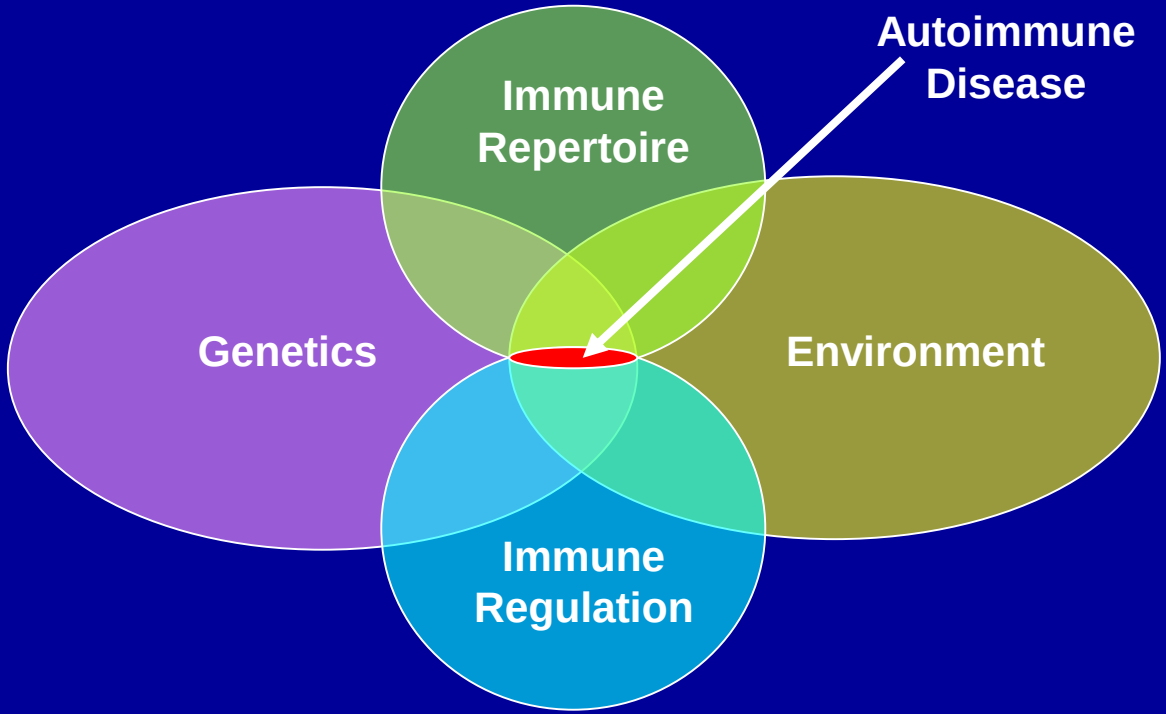
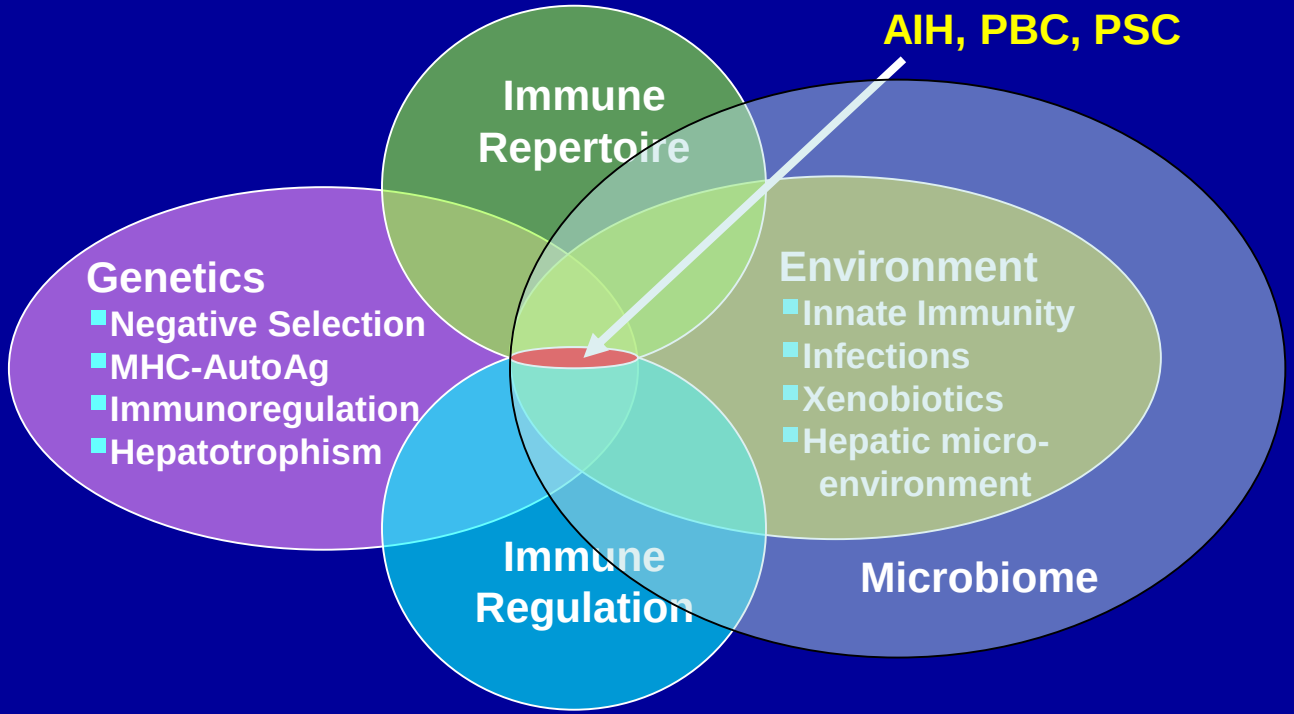
PBC-AIH
Cholestatic Variant or “Overlap Syndrome”

