSC)
Independent Risk Factor for Colorectal Carcinoma

Historic Cumulative Rate



Current Cumulative Rate



Broome U, et al: Hepatology 1995; 22: 1404-8.

Vierling JM: PSC. Schiff's Liver Diseases, 12th Ed, 2017

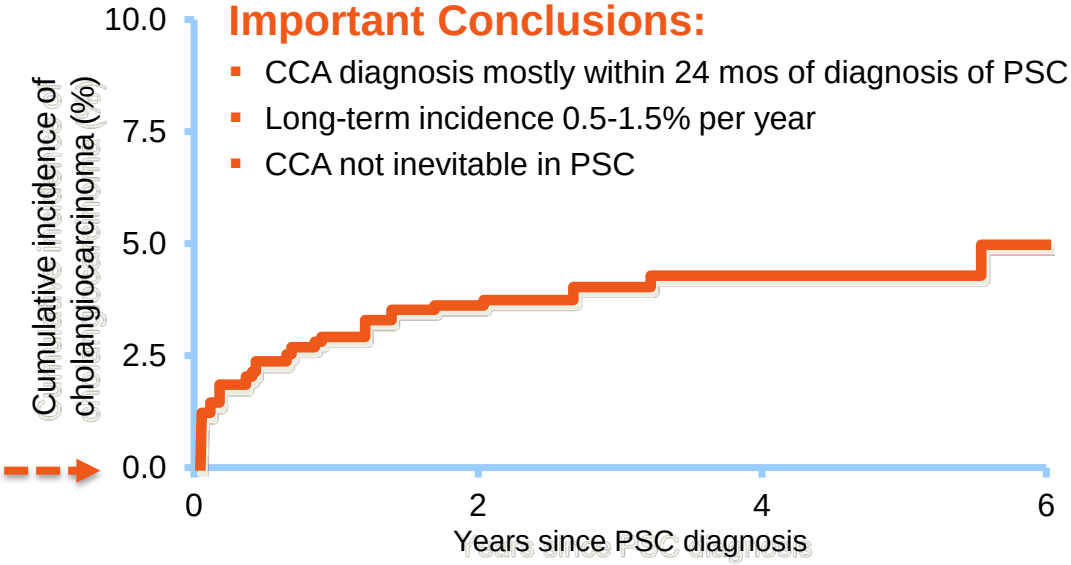
Primary Sclerosing Cholangitis (PSC)
Risk Factor for Cholangiocarcinoma

Cholangiocarcinoma:

- Relative Risk = 160 to 1560
- Prevalence = 4.8% to 36.4%
- Annual incidence = 0.6% to 1.5%
- 38% to 50% of cases diagnosed within 1-year
- ~2.5% incidence in first year

Important Conclusions:

- CCA diagnosis mostly within 24 mos of diagnosis of PSC
- Long-term incidence 0.5-1.5% per year
- CCA not inevitable in PSC



Am J Gastroenterol 2004;99:523-526. J Hepatol 2002;36:321-327.
Am J Surg Pathol. 2007;31:907-13. J Hepatol. 2010;53:313-7.

Burak et al. Am J Gastroenterol. 2004;99:523.

Primary Sclerosing Cholangitis (PSC)
Risk Factor for Gallbladder Adenocarcinoma

Gallbladder Adenocarcinoma:

- Prevalence = 0.9% to 14%
- High rate of dysplastic polyps
- Cholecystectomy appropriate:
  - Any growing polyp (regardless of size)
  - Any polyp ≥1 cm

Am J Gastroenterol 2004;99:523-526. J Hepatol 2002;36:321-327.
Am J Surg Pathol. 2007;31:907-13. J Hepatol. 2010;53:313-7.

Primary Sclerosing Cholangitis (PSC)
Ursodeoxycholic Acid (UDCA) Therapy

Bile Acids

UDCA

No!
AASLD

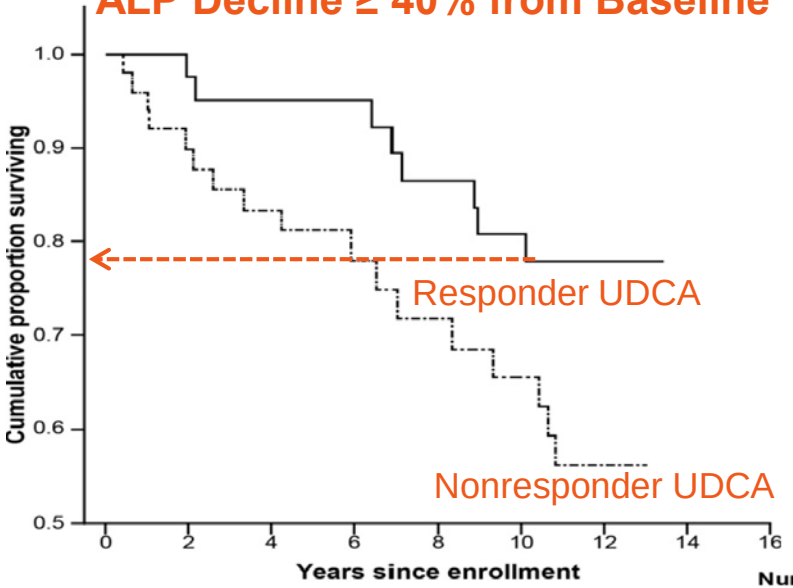
Maybe!
EASL + AASLD

Dose?

Low (13-15 mg/kg/d: Ineffective
High (28-32 mg/kg/d: toxic
Medium (17-23 mg/kg/d: Survival benefit in a subgroup

Long-term Survival of PSC Patients in the 5 year Scandinavian RCT of Medium Dose UDCA

