Challenging Patients/Cases in Immune Mediated Liver Diseases

-Primary Biliary Cholangitis (PBC)
-Autoimmune Hepatitis (AIH)
-Primary Sclerosing Cholangitis (PSC)

UTSW 6th Annual Update on Liver Disease
October 8, 2022

DISCLOSURES

Marlyn J Mayo, MD

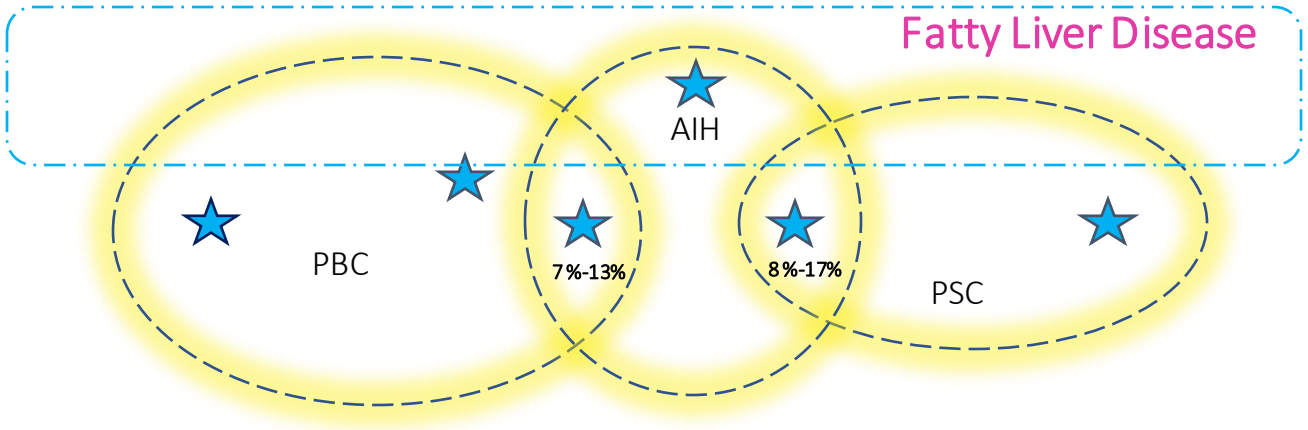
Clinical Trial Agreements: CymaBay, Genfit, GSK, Intercept, Mallinckrodt, Mirum, Target-PBC

Consulting/Advisory Agreements: CymaBay, GSK, Mallinckrodt, Target-PBC

Prevalence and distribution of overlap/variant syndromes of autoimmune liver disease

- **ADULTS**

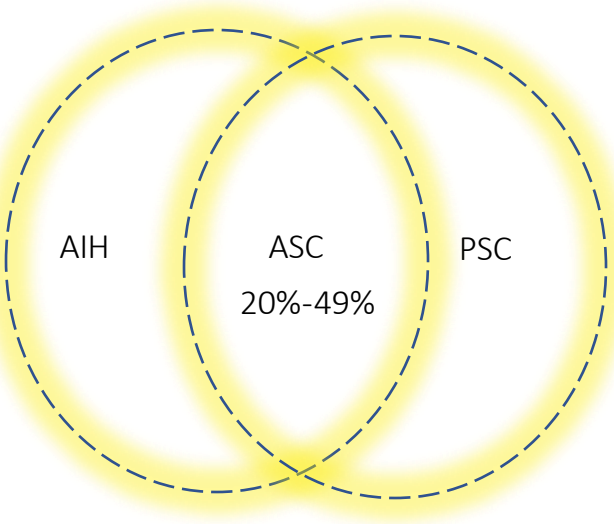
PBC: primary biliary cholangitis
AIH: autoimmune hepatitis
PSC: primary sclerosing cholangitis



❖ PBC+ PSC 0.7% (few cases)

Prevalence and distribution of variant syndromes of autoimmune liver disease

- **PEDIATRICS**



ASC (N=28) vs AIH (N=106)

- Males > Females
- More asymptomatic at presentation
- Progression to cirrhosis similar

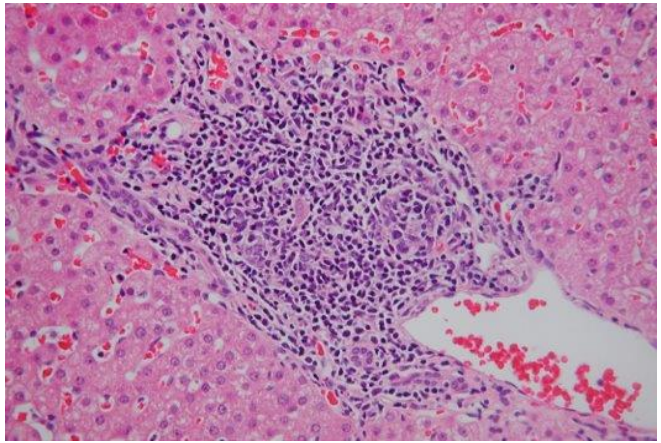
Autoimmune Sclerosing Cholangitis (ASC)

