# Hepatobiliary Overlap syndrome

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- In hepatology, the term overlap syndrome describes variant forms of the major hepatobiliary autoimmune diseases, autoimmune hepatitis (AIH) on one hand with primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC) on other.

- Patients with overlap syndromes present with both hepatitic and cholestatic biochemical and histological features of AIH, PBC, and/or PSC

## Epidemiology……

- AIH-PBC overlap syndromes were first reported in the 1970s[1]
- AIH-PBC overlap syndromes have been reported in almost 10% of adults[2] and 3%-7% of patients[3] with autoimmune liver disease
- AIH-PSC overlap syndromes were found in 6 to 8% of children, adolescents, and young adults with AIH or PSC[2]

1. Geubel AP, Baggenstoss AH, Summerskill WH. Responses to treatment can differentiate chronic active liver disease with cholangitic features from the primary biliary cirrhosis syndrome. Gastroenterology 1976;71:444-449

2. Beuers U. Hepatic overlap syndromes. J Hepatol 2005;42(suppl 1):S93-S99 Beuers U. Hepatic overlap syndromes. J Hepatol 2005;42(suppl 1):S93-S99

3. Czaja AJ. The overlap syndromes of autoimmune hepatitis. Dig Dis Sci. 2013;58(2):326–43. [PubMed] [Google Scholar]

## Epidemiology……

- Single case of AIH and autoimmune cholangitis (antimitochondrial antibody-negative PBC) overlap have also been reported

- A minority of patients may also show transition from stable PBC to AIH, AIH to PBC, or AIH to PSC, as documented by single case reports and small case series[4,5]


4. Colombato LA, Alvarez F, Cote J, Huet PM. Autoimmune cholangiopathy: the result of consecutive primary biliary cirrhosis and autoimmune hepatitis?. Gastroenterology 1994;107:1839-1843

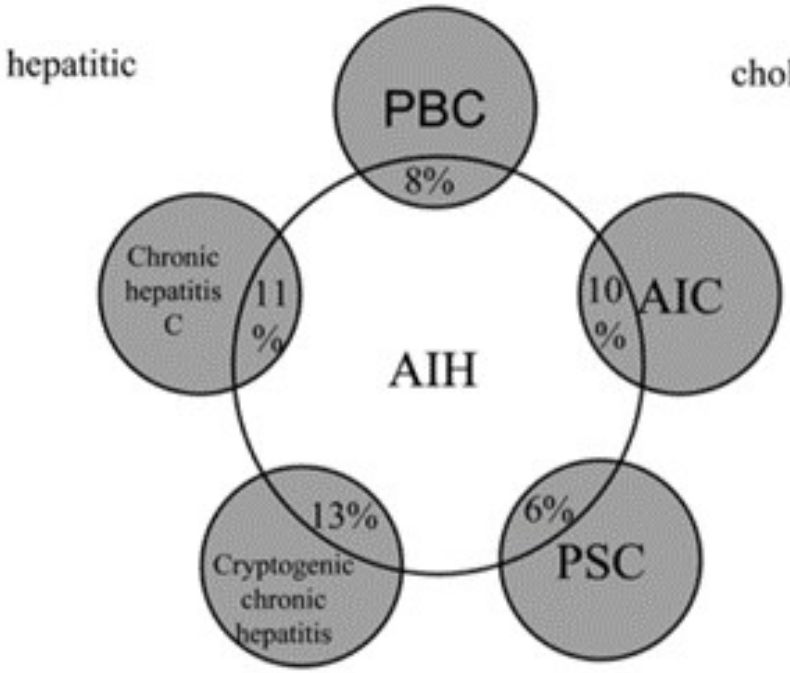
5. Gregorio GV, Portmann B, Karani J, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology 2001;33:544-553

## Pathophysiology……

- The overlap syndromes may simply be variants or atypical forms of classic diseases.[3,6]
- Could be transition stages in the evolution of classic diseases.
- Lastly, the overlap syndromes could be separate pathological entities with their own distinctive pathogenic mechanisms and clinical outcomes. [3,6]

3. Czaja AJ. The overlap syndromes of autoimmune hepatitis. Dig Dis Sci. 2013;58(2):326–43. [PubMed] [Google Scholar]
6. Czaja AJ. Diagnosis and management of the overlap syndromes of autoimmune hepatitis. Can J Gastroenterol 2013;27:417-423.

