# Formes Frontières des Hépatites Auto-Immunes

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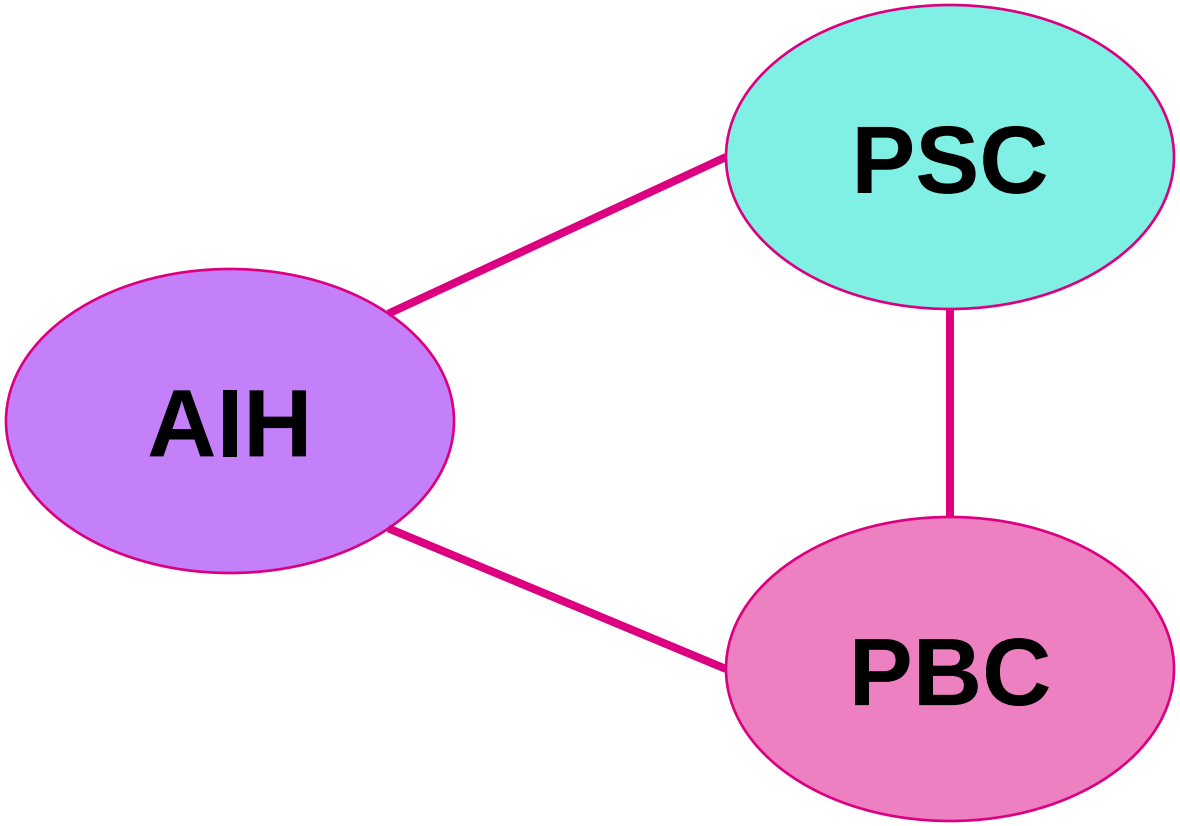
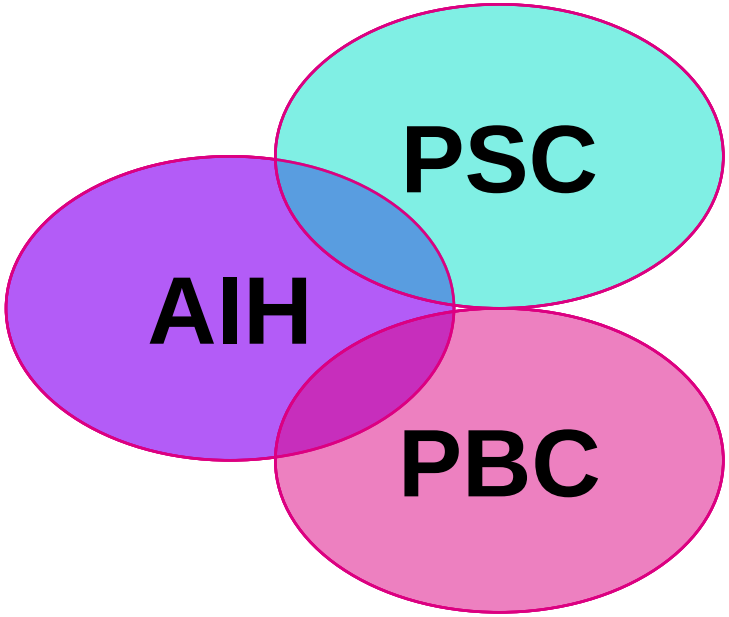
# Main Autoimmune Liver Diseases