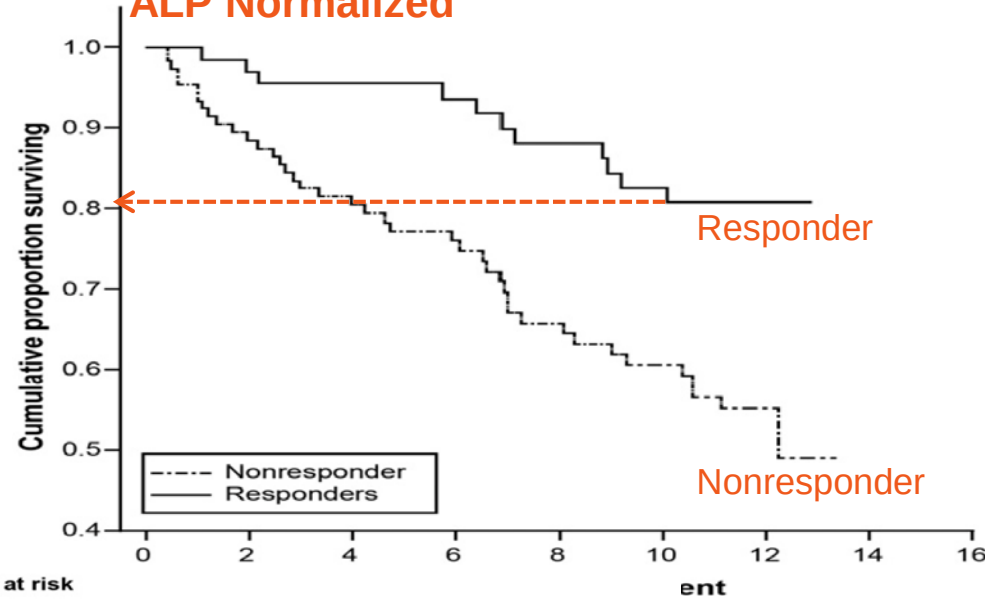
ALP Decline ≥ 40% from Baseline



Numbers at risk

Years	0	2.5	5	7.5	10
Responder	43	40	34	24	23
Nonresponder	51	45	35	19	15

ALP Normalized



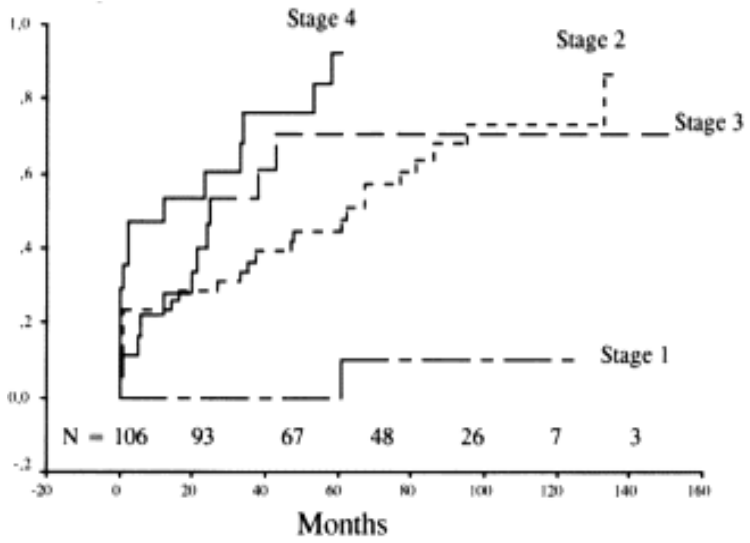
Numbers at risk

Years	0	2.5	5	7.5	10	12.5
Responders	79	72	69	56	53	17
Nonresponders	116	93	78	56	52	21

Lindstrom L, Hultcrantz R, Boberg KM,, et al. Assoc. between reduced levels of ALK and Survival Times of Patients with PSC. Clin Gastro Hep. 2013;11(7):841-846.

Primary Sclerosing Cholangitis (PSC)
UDCA Does Not Prevent Dominant Strictures

Occurrence of Dominant Strictures

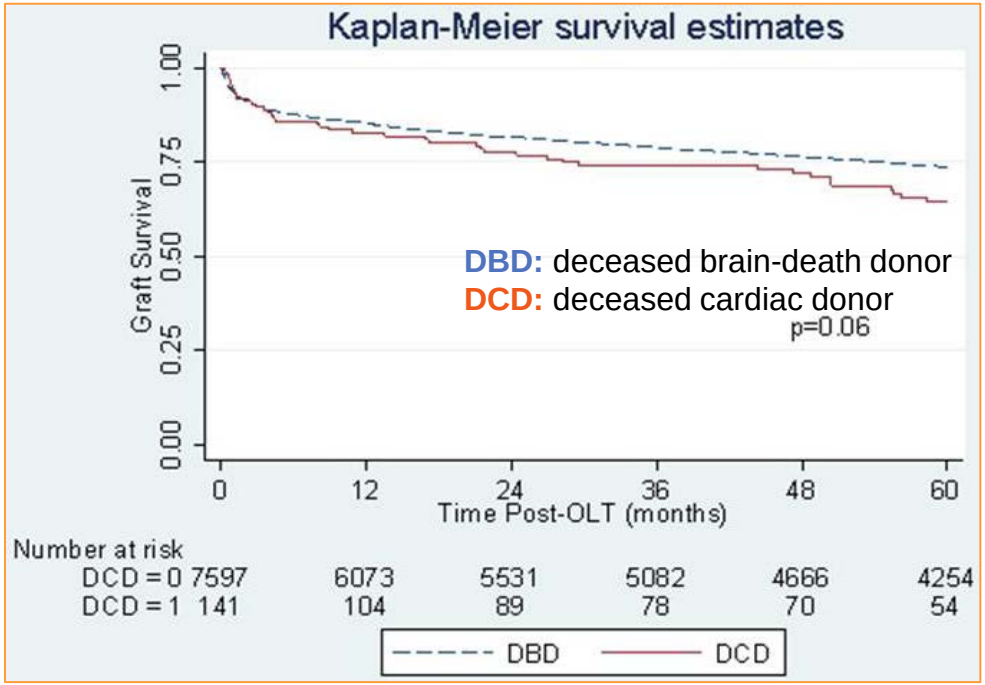


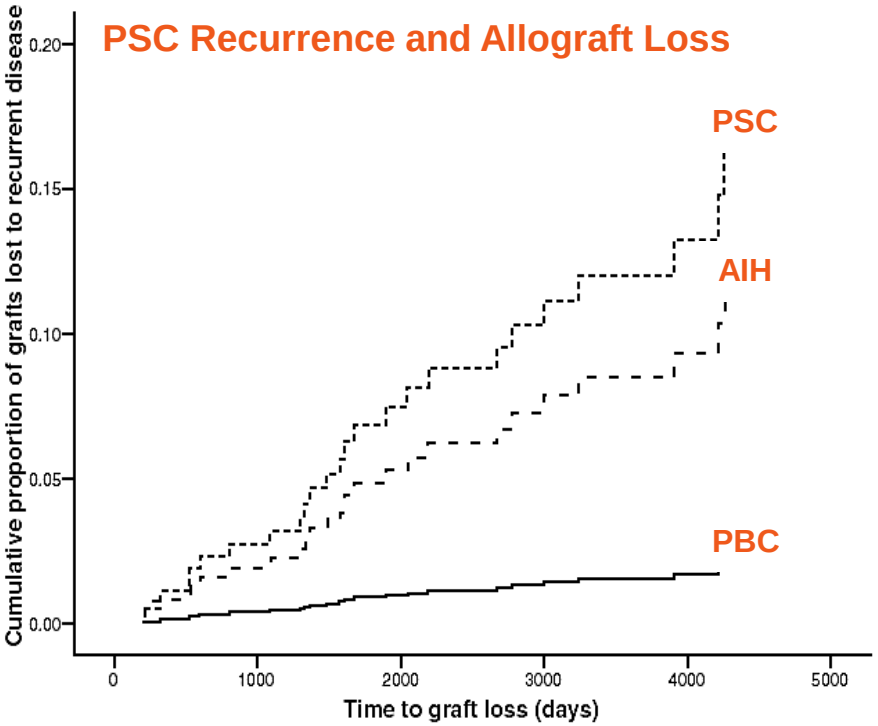
Stiehl A, et al: J Hepatol 2002; 36: 151-6.