# Pathophysiology……




**Variants of Autoimmune Liver Diseases**

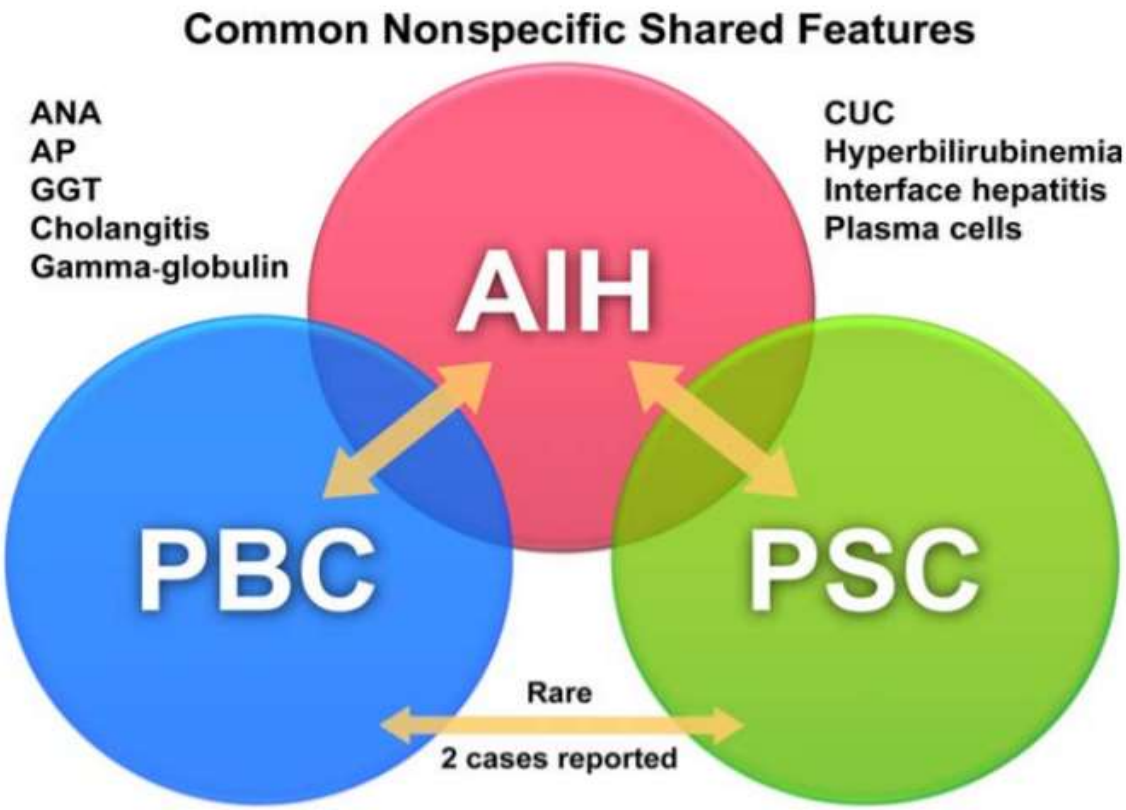
**Overlap syndromes**
- AIH - PBC
- AIH - PSC
- AIH - AIC

**Outlier syndrome**
- AIC

**Change of diagnosis of autoimmune liver disease**
- PBC ↔ AIH
- AIH ↔ PSC

Abbreviations: AIC, autoimmune cholangitis; AIA, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

Pathophysiology……



# Characteristics of the patients with autoimmune liver diseases[7]

| Characteristic | AIH | PBC |
|---|---|---|
| *Age at onset* | All ages (bimodal peak), 10-20 years and 40-50 years | Mean age 40 years | All ages (usually ≈ 40 years) |
| *Sex* | Women > men (4:1) | Women > men (9:1) | Men 7:3 women |
| *Serology* | | | |
| ANA | Titers > 1:40 (70-80%) | Present in ≈ 30-40% of the cases | Not specific for PSC. Present in 70-80% |
| ASMA | Titers > 1:40 (70-80%) | Can be present | Greater than 83% |
| Anti-LKM-1 | 3-4% (classifies AIH as type 2) | | |
| Anti-SLA/LP | 10-30% | Can be present | Can be present |
| pANCA | Greater than 92% | | 26-94% |
| AMA | In low titers in ≈ 5-10% | 95% of the cases (highly specific) | If it is present it is coincidental |
| Immunoglobulins | Elevated IgG (> 1.2 X over the ULN) | elevated IgM in the majority of cases | Elevated IgG in 61%<br>Elevated IgM in 45% |