Rodrigues. J Ped Gastro Nutr 2016

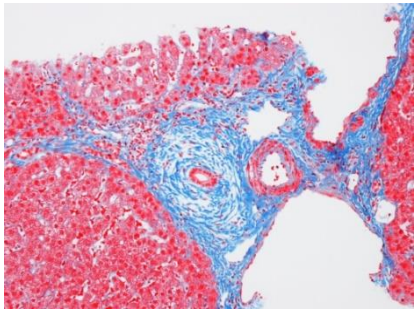
Diagnosis of PBC

2 of 3:

1. Biochemical evidence of cholestasis (elevated alkaline phosphatase)
2. Presence of anti-mitochondrial antibody (AMA) or PBC- specific ANA (anti-gp-210 or anti-sp-100)
3. Histological evidence of nonsuppurative destructive cholangitis and destruction of intralobular bile ducts

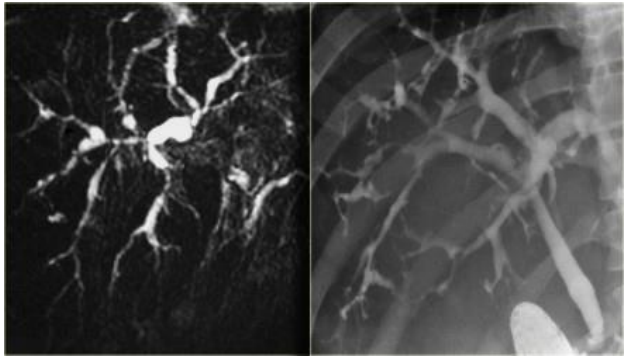


Diagnosis of PSC



1. Cholestatic liver tests (elevated alkaline phosphatase)
2. Cholangiography with stricture(s) +/- dilations
3. Exclusion of secondary causes of sclerosing cholangitis

{Drug-induced (floxuridine), hepatic artery ischemia (post-transplant, post arterial embolization, hypercoagulable, critical illness/COVID19), malignancy, IgG4 disease, infectious: (Clonorchis, Opisthorchis, Ascaris, Fasciola, Cryptosporidium, Microsproidium, Isosporidium) }

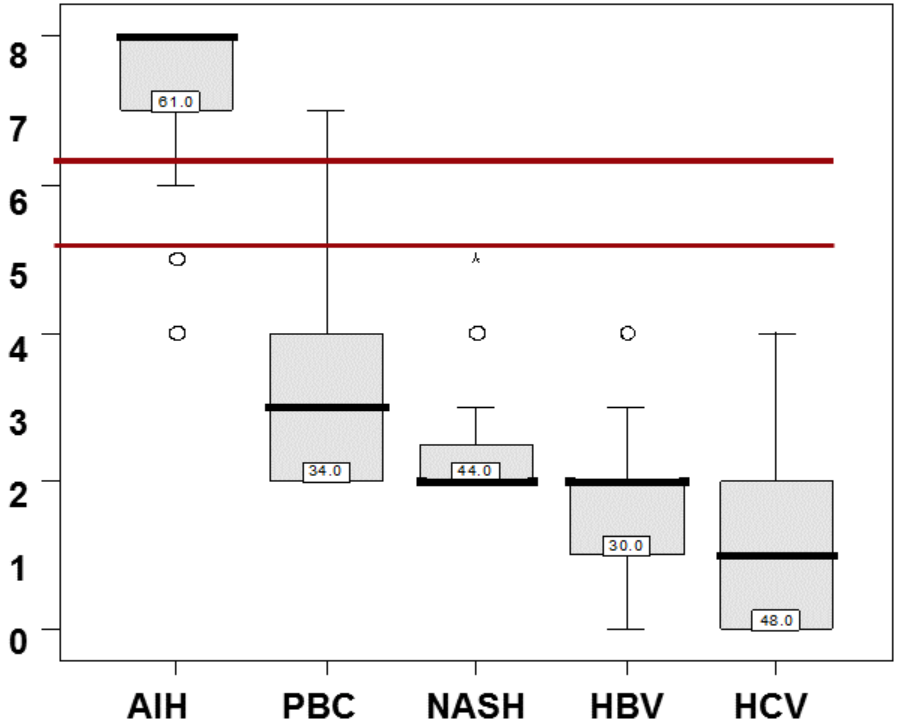


MRCP ERCP

<u>Biopsy not required for the diagnosis</u>

- Histology unreliable at distinguishing from other chronic liver diseases (PBC, DILI)
- Onion-skinning seen in 12%
- Helpful to r/o IgG4 cholangitis ?
  - Minimum >10 IgG4+ cells /HPF
  - 30-50% PSC has >10 IgG4+ cells /HPF