Endoscopic Approaches:

- Dilation alone?
- Dilation + Stent?
- CCA detection:
  - Cholangioscopic biopsy
  - Evaluation:
    - Dysplasia
    - FISH for aneuploidy

Primary Sclerosing Cholangitis (PSC)
Excellent Outcomes of OLT Despite Reccurrence

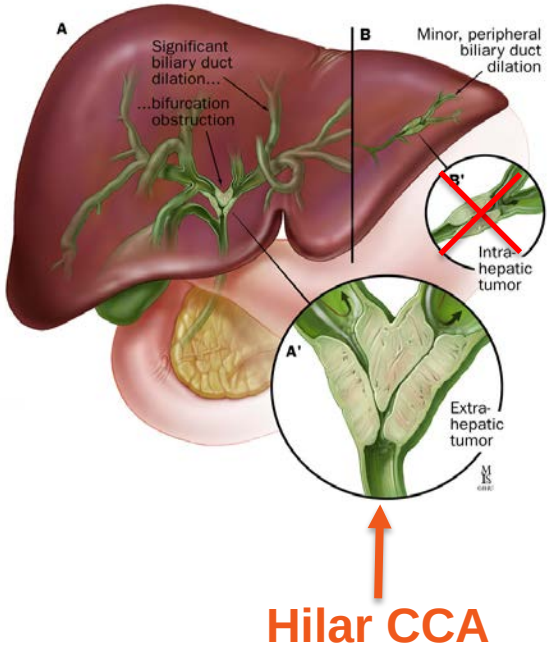


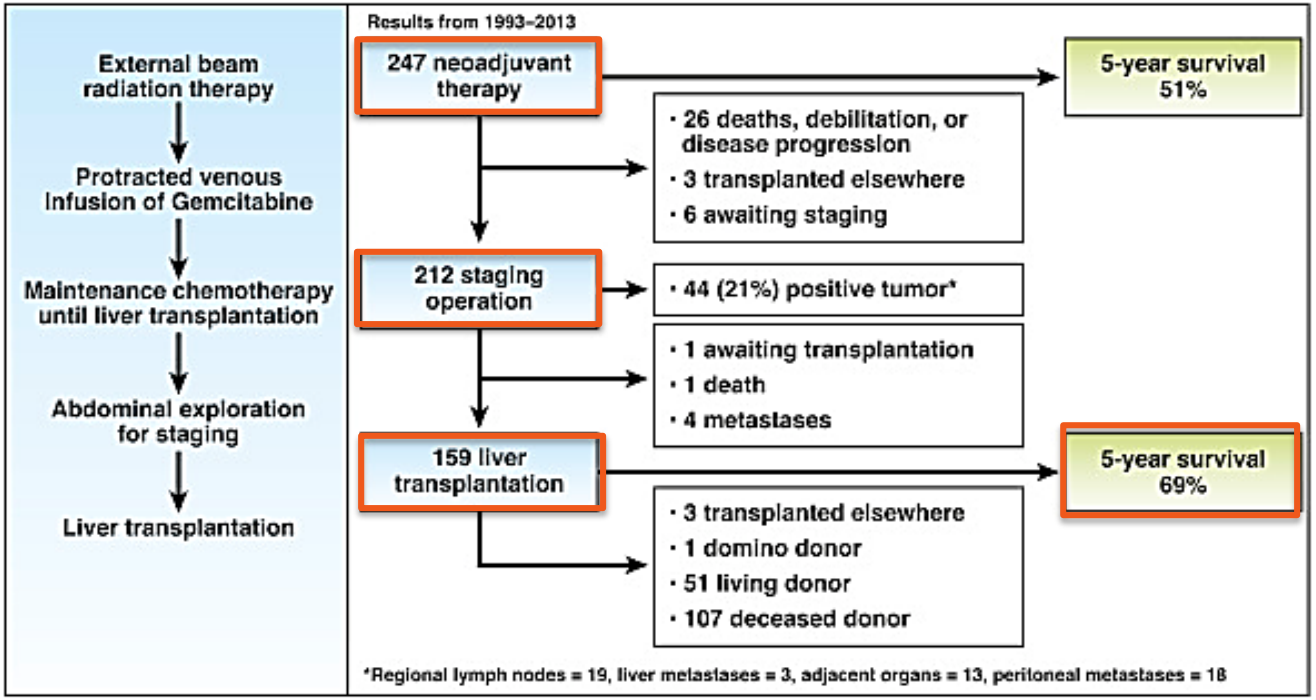


Mousa O, et al. Am J Transpl. 2017

Schreuder et al. Transplant Int. 2009; 22:144

Primary Sclerosing Cholangitis (PSC) Liver Transplantation for Cholangiocarcinoma