John M Vierling, MD, FACP, FAASLD, AGAF
Professor Medicine and Surgery
Chief of Hepatology
Director, Advanced Liver Therapies
Baylor College of Medicine
Houston, Texas

Pathogenesis of All Autoimmune Diseases

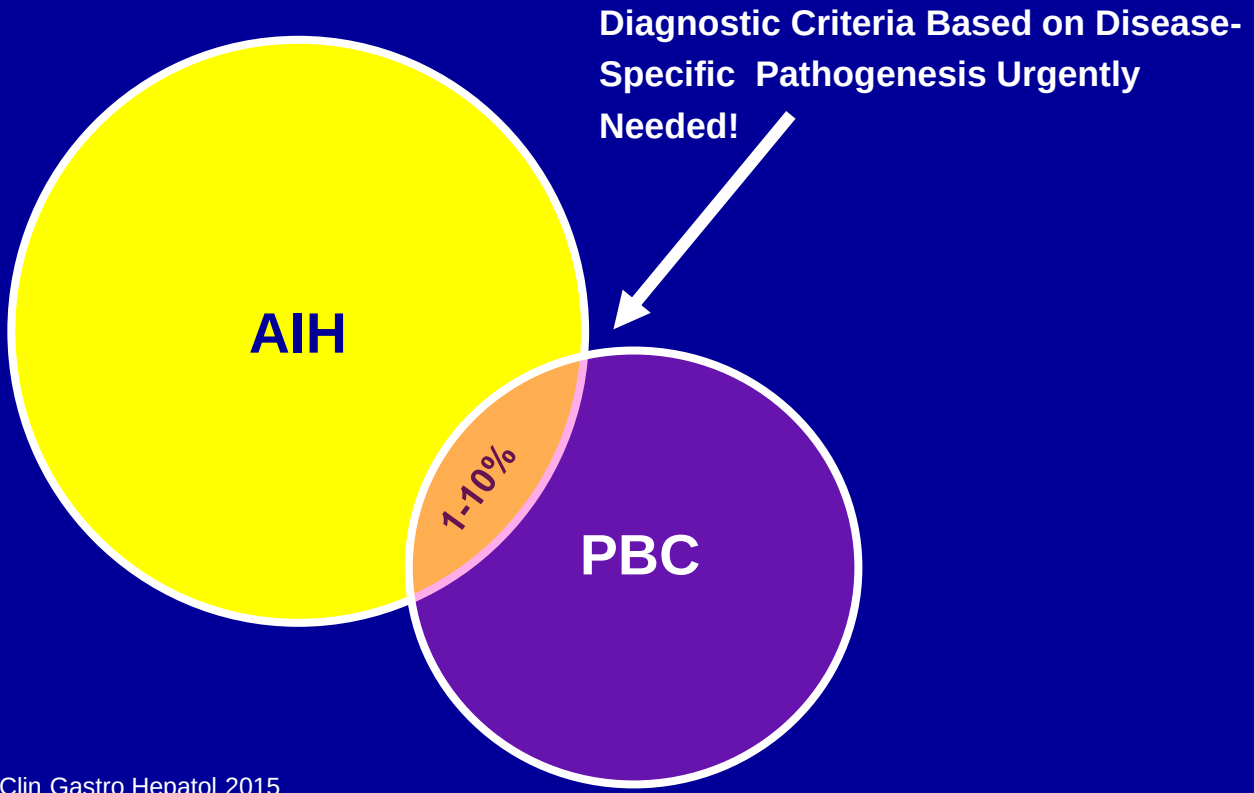


Pathogenesis of Autoimmune Liver Diseases



Cholestatic Variants or “Overlap Syndromes”