Simplified diagnostic criteria are discriminative



Elevation of serum IgG

IgG> 16 g/l • 1 point

IgG > 18.5 g/l • 2 points

Autoantibodies

ANA, SMA, or LKM> 1:40 • 1 point

1:80 or SLA/LP positive • 2 points

Histology

Compatible with AIH • 1 point

Typical of AIH • 2 points

Absence of viral hepatitis • 2 points

Hennes EM. Hepatology 2008

Diagnostic Challenge: autoimmune liver diseases share features

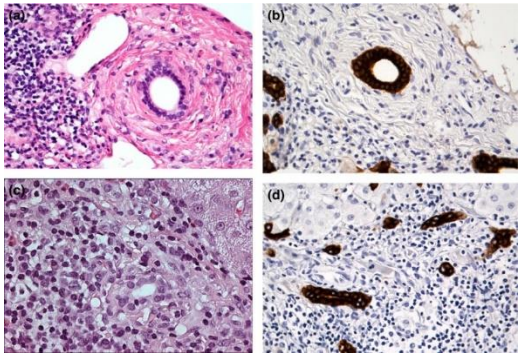
	AIH	PBC
ANA	70-80%	30%-50%
ASMA	70%-80%	May be present
AMA	5%-10%	95%
IG	IgG	IgM>IgG
Cholangitis	10-80%	85%
Interface Hepatitis	Characteristic	Variably Present

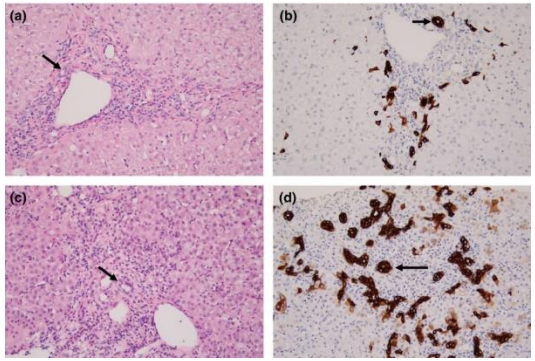
- Fulminant AIH often negative for all of the above, but rare in overlap patients
- Diagnosis of autoimmune overlap diseases is clinicopathological

Trivedi. Alim Pharm Ther 2012

Ductular reaction and bile duct injury in AIH (without overlap) persists over time

- Bile duct injury 29/35 (83%)
- Ductular reaction 25/35 (71%) 30/32 (94%) using IHC
- Correlated with interface hepatitis and centrilobular necrosis
- 11/14 present on 2 year follow up biopsy