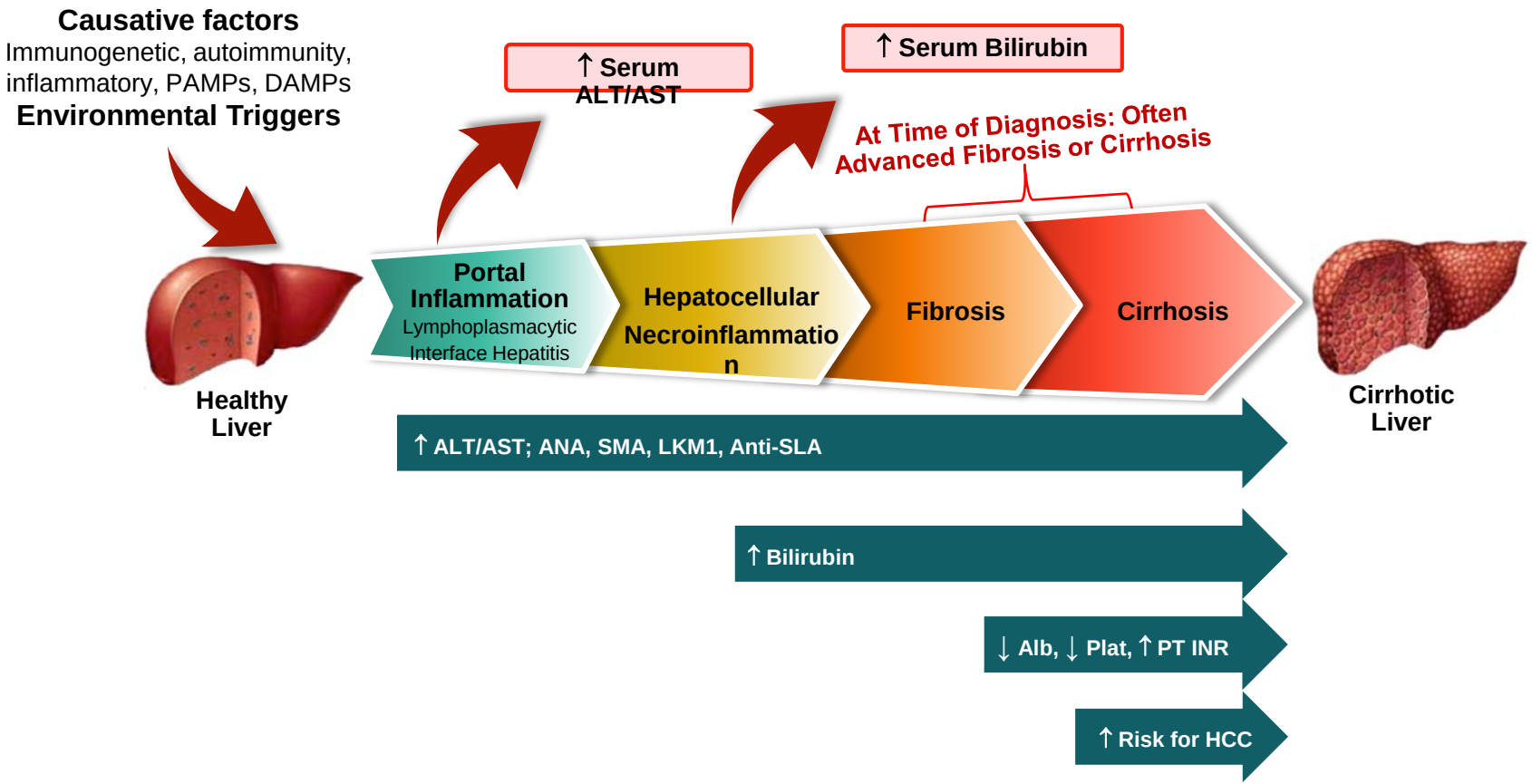




https://hopkinsmedicine.org/liver_tumor_center/conditions/bile_duct_cancers.html; Dulkowski P, et al. Gastroenterology 2015; 148: 307-23

Autoimmune Hepatitis: A Progressive Disease if Untreated

Baylor College of Medicine



Autoantibodies in Classification of Autoimmune Hepatitis

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AIH Type	AutoAbs	AutoAgs	Specificity	
			Liver	AIH
	ANA	Histone/DNA	No	No
	SMA	F-actin 50%	No	No
	pANCA	β-tubulin	No	No
	ASGPR	ASGPR	Yes	No
	LKM1	CYP2D6	No	No (HCV infection)
	LKM3	UGT1A	No	No
	LC-1	FTCD	Yes	Yes, type 2
	ASGPR	ASGPR	Yes	No
	SLA/LP	SepSecS protein	No	Yes (prognostic)
	Tubulin-β-5	ANNA	No	No

Sahebjam F and Vierling JM Front Med, 2015
Vierling JM Clin Gastro Hepatol 2015

Autoimmune Hepatitis
Extrahepatic Autoimmune and Immune-Mediated Diseases

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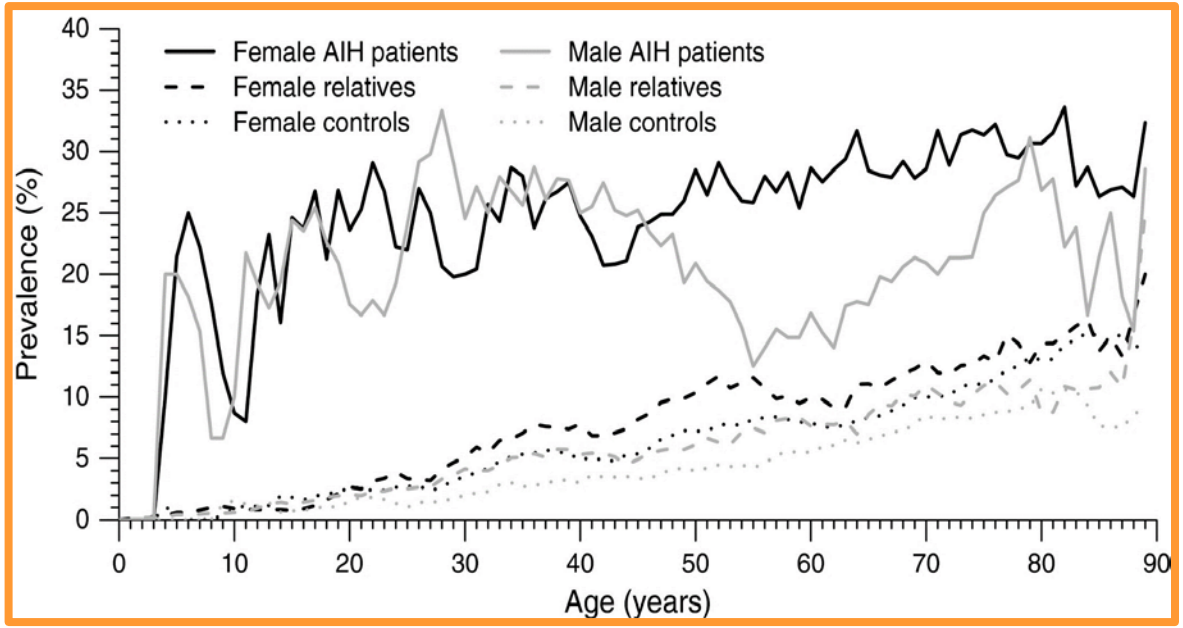
- More common in Type 2 (40%) than Type 1 (10-20%)
- Spectrum:
  - Thyroid disease:
    - Hashimoto
    - Graves
  - Rheumatoid arthritis
  - Ulcerative colitis
  - Miscellaneous
    - Diabetes mellitus type 1
    - Sjögren syndrome
    - Vitiligo
    - Addison disease
    - Celiac sprue