PBC-AIH



Vierling JM Clin Gastro Hepatol 2015
*Gossard AA, Lindor KD Liver Int 2007; 27: 1086-90

Cholestatic Variant/Overlap Syndromes
Clinical Rationale for Precise Nomenclature

Cholestatic Variant Syndrome:

- Coexistence of AIH and cholestatic features resembling PBC or PSC
- Prompts investigation of etiology of cholestasis, including biliary obstruction, granulomatous or other infiltrative diseases, cholestatic viral hepatitis and cholestatic DILI

Overlap Syndrome:

- Implies coexistence of AIH with either PBC or PSC
- IAIHG Consensus Definition: AILD with ≥1 features of another AILD
- May not prompt differential diagnostic testing

Misdiagnosis of “Overlap Syndromes”
rampant in clinical practice!

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

Diagnostic Criteria for AIH

- Diagnosis of exclusion
- Revised vs. Simplified Diagnostic Scoring Systems
- Liver biopsy required

Autoimmune Hepatitis: Revised Diagnostic Criteria

International Autoimmune Hepatitis Group

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

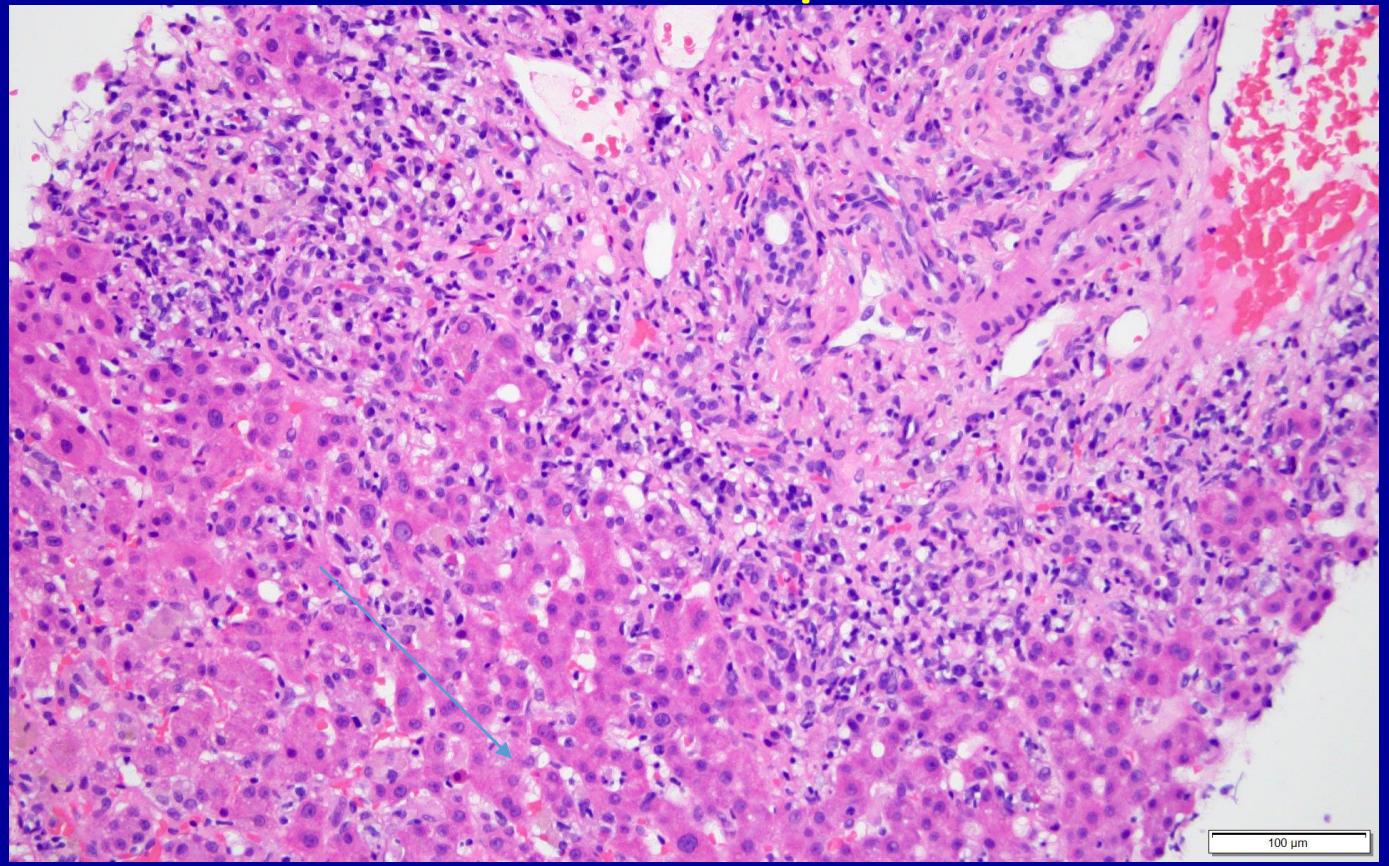
Autoantibodies:		
ANA or SMA	≥1:40	+1
	≥1:80	+2
LKM-1	≥1:40	+2
Anti-SLA	Positive	+2
Immunoglobulin Level		
IgG or	>ULN	+1
γ-globulin	>1.1 X ULN	+2
Histological Features:		
Compatible with AIH		+1
Typical of AIH*		+2
Absence of Viral Hepatitis:		
Yes		+2
No		0
Pretreatment Aggregate Score:		
Definite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