Verdonk. Liver Int 2016

Paris criteria for overlap PBC + AIH

AIH

1. Moderate to severe interface hepatitis
2. ALT ≥ 5X ULN, IGG ≥ 2XULN, or Smooth Muscle Ab

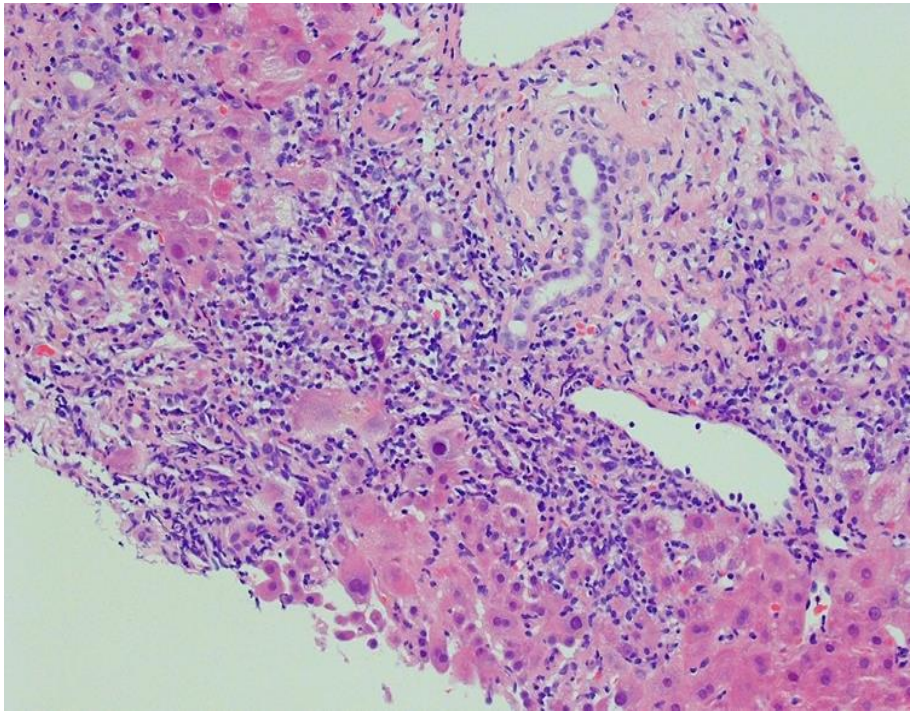
PBC

2 out of 3 of the following:

1. AMA positive
2. Compatible histology
3. ALP > 2X ULN or GGT > 5XULN

Chazouilleres O .Hepatology 1998

BIOPSY is essential for diagnosis of AIH overlap (but not sufficient)

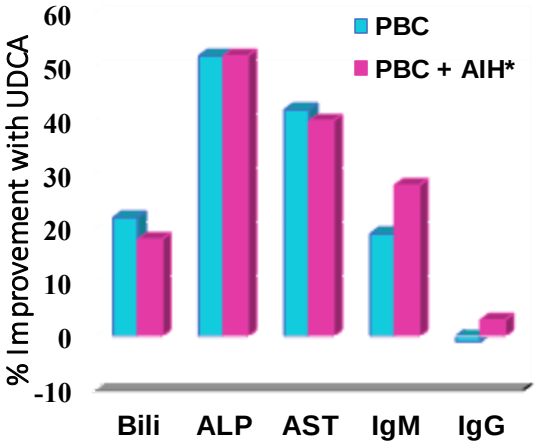


Interface Hepatitis

If biopsy absolutely not possible may use ALT + one other criteria (IgG or SMA)

“PBC with features of AIH”

- May meet Paris criteria but they resolve with UDCA
- Treat PBC 1st with ursodiol (15 mg/kg) unless evidence for AIH is overwhelming (e.g transaminases >1000) because ursodiol is less toxic than steroids
- PBC + features of AIH will respond just as well to ursodiol as pts with classical PBC



*transaminases > 5X ULN
IgG > 2X ULN
severe lobular inflammation

Joshi et al. Hepatology 2002 Czaja et al, J. Hepatol 2008 Chazouilleres et al, J Hepatology 2006

61 year-old “Audrey” seen via telehealth with fatigue, RUQ discomfort, abnormal liver tests by PCP:

TEST	RESULT		NORMAL RANGE
Bilirubin	**1.5**	**H**	0.2-1.3 mg/dL
Alk Phos	**632**	**H**	35-104 U/L
AST	**278**	**H**	10-35 U/L
ALT	**225**	**H**	10-40 U/L
Creatinine	0.8		0.51-0.95 mg/dL
Albumin	**3.3**	**L**	3.5-5.2 g/dL
INR	1.2		0.9-1.3
WBC	3.7	L	4.00-11.00 X 10(9)/L
HCT	33	L	34.0-44.0%
Platelets	**99**		150-450 X 10 (9)/L

TEST	RESULT		NORMAL RANGE
AMA	**1:640**	**H**	not detected
ANA	**1:2560**	**H**	not detected
smAb	negative		not detected
IgG	**3850**	**H**	694-1618 mg/dL
IgM	**532**	**H**	48-271 mg/dL
IgA	393		81-463 mg/dL

Ultrasound: heterogeneous echotexture with **subtly nodular contour of liver, splenomegaly**, normal gallbladder/bile ducts

What would you do next?

- Start ursodiol, 15 mg/kg
- Start prednisone 40 mg daily
- Start azathrioprine 50 mg daily
- Start budesonide, 9 m g daily
- Bring in for biopsy of liver

6 month follow up

TEST	BASELINE	FOLLOW UP	NORMAL RANGE
Bilirubin	**1.5 H**	**1.2**	0.2-1.3 mg/dL
Alk Phos	**632 H**	**220 H**	35-104 U/L
AST	**278 H**	**182 H**	10-35 U/L
ALT	**225 H**	**240 H**	10-40 U/L
Creatinine	0.8	0.8	0.51-0.95 mg/dL
Albumin	3.2 L	3.3 L	3.5-5.2 g/dL
INR	1.2	1.1	0.9-1.3
WBC	3.2 L	3.1 L	4.00-11.00 X 10(9)/L
HCT	33 L	32 L	34.0-44.0%
Platelets	99 L	114 L	150-450 X 10 (9)/L
IgG	**3850 H**	**3300 H**	694-1618 mg/dL
IgM	**532 H**	**350 H**	48-271 mg/dL
IgA	393		81-463 mg/dL