Autoimmune Hepatitis: Revised Diagnostic Criteria

International Autoimmune Hepatitis Group

Baylor College of Medicine

Gender	Female	+2
AP:AST (or ALT) ratio	>3	-2
	<1.5	+2
γ-globulin or IgG level above normal	>2.0	+3
	1.5-2.0	+2
	1.0-1.5	+1
	<1.0	0
ANA, SMA, or anti-LKM1 titers	>1:80	+3
	1:80	+2
	1:40	+1
	<1:40	0
AMA	Positive	-4
Viral markers	Positive	-3
	Negative	+3
Drugs	Yes	-4
	No	+1
Alcohol	<25 g/day	+2
	>60 g/day	-2

HLA	DR3 or DR4	+1
Immune disease	Thyroiditis, colitis, others	+2
Other markers	Anti-SLA, actin, LC1, pANCA	+2
Histological features	Interface hepatitis	+3
	Plasmacytic	+1
	Rosettes	+1
	None of above	-5
	Biliary changes	-3
	Other features	-3
Treatment response	Complete	+2
	Relapse	+3

Pretreatment aggregate score:
- Definite diagnosis >15
- Probable diagnosis 10-15

Post-treatment aggregate score:
- Definite diagnosis >17
- Probable diagnosis 12-17

*Adapted from Alvarez F, Berg PA, Bianchi FB, et al. J. Hepatology 1999;31:929-938.

Autoimmune Hepatitis Simplified Diagnostic Criteria

International Autoimmune Hepatitis Group

Baylor College of Medicine

Autoantibodies:		
ANA or SMA	≥1:40	+1
	≥1:80	+2
LKM-1	≥1:40	+2
Anti-SLA	Positive	+2
Immunoglobulin Level		
IgG or	>ULN	+1
γ-globulin	>1.1 X ULN	+2
Histological Features:		
Compatible with AIH		+1
Typical of AIH*		+2
Absence of Viral Hepatitis:		
Yes		+2
No		0
Pretreatment Aggregate Score		
Definite Diagnosis:	≥7	

Heneghan MA, et al. Lancet 2013;382:1433-1444.

Caveats:

- Whenever "Probable" or "Non-diagnostic", recalculate score using RDC!
- SDC better for classic cases
- RDC better for complex or unusual cases
- Neither validated for use in Cholestatic Variant/Overlap Syndromes

Boberg KM, et al. J Hepatol 2011
Sahebjam F and Vierling JM Front Med, 2015
Vierling JM Clin Gastro Hepatol 2015

2010 AIH Treatment Goals
Revised the Concept of "Remission"

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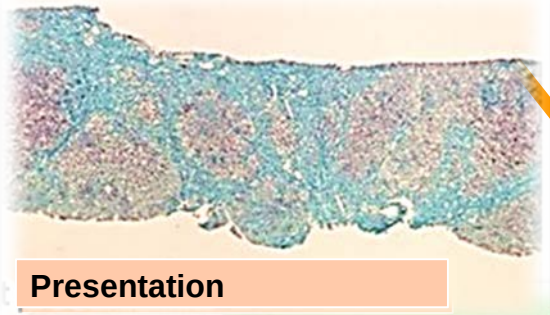
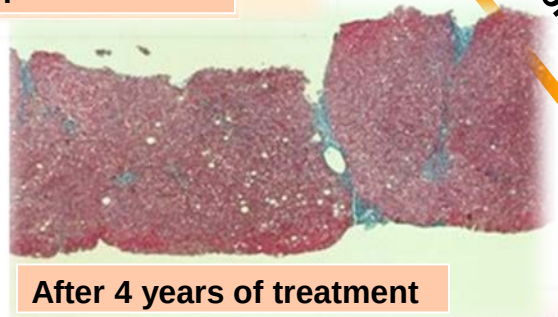
- Prevent progression and OLT
- Relieve symptoms
- Normalize ALT
  - <19 U/L for women
  - <30 U/L for men
- Histology:
  - Eliminate portal lymphoplasmacytic inflammation
  - Eliminate interface hepatitis
  - Prevent progression to cirrhosis
- Use combinations of immunosuppressive drugs to
  - inhibit immunopathogenetic mechanisms at multiple sites
  - minimize adverse events

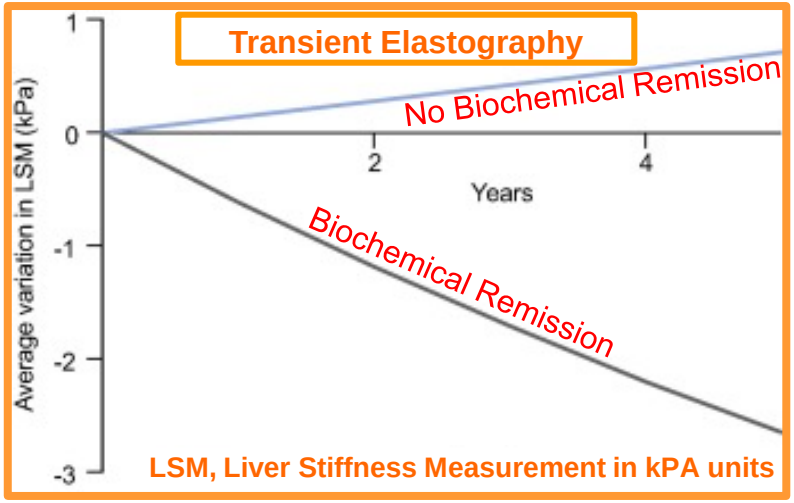
Remission in Autoimmune Hepatitis

Associated with Resolution of Fibrosis, Including Cirrhosis





Cirrhosis Resolution During Remission



Transient Elastography Caveats in AIH:

- Liver stiffness (LS)= fibrosis + inflammation
- ↓ LS first 6-12 mos due to ↓ inflammation
- ↓ LS thereafter indicative of ↓ fibrosis

Modified & Images from 2016 Tiniakos–AASLD 2016
Images from Czaja & Carpenter J Hepatology 2004