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

Anti-Nuclear Antibodies (ANA) in AIH and PBC

AIH	PBC
ANAs: - Homogeneous pattern - Speckled pattern	**ANAs:** - Sp100: nuclear dot pattern - gp210: nuclear pore pattern - Anti-Centromere with scleroderma

Primary Liver Biopsy Lesion of AIH: Interface Hepatitis



Cholestatic Variants or Overlap Syndromes

Five postulated explanations for AIH-PBC CVS or OS:

1. Sequential or concurrent occurrence of 2 distinct and independent AILDs
2. Distinct pathologic entity that differs from either of the individual AILDs
3. Clinicopathological midpoint in a continuum (AIH to a cholestatic AILD)
4. One of several heterogeneous expressions of AIH
5. Primary AILD with ≥1 feature of another AILD (IAIHG)

Boberg KM, et al. J Hepatol. 2011; 54: 374-85; Vierling JM. Clin Gastro Hepatol. 2015.

Cholestatic Variants or Overlap Syndromes

Five postulated explanations for AIH-PBC or AIH-PSC CVS or OS:

1. Sequential or concurrent occurrence of 2 distinct and independent AILDs
2. Distinct pathologic entity that differs from either of the individual AILDs
3. Clinicopathological midpoint in a continuum (AIH to a cholestatic AILD)
4. One of several heterogeneous expressions of AIH
5. **Primary AILD with ≥1 feature of another AILD (IAIHG)**

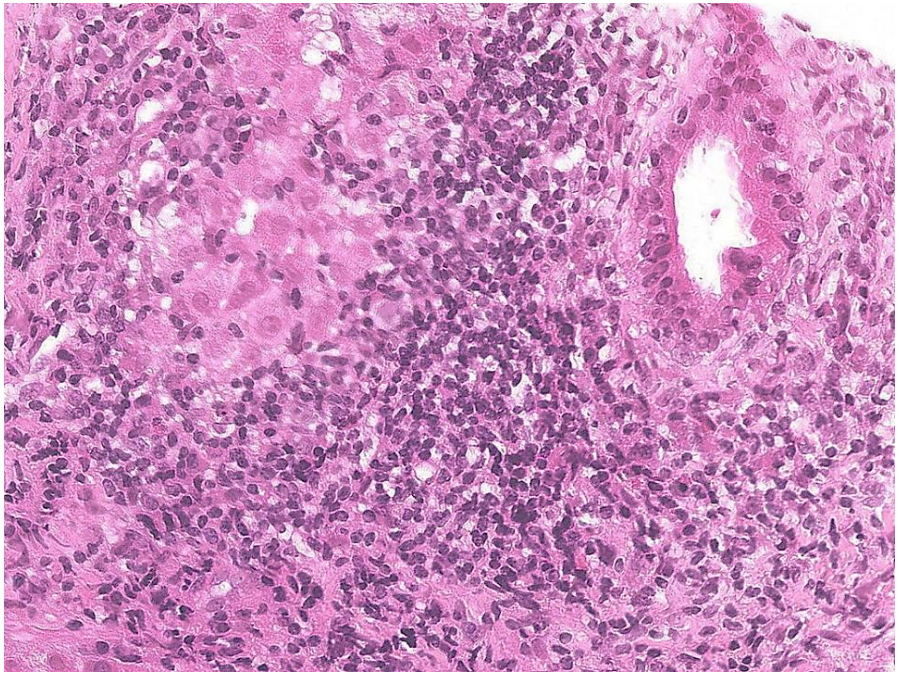
Current Status:

1. **Expert IAIHG Consensus → available data favor the 5th explanation**
2. Coexistence of AIH and either PBC or PSC (1st explanation) currently not provable nor refutable
3. Future discovery of biomarkers for disease-specific mechanisms in AIH, PBC required to settle this issue.