# Autoimmune Overlap Syndromes




**General definition:**
**conditions with features of both AIH and PBC or PSC**

*Digestive Diseases and Sciences, Vol. 40, No. 5 (May 1995), pp. 1069–1073*

**CASE REPORT**

# Primary Biliary Cirrhosis–Autoimmune Hepatitis Overlap Syndrome

## Corticoresistance and Effective Treatment by Cyclosporine A

JEAN-CHARLES DUCLOS-VALLÉE, MD, ANTOINE HADENGUE, MD,
NATHALIE GANNE-CARRIÉ, MD, EDITH ROBIN, MD,
CLAUDE DEGOTT, MD, and SERGE ERLINGER, MD



Gastroenterol Clin Biol 2007;31:17-25

ORIGINAL ARTICLE

# Overlap syndrome of primary biliary cirrhosis and autoimmune hepatitis: a retrospective study of 115 cases of autoimmune liver disease

*Alexandra HEURGUÉ (1), Fabien VITRY (2), Marie-Danièle DIEBOLD (3), Nahla YAZIJI (3), Brigitte BERNARD-CHABERT (1), Jean-Loup PENNAFORTE (4), Rémi PICOT (5), Hervé LOUVET (6), Luc FRÉMOND (7), Patrick GEOFFROY (8), Jean-Luc SCHMIT (9), Guillaume CADIOT (1), Gérard THIÉFIN (1)*

# Autoimmune Overlap Syndromes: Issues

- **Practical definition**

**« overlap syndrome is one of the most abused descriptive term currently used in hepatology »**

***(Heathcote, Am J Gastroenterol 2002)***

- **Pathogenesis (is overlap a distinct entity?)**

- **Therapeutic consequences**

# Autoimmune Diseases: Overlapping Features

- **Challenge: no autoimmune liver disease has an absolute diagnostic test, especially AIH.**

| | AIH | PBC | PSC |
|---|---|---|---|
| ANA | 70-80% | 30-50% | 30-70% |
| ASMA | 70-80% | May be present | 0-80% |
| AMA | 5-10% | 95% | Coincidental |
| pANCA | Up to 90% | 0-5% | 25-95% |
| Immunoglob ↑ | IgG | IgM | IgG (2/3), IgM (45%) |
| Biliary changes | 10%* | Inflammatory duct lesion | Periductal fibrosis |
| Interface hepatitis | Characteristic | Variably present * (25-30%) | Variably present * (25-30%) |

*** bystander, collateral injury ?**

***(Trivedi et Hirschfield, Aliment Pharmacol Ther 2012)***

# Autoimmune Diseases: Overlapping Features

- **Numerous variant forms of PBC, PSC and AIH:**
  - **PBC AMA-, ASMA+ ("autoimmune cholangitis")**
  - **AIH with AMA** ***(Muratori et al, Eur J Gastroenterol Hepatol 2017)***
  - **AIH with biliary injury: 10-20% (rarely destructive or fibro-obliterative cholangitis, biological cholestasis or AMA uncommon)**
  - **PSC with ALT > 5 ULN: early phase of any acute cholestatic process (+/- infection)?**

- **These variant forms generally behave like typical forms (including response to standard therapy)**