7. C. Rust, U. Beuers Overlap syndromes among autoimmune liver diseases. World J Gastroenterol, 14 (2008), pp. 3368-3373

| Characteristic | AIH | PBC | PSC | |
|---|---|---|---|---|
| *Radiology* | | | | |
| Cholangiography | Usually normal. ≈ 10% of the cases can have changes in the intrahepatic ducts | Normal | | Multifoca pattern) tree. It c of the sm |
| *Histology* | | | | |
| Interface hepatitis | Characteristic finding | Present in a variable manner | | Present i |
| Portal inflammation | Lymphoplasmacytic infiltrate | Lymphocytic infiltrate | | Lymphoc |
| Biliary changes | ≈ 10% of the cases | Inflammatory ductal lesion | | Periducta skin'' les |
| Granulomas | No | Characteristic lesion, present in only some cases | | Atypical |

7. C. Rust, U. Beuers Overlap syndromes among autoimmune liver diseases. World J Gastroenterol, 14 (2008), pp. 3368-3373

# Diagnosis……

| Overlap Syndrome | Laboratory Features | Histological Findings |
|---|---|---|
| AIH-PBC (Paris criteria modified by EASL)[4-6] | AIH features (1 of 2):<br>ALT ≥ 5-fold ULN<br>IgG ≥ 2-fold ULN or SMAs | Interface hepatitis (required) |
| | PBC features (2 of 3, including histology):<br>AP ≥ 2-fold ULN or GGT ≥ 5-fold ULN<br>AMAs | Florid duct lesions |
| AIH-PBC (outside Paris criteria)[1,2,8] | Predominant AST/ALT abnormalities<br>AP < 2-fold ULN and GGT < 5-fold ULN<br>Hypergammaglobulinemia (IgG > ULN)<br>ANAs or SMAs<br>AMAs | Interface hepatitis and bile duct injury or loss (lymphocytic, pleomorphic, or destructive cholangitis) |
| AIH-PSC[4,6,10] | AIH features<br>AMAs absent<br>Focal strictures and dilations by ERC or MRC | Interface hepatitis and portal edema, fibrosis, or ductopenia (obliterative fibrous cholangitis possible but rare) |
| AIH--indeterminate cholestasis (possibly AMA-negative PBC or AIH--small-duct PSC)[1,2,8] | AIH features<br>AP ≥ 2-fold ULN or GGT > ULN<br>AMAs absent<br>Normal ERC or MRC | Interface hepatitis and bile duct injury or loss |


1→ 3. Czaja AJ. The overlap syndromes of autoimmune hepatitis. Dig Dis Sci. 2013;58(2):326–43. [PubMed] [Google Scholar]
2→ 6. Czaja AJ. Diagnosis and management of the overlap syndromes of autoimmune hepatitis. Can J Gastroenterol 2013;27:417-423

4→ 8. Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrumpf E. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 2011;54:374-385
6→ 2. Beuers U. Hepatic overlap syndromes. J Hepatol 2005;42(suppl 1):S93-S99 Beuers U. Hepatic overlap syndromes. J Hepatol 2005;42(suppl 1):S93-S99

8→ 9. Czaja AJ. Frequency and nature of the variant syndromes of autoimmune liver disease. Hepatology 1998;28:360-365

10→ 10. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology2010;51:660-678

# Treatment……

| Overlap Syndrome | Predominant Component | Treatment Regimen | Outcomes |
|---|---|---|---|
| AIH-PBC | PBC and AIH equivalent by Paris criteria | Corticosteroids and UDCA* | Improves serum AP, GGT, and ALT[5]<br>Prevents progressive hepatic fibrosis[5]<br>Better than UDCA or corticosteroids alone[5] |
| AIH-PBC | PBC | UDCA | Same laboratory improvements found for classic PBC[9] |
| AIH-PBC | AIH | Corticosteroids alone or with azathioprine | Laboratory and histological improvements as frequently as for classic AIH (improvement, 81% versus 86%; treatment failure, 14% versus 9%)[1,2,8] |
| AIH-PSC | AIH or PBC | Corticosteroids and UDCA† | Variable responses (20%-100%) possibly related to level of cholestasis[1,2] |
| AIH--indeterminate cholestasis (including AMA-negative PBC and small-duct PSC) | AIH or cholestatic phenotype | Empirical and unendorsed | Uncertain response[1,2] |
| | | Directed by predominant component: corticosteroids, UDCA, or corticosteroids and UDCA | Anecdotal experience[1,2] |


1→ 3. Czaja AJ. The overlap syndromes of autoimmune hepatitis. Dig Dis Sci. 2013;58(2):326–43. [PubMed] [Google Scholar]
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Nutshell……

- Rare entities of overlapping pathognomic clinical features
- High index of suspicion is warranted
- Treatments can be individualized, and they should be directed at the predominant disease component

# THANK YOU