Boberg KM, et al. J Hepatol. 2011; 54: 374-85; Vierling JM. Clin Gastro Hepatol. 2015.

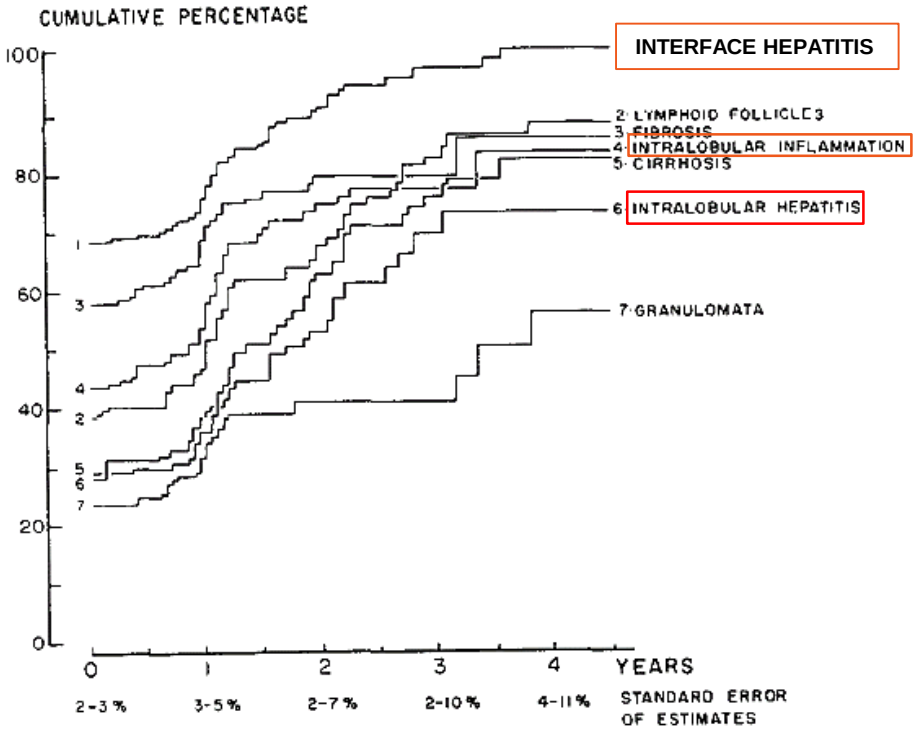
Biopsy of PBC Patient with Possible AIH Ovelap

Percutaneous Liver Biopsy: Lymphoplasmacytic infiltrates, lymphocytic cholangitis and moderate interface hepatitis



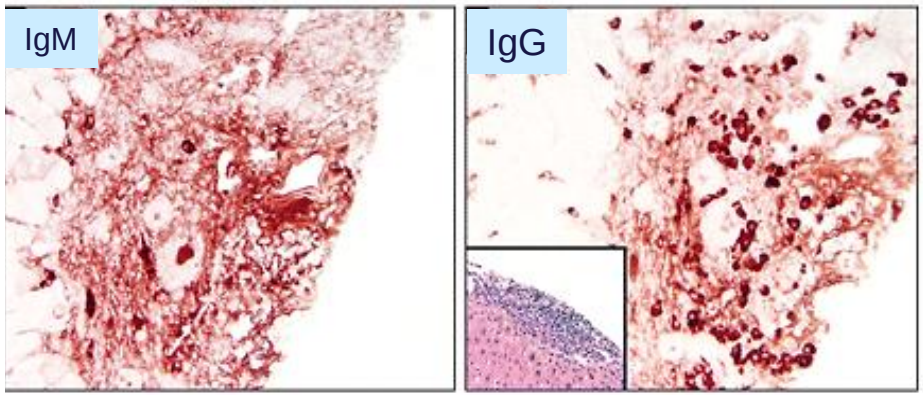
PBC- AIH "Overlap Syndrome"
Inconvenient Truths

Interface Hepatitis Obligatory in PBC:



Christensen, Gastroenterology 1980; 78: 236-246

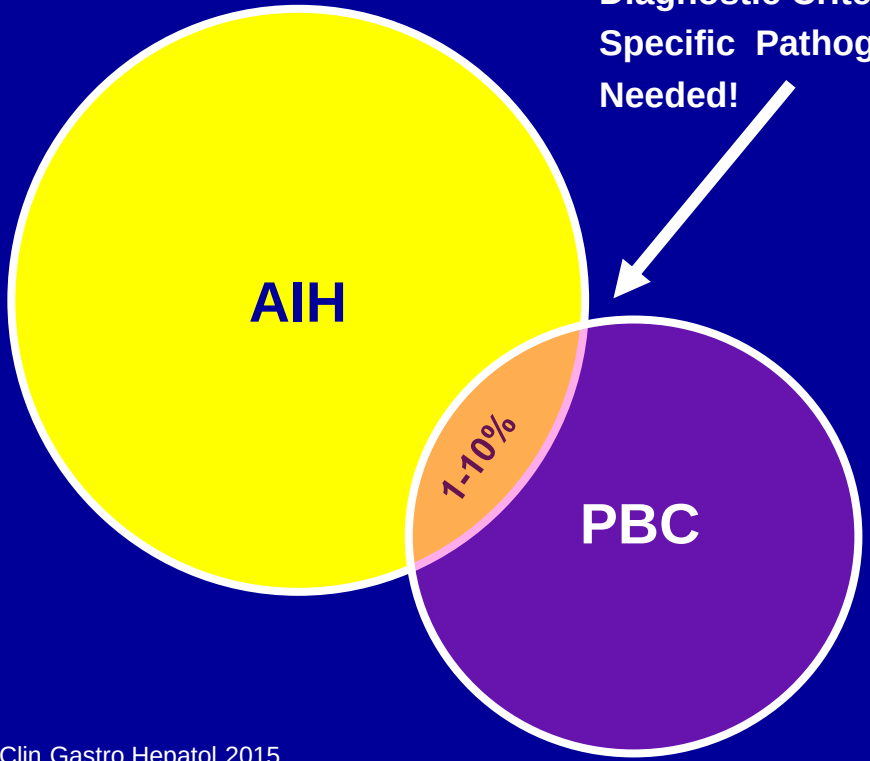
Portal B Cells and Plasma Cells Abundant in PBC:



Lee H, et al. Am J Clin Pathol 2010; 133: 430-7

Cholestatic Variants or "Overlap Syndromes"

PBC-AIH



Mayo Clinic Cohort*
1996-2006

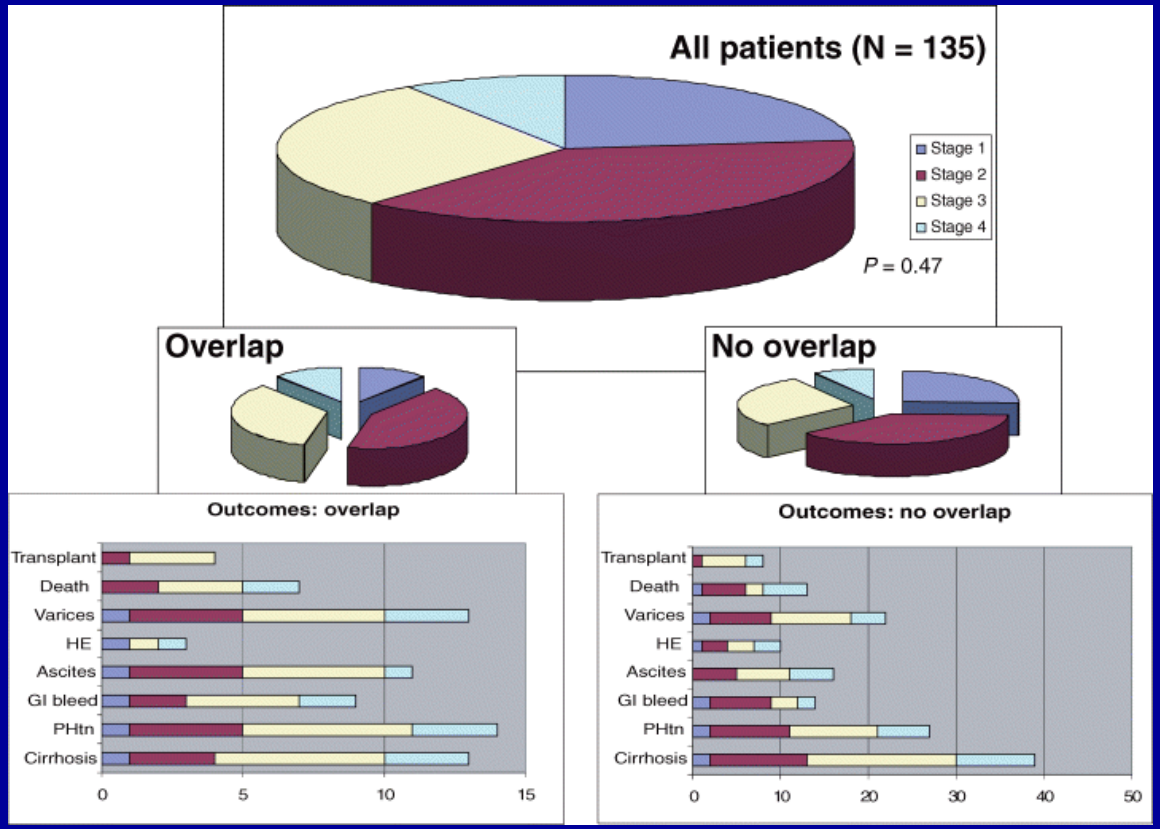
- PBC n= 1476
- n= 8 (0.54%) developed AIH OS