Autoimmune Hepatitis

Relationship of Liver-Related Mortality and Hepatic Inflammation

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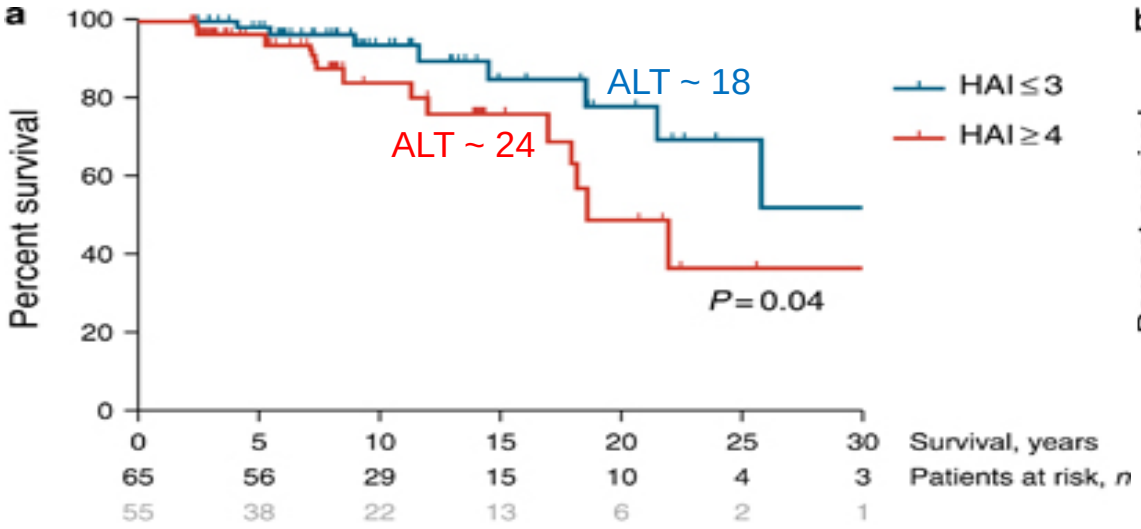

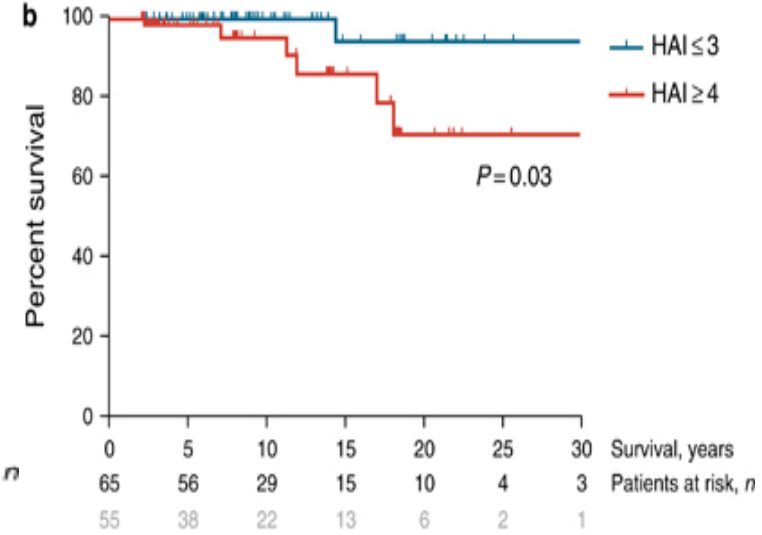

Real world registry: 1,500 pts

41% not in remission!

(UK-AIH registry, 25% AIH pts UK)

Dhaliwal HK et al. Am J Gastroenterol. 2015: 993, Hoeroldt B et al *Gastroenterology* 2011; Jones D et al. The Lancet Gastro Hep 2018

Autoimmune Hepatitis
Conventional Immunosuppression in Responders

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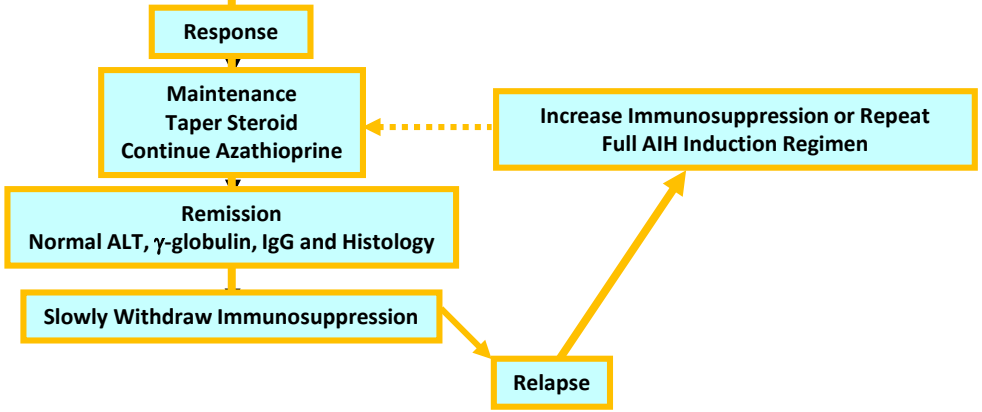
Prednisone + Azathioprine			Budesonide	Prednisone Monotherapy	
Week 1	30 mg/d	50 mg/d or 1-2 mg/kg/d*	3 mg TID	Week 1	60 mg/d
Week 2	20 mg/d	50 mg/d or 1-2 mg/kg/d	+	Week 2	40 mg/d
Week 3	15 mg/d	50 mg/d or 1-2 mg/kg/d	Azathioprine	Week 3	30 mg/d
Week 4	15 mg/d	50 mg/d or 1-2 mg/kg/d	1-2 mg/kg/d	Week 4	30 mg/d
Maintenance:				*Maintenance:*	≤20 mg/d
	10 mg/d	50 mg/d or 1-2 mg/kg/d	Non-cirrhotics only!		