**Need to identify variants that require treatment tailoring (overlap syndromes)**

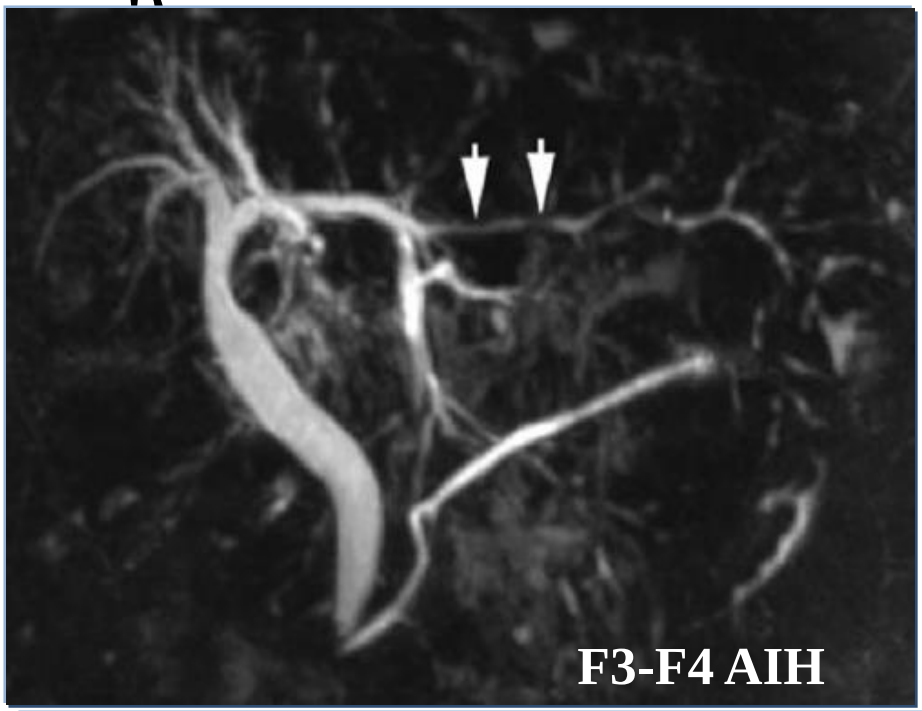
# Autoimmune Diseases: Overlapping Features

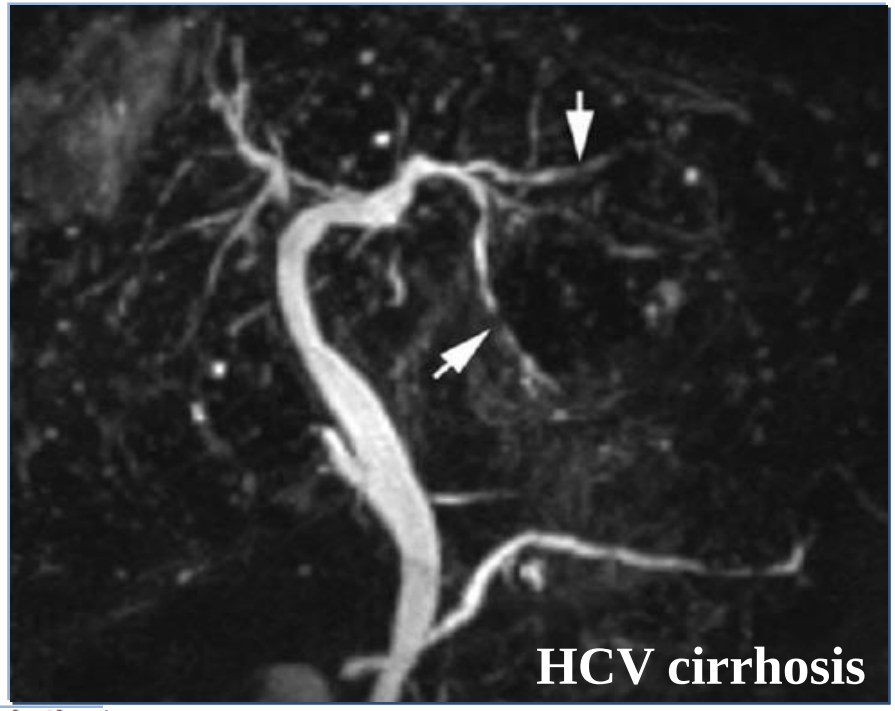
- **Intrinsic scope for individuals to present with overlapping features of more than one these autoimmune conditions**

- **Overlap features with various significance:**
  - **Never use autoantibodies in isolation (AMA: best specificity)**
  - **Role of <u>good-quality</u> liver biopsies and cholangiograms**

# Cholangiography (MRCP): Potential Pitfalls

**Be cautious about (over) interpretating « mild changes » of the intra-hepatic bile ducts (take fibrosis stage into account) !)**