Vierling JM Clin Gastro Hepatol 2015
*Gossard AA, Lindor KD Liver Int 2007; 27: 1086-90

Cholestatic Variants/Overlap Syndromes

PBC-AIH Cholestatic Variant/Overlap Syndrome

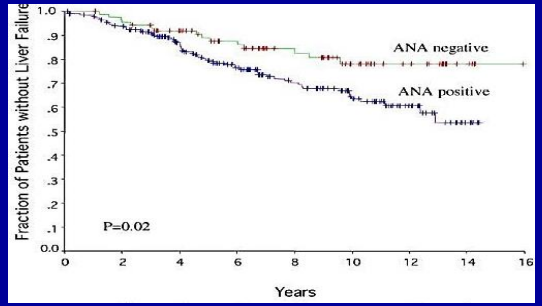
Infrequent but Indicative of Progressive Disease



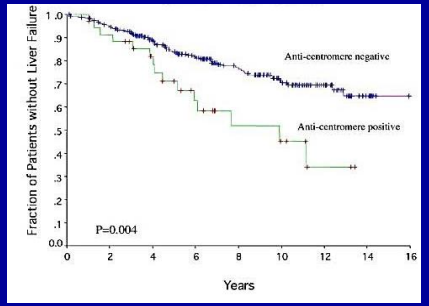
Silveira MG, et al. Am J Gastroenterol. 2007; 102: 1244-50