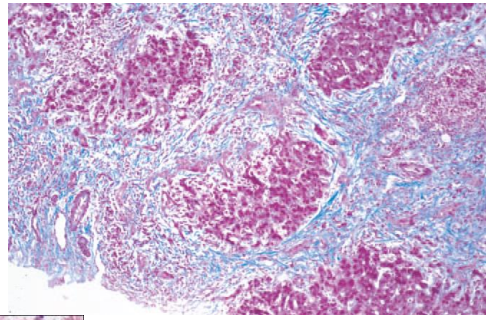
TEST	Baseline	NORMAL RANGE
AMA	1:640 H	not detected
ANA	1:2560 H	not detected
smAb	negative	not detected

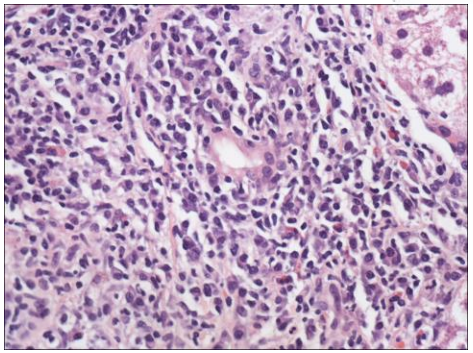
What would you do next?

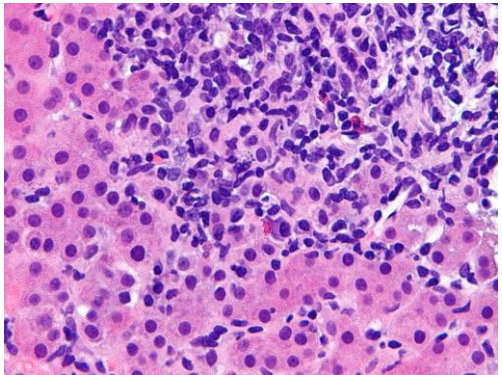
- Start prednisone 40 mg daily
- Start azathrioprine 50 mg daily
- Start budesonide, 9 mg daily
- Add obeticholic acid, 5 mg weekly
- Bring in for biopsy of liver

Liver Biopsy Results

- Cirrhotic nodules
- Ductopenia (6/20 portal tracts with bile ducts)
- 5/6 Remaining ducts damaged by surrounding chronic inflammation
- Moderate interface hepatitis and foci of lobular hepatitis







What would you do next?

- Start prednisone 40 mg daily → Effective in AIH, and PBC-AIH overlap
- Start azathrioprine 50 mg daily → Not effective as monotherapy to induce remission in AIH
- Start budesonide, 9 mg daily → Effective in PBC-AIH overlap, but loss of first pass benefit in cirrhosis.
- Add obeticholic acid, 5 mg weekly → Weekly dosage proposed dosage for Childs B, C ALT > 5X ULN should prompt eval for AIH

PBC-AIH overlap has a worse prognosis than PBC

	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
SMA or SLA	0	3%	NS
Cirrhosis	17%	8%	NS
Splenomegaly	39%	42%	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
Long Term Follow Up			
5 year Event-free* Survival	81%	56%	0.038

* Liver related death, liver transplant, complication of cirrhosis

Fan.Clin Rev All Immunol 2016

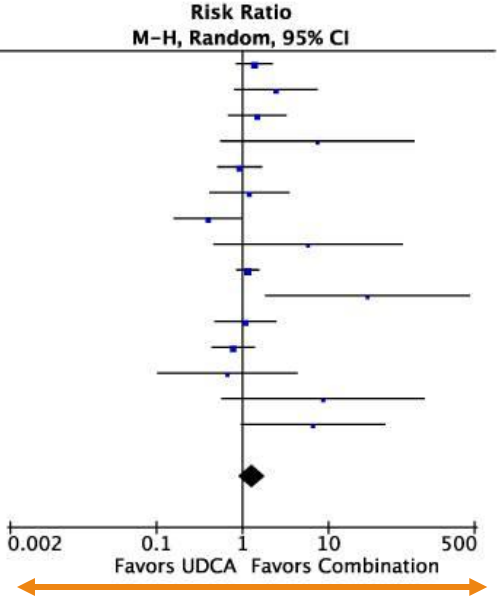
Treatment of PBC-AIH Overlap : UDCA + Steroid + AZA