Modified from: Vierling JM Clin Gastro Hepatol 2015

Autoimmune Hepatitis: Relapse of AIH After Withdrawal of Therapy

Increased Probability of Cirrhosis and Need for OLT

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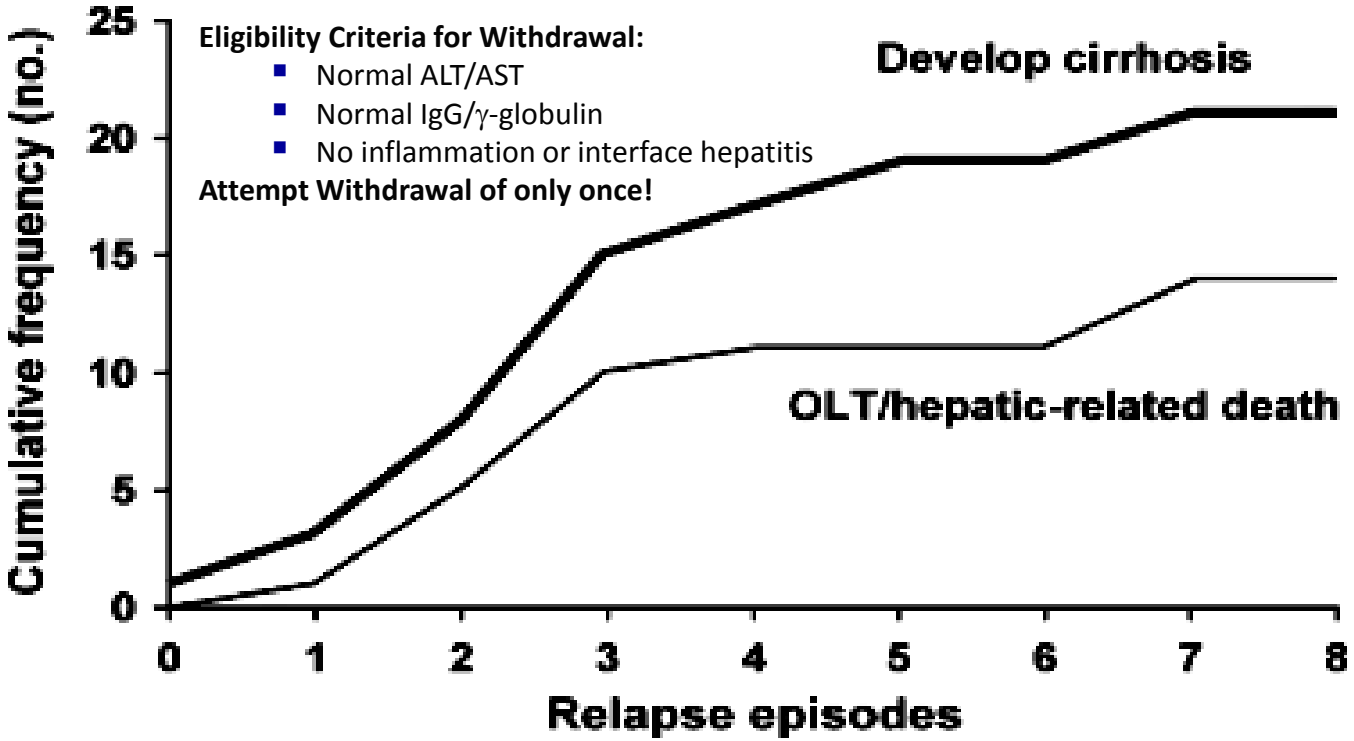
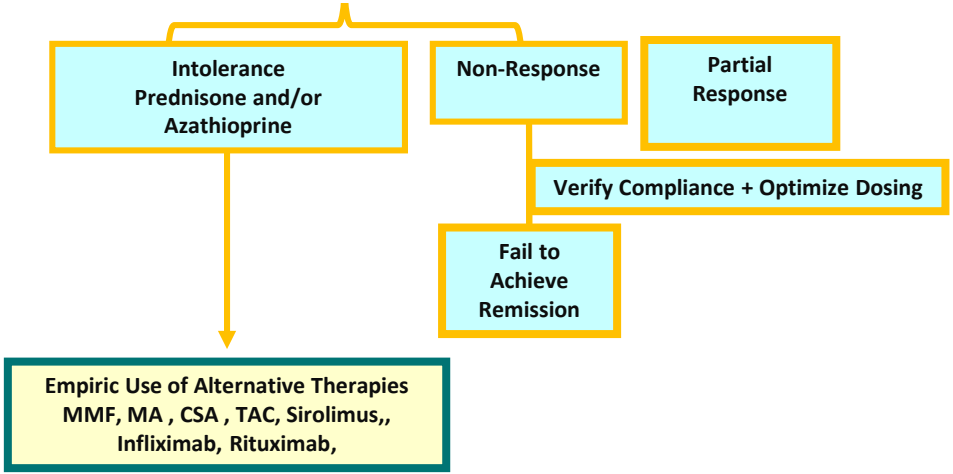


Montano-Loza AJ et al. Liver Int 2007; 27: 507-15

Autoimmune Hepatitis
Alternative Immunosuppression for Non-Response or Partial Response

Baylor College of Medicine

Prednisone + Azathioprine			Budesonide	Prednisone Monotherapy	
Week 1	30 mg/d	50 mg/d or 1-2 mg/kg/d*	3 mg TID	Week 1	60 mg/d
Week 2	20 mg/d	50 mg/d or 1-2 mg/kg/d	+	Week 2	40 mg/d
Week 3	15 mg/d	50 mg/d or 1-2 mg/kg/d	Azathioprine	Week 3	30 mg/d
Week 4	15 mg/d	50 mg/d or 1-2 mg/kg/d	1-2 mg/kg/d	Week 4	30 mg/d
Maintenance:				*Maintenance:*	≤20 mg/d
	10 mg/d	50 mg/d or 1-2 mg/kg/d	Non-cirrhotics only!		



Modified from: Vierling JM Clin Gastro Hepatol 2015

Cholestatic Variants or "Overlap Syndromes"
AIH-PSC and AIH-PBC

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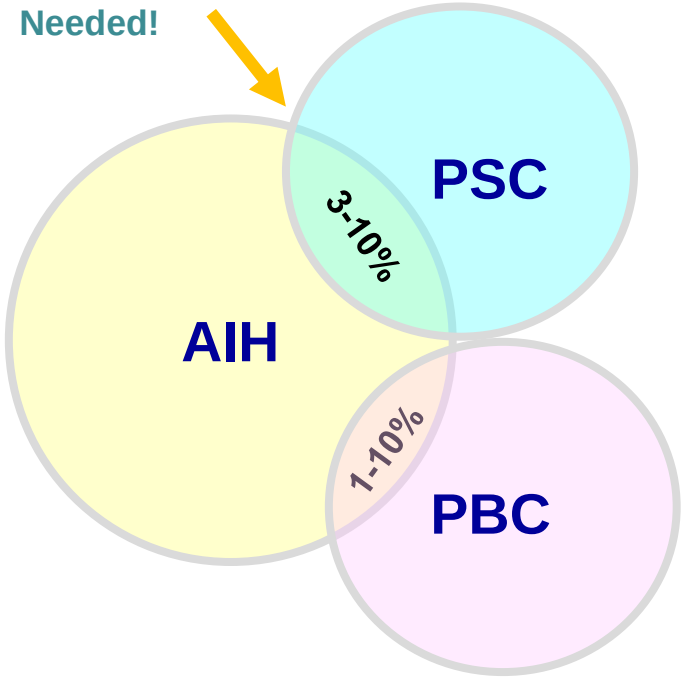
Diagnostic Criteria Based on Disease-Specific Pathogenesis Urgently Needed!