PBC
ANA a Predictor of Prognosis

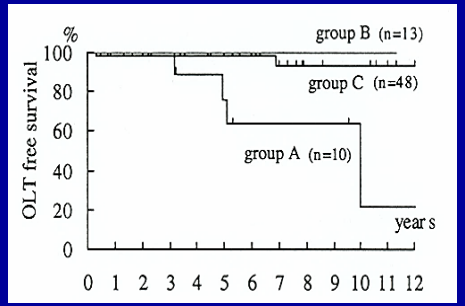
Classic ANA



Anti-Centromere Antibodies



PBC-Specific ANA/gp210

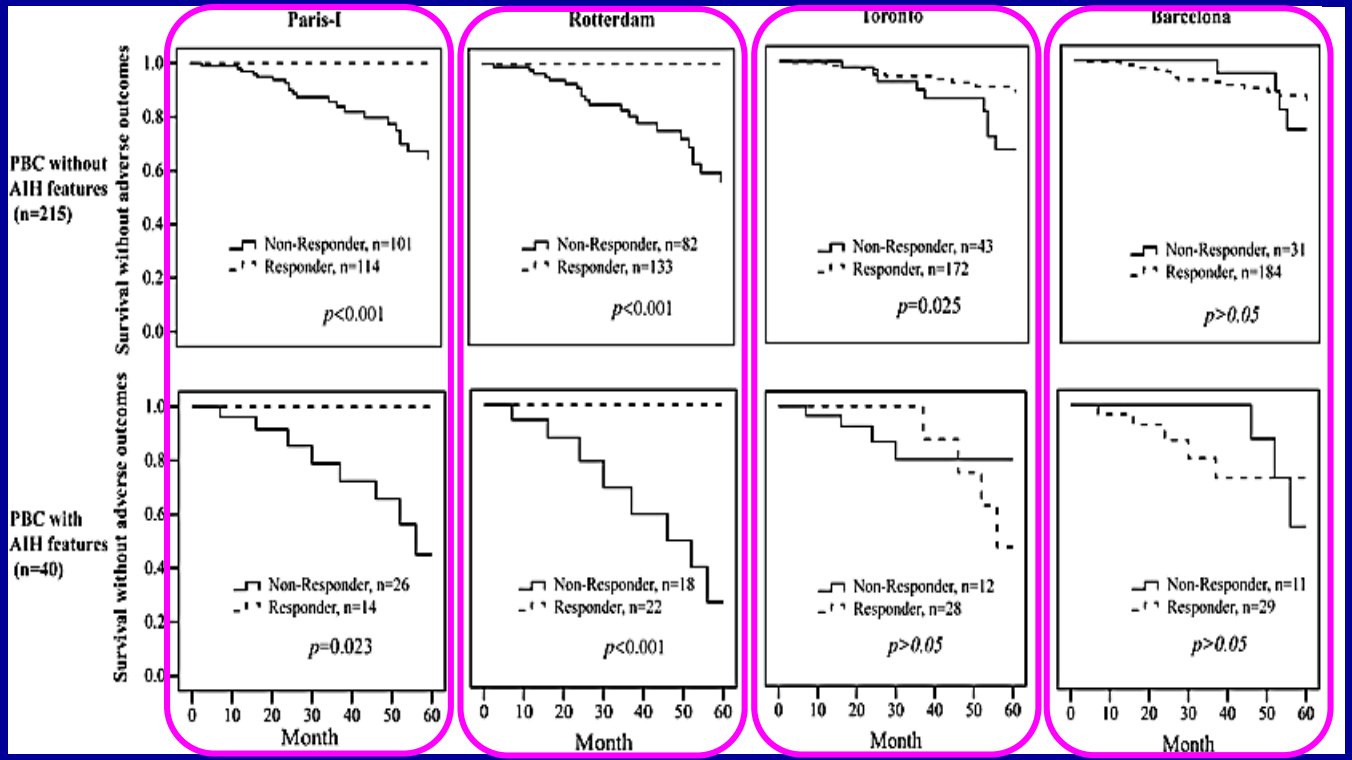


Yang W, Yu JH, Nakajima,et al. Do antinuclear antibodies in primary biliary cirrhosis patients identify increased risk for liver failure? Clin Gastroenterol Hepatol 2004;2(12):1116-22

Nakamura M, Shimizu-Yoshida Y, Takii Y, et al. Antibody titer to gp210-C terminal peptide as a clinical parameter for monitoring primary biliary cirhossis. J Hepatol 2005;42(3):386-92.

PBC-AIH Cholestatic Variant/Overlap Syndrome

Worse Prognosis

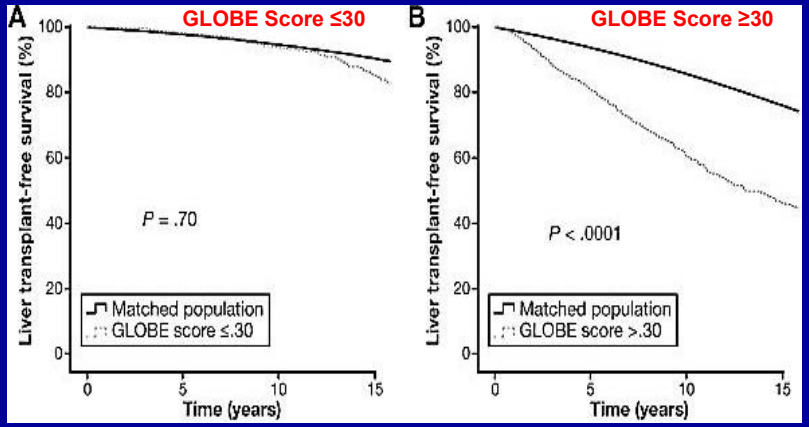


Yang F, et al. Clin Rev Allergy Immunol. 2016; 50: 114-23.

Cholestatic Variants/Overlap Syndromes
Treatment of AIH-PBC

General Principles:

- Optimize therapy for AIH and observe response
- Add UDCA 13-15 mg/kg/d for partial or inadequate responses
- Goals:
  - Remission criteria for AIH (normalization ALT, IgG)
  - GLOBE score ≤30 for PBC after 12 mos of UDCA therapy



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

Cholestatic Variants/Overlap Syndromes
Worse Prognosis for AIH-PBC than PBC Alone

	PBC (N=46)	PBC +AIH (N=122)	p value
Baseline Characteristics			
Age	50 ±10	46 ± 10	NS
Fatigue	55%	54%	NS
Itch	36%	37%	NS
ALP X ULN	3.3 ± 1.7	3.2 ± 1.6	NS
ALT X ULN	2.9 ± 1.5	7.2 ± 4.0	<0.001
IgG X ULN	1.1 ± 0.4	1.4 ± 0.4	<0.001
Cirrhosis	17%	8%	NS
Splenomegaly	39%	42%	NS
Long Term Follow Up			
5 yr Event Free* Survival	81%	56%	0.038
	(* Liver related death, OLT, complication of cirrhosis)		

Fan, Clin Rev All Immunol 2016