Biochemical Improvement

Study or Subgroup	Combination Events	Combination Total	UDCA Events	UDCA Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Gunsar et al.	4	4	8	12	12.2%	1.38 [0.84, 2.25]	2002
Chazouilleres et al.	4	6	3	11	6.4%	2.44 [0.80, 7.48]	2006
Saito et al.	6	6	2	3	9.1%	1.49 [0.68, 3.26]	2006
Wu et al.	6	6	0	3	1.8%	7.43 [0.55, 100.11]	2006
Poupon et al.	8	10	2	2	11.0%	0.93 [0.51, 1.69]	2006
Heurgue et al.	3	5	3	6	6.7%	1.20 [0.41, 3.51]	2007
Ozaslan et al.	3	9	3	3	7.8%	0.40 [0.16, 1.01]	2010
Yokokawa et al.	13	13	0	2	1.8%	5.79 [0.46, 72.80]	2010
Ozaslan et al.	49	67	19	30	14.1%	1.15 [0.85, 1.57]	2014
Liu C et al.	12	14	0	16	1.6%	28.33 [1.83, 438.84]	2014
Efe et al.	15	18	1	1	8.7%	1.09 [0.48, 2.49]	2014
Levy et al.	10	21	11	18	11.2%	0.78 [0.44, 1.39]	2014
Park et al,.	1	3	2	4	3.1%	0.67 [0.10, 4.35]	2015
Yang et al.	13	27	0	8	1.6%	8.68 [0.57, 131.87]	2016
Fan et al.	6	10	1	11	2.9%	6.60 [0.95, 45.75]	2018
Total (95% CI)		**219**		**130**	**100.0%**	**1.30 [0.90, 1.87]**	
Total events	153		55				

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 32.69$, df = 14 (P = 0.003); $I^2 = 57\%$

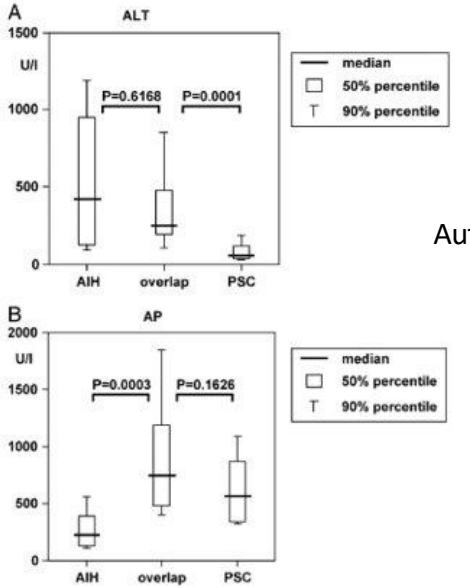
Test for overall effect: Z = 1.40 (P = 0.16)

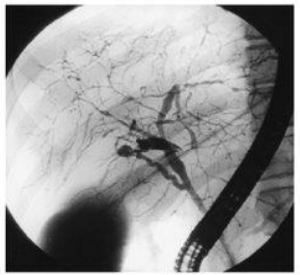


Freedman et al J Clin Med May 2020

AIH-PSC Overlap (Autoimmune sclerosing cholangitis in children)

- In adults, use diagnostic criteria for AIH and PSC
- In children, diagnosed by ↑ IgG, + ANA /SMA/LKM interface hepatitis, positive cholangiography
- Usually sequential with AIH diagnosed first
- 26% AIH+PSC in adults = small duct PSC
- ALT is slightly lower in PSC-AIH than in AIH
- ALP is similar in PSC-AIH vs PSC
- Survival better than classical PSC, but poorer than AIH