Five Postulated Explanations:

1. Distinct, independent AILDs occurring sequentially or concurrently
2. Distinct disease differing from either of the AILDs
3. Clinicopathological midpoint in a continuum of AILDs
4. One of several expressions of AIH
5. Primary AILD with ≥1 feature of another AILD (IAIHG)

Boberg KM, et al. J Hepatol 2011
Vierling JM Clin Gastro Hepatol 2015

Autoimmune Liver Diseases
Excellent Outcomes of OLT Despite Recurrence

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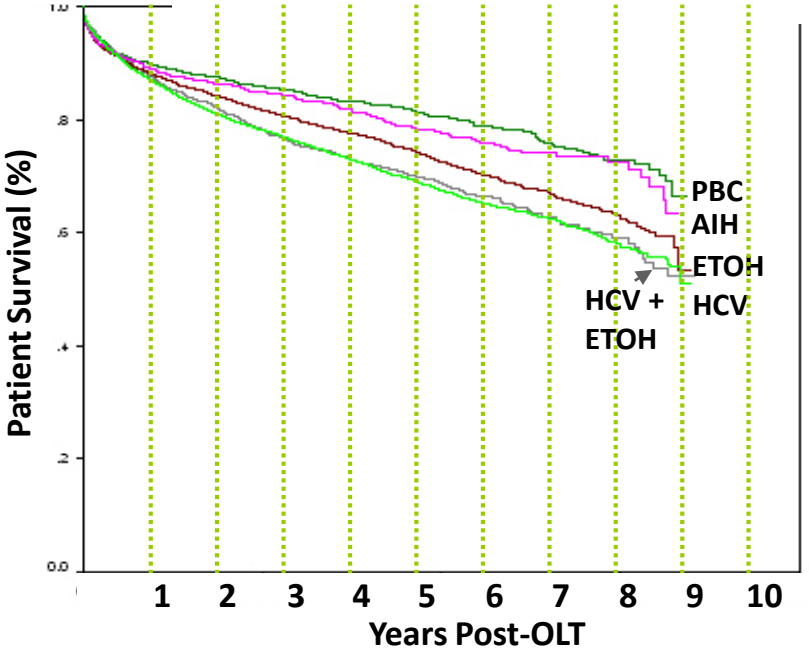
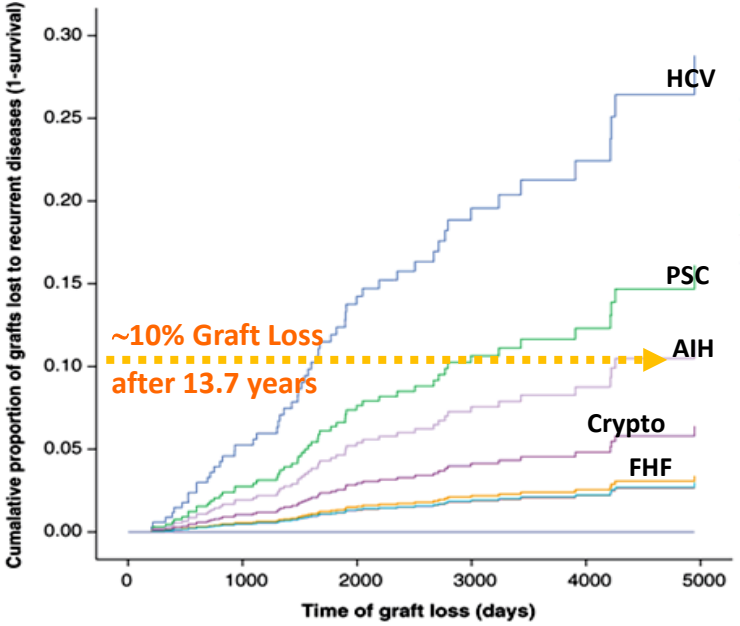


Ilyas J, O'Mahony C, Vierling. Best Pract Res Clin Gastro; 2011

Long-Term Graft Survival



Rowe IA et al. Transplant Int 2008; 21: 459-65

Overview PBC, PSC and AIH
Key Points 1

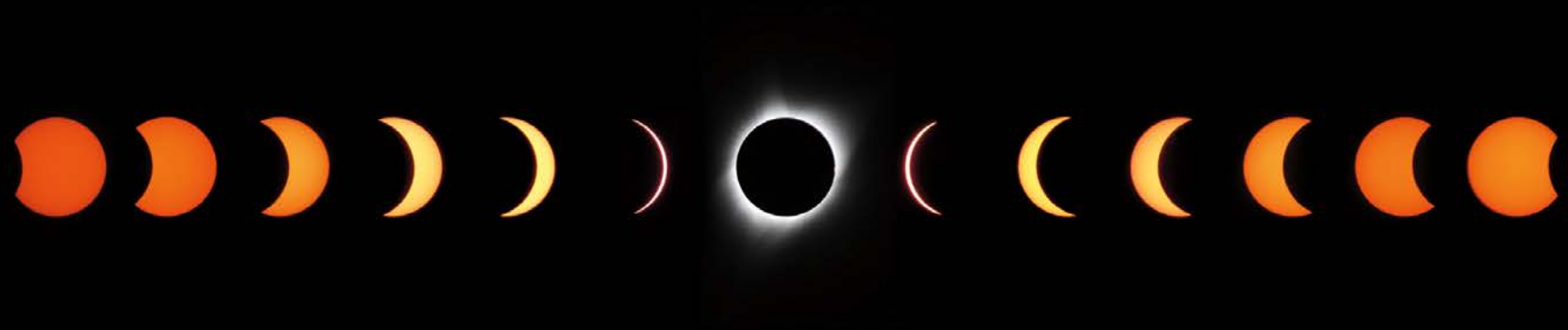
- AILDs exhibit typical and atypical features of classic AI diseases
  - All associated with extrahepatic AI diseases
  - PSC>>AIH associated with IBD
  - PSC a premalignant disease with risk for CRC, CCA, Gallbladder adenoca
- Diagnostic criteria established:
  - PBC: cholestatic liver tests, AMA (+) or if AMA (-), compatible liver biopsy
  - PSC: cholestatic liver tests, pANNA (68%) + MRCP or ERCP showing strictures/ectasias
    - Liver biopsy for diagnosis of small duct PSC
    - IgG4-SSC in up to 10% of previously diagnosed!

Overview PBC, PSC and AIH
Key Points 2

- AIH: revised and simplified criteria REQUIRE liver biopsy
- Fibrosis staging/monitoring with non-invasive Fibroscan
- Risk of HCC in AILDs merits surveillance imaging + AFP
- PSC: surveillance colonoscopy, MRCP?, CA-19-9?, GB imaging
- Therapies;
  - Established first and second line for PBC and ± AIH
    - Prognosis excellent for responders
    - Nonresponders progress
  - No established therapy for PSC
    - Prognosis excellent for subgroup normalizing ALP
    - Nonresponders progress

Overview PBC, PSC and AIH
Key Points 2

- No validated criteria for diagnosis of Overlap Syndromes
- Excellent outcomes after OLT, despite recurrence in allografts
- Encourage participation in clinical trials



TOTAL SOLAR ECLIPSE

Jackson Hole, Wyoming | August 21, 2017