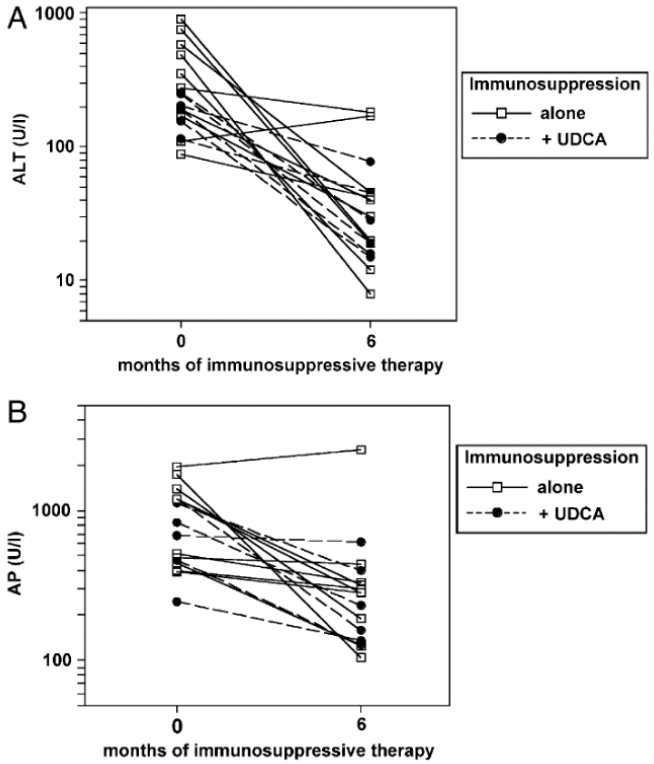


Autoimmune Sclerosing Cholangitis

Luth S. J Clin Gastroenterol. 2009 Mieli-Vergani G. Best Pract Res Clin Gastro 2001

Treatment of AIH-PSC: Steroids +/- AZA

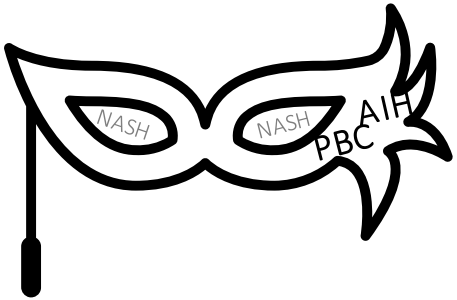
- Ursodiol is controversial. Appears to have little impact.

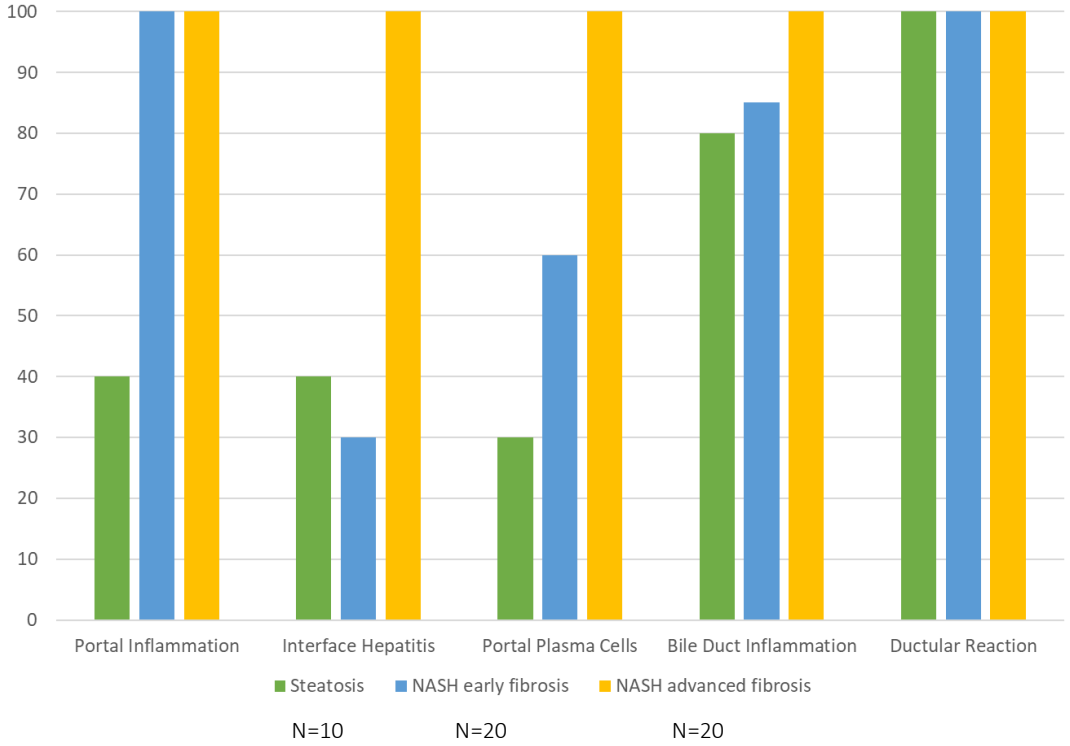


Luth S.J Clin Gastroenterol. 2009

AIH/PBC/PSC+ Concurrent Fatty Liver Disease

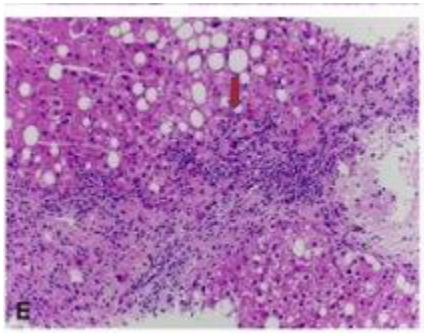
- Statistically will happen (25 % US has NAFLD/MAFLD, 5% NASH)
- NASH may have AIH /PBC/PSC- like histological features



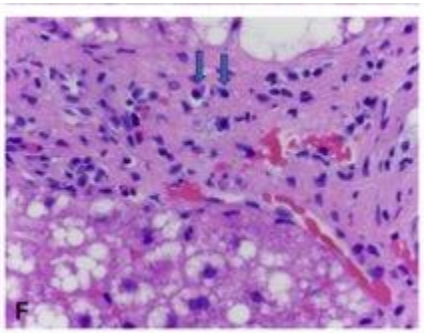


Dhingra et al Pathology 2022

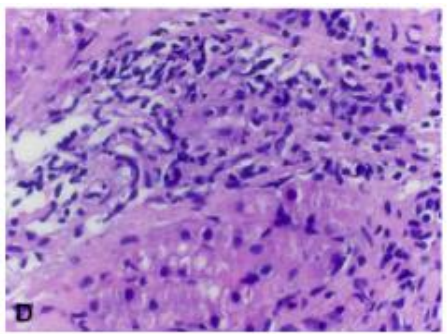
Fatty liver may have AIH-PBC-PSC like histological features



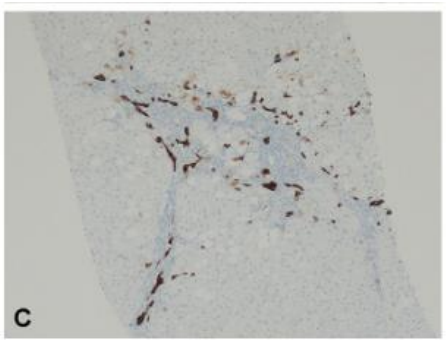
Interface Hepatitis



Plasma Cells



Bile Duct Injury

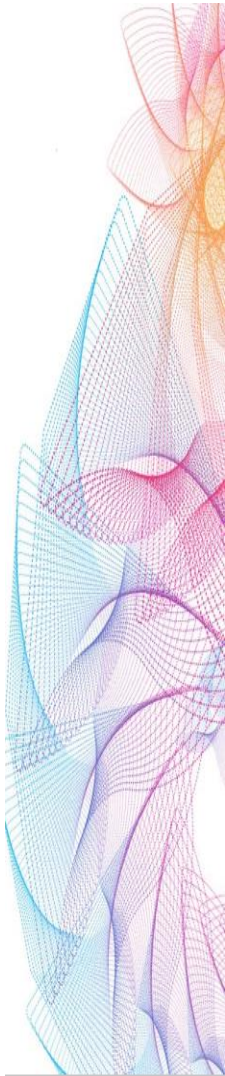


Bile Ductular Proliferation

Dhingra et al Pathology 2022

Autoantibodies in Fatty Liver

- Overall: 35.7% (30/84),
- ANA: 21.4% (18/84)
- SMA: 4.7% (4/84)
- Both ANA and SMA: 7.1% (6/84)
- AMA: 2.4% (2/84)



Loria et al Dig Dis Sci 2003

Key points-PBC-AIH

- Autoimmune Hepatitis Overlap Syndromes require a clinicopathological diagnosis
  - Liver biopsy is necessary but not sufficient

- PBC-AIH Overlap is best defined by the Paris Criteria

PBC	***AIH***
2 out of 3 of the following: 1. AMA positive 2. Compatible histology 3. ALP > 2X ULN OR GGT > 5XULN	1. Moderate to Severe Interface Hepatitis 2. *Either:* ALT ≥ 5X ULN OR IgG ≥ 2XULN OR SMA

- PBC-AIH Overlap is best treated with UDCA 15 mg/kg and steroids/AZA

  To achieve normal liver enzymes and IgG

Key points- AIH-PSC

- AIH-PSC Overlap in adults is best defined in adults by standard individual criteria

- Treatment of AIH-PSC is dictated by the AIH : steroids +AZA in adults

AIH-simplified diagnostic score ≥ 5	PSC
IgG > 16g/L =1 IgG > 18.5 g/L =2	↑alkaline phosphatase
ANA, SMA, LKM>1:40=1 SLA/LP>1:80=2	positive cholangiogram
Compatible Histology=1 Typical Histology=2	lack of 2^{ary} sclerosing cholangitis
Absence of Viral hepatitis=2	

Key points PBC/AIH/PSC + NAFLD/MAFLD

- Expect to occasionally see fatty liver disease in a patient with PBC-AIH-PSC
- NASH alone may have serological and histological features of AIH or PBC
  - Treatment is weight loss, not steroids