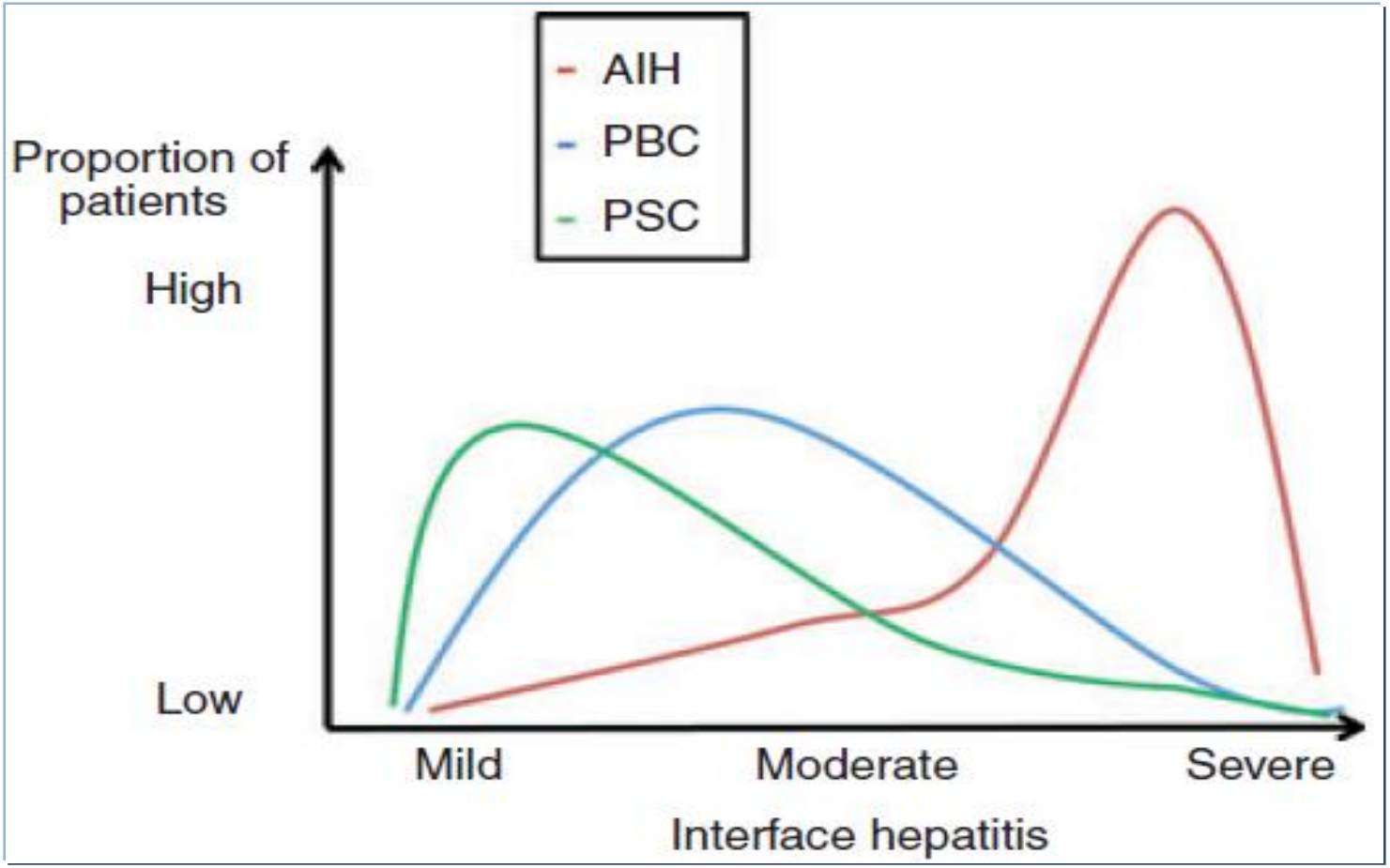



| | F0-F2 AIH (n = 35) | F3-F4 AIH (n = 24) | Cirrhotic controls (n = 27) |
|---|---|---|---|
| IHBD changes* | 3 (9%) | 11 (46%) | 16 (59%) |
| Increase bile duct visualization | 1 (3%) | 3 (12%) | 4 (15%) |
| Irregularities | 1 (3%) | 10 (42%) | 16 (59%) |
| Strictures | 1 (3%) | 4 (17%) | 3 (11%) |
| Dilatation | 1 (3%) | 1 (4%) | 3 (11%) |

*(Lewin et al, Hepatology 2009)*

# Interface Hepatitis




*(Trivedi et Hirschfield, Aliment Pharmacol Ther 2012)*

# Autoimmune Overlaps: Which Criteria?

- **AIH scores?**
  - **Not intended for such use**
  - **Sensitivity and specificity < 80%**

    **« pure » PBC: 8%** + ***(Muratori et al, Hepatology 2008)***
  - **Use of AIH scores not recommended in this setting**

    ***(Boberg et al, J Hepatol 2011)***

- **Appraisal should be performed longitudinally rather than at a single point in time**

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:530–534

# ORIGINAL ARTICLES—LIVER, PANCREAS, AND BILIARY TRACT

## Paris Criteria Are Effective in Diagnosis of Primary Biliary Cirrhosis and Autoimmune Hepatitis Overlap Syndrome

EDITH M. M. KUIPER,* PIETER E. ZONDERVAN,‡ and HENK R. VAN BUUREN*

**CONCLUSIONS:**

The Paris diagnostic criteria detect overlap syndrome (PBC and AIH) with high levels of sensitivity and specificity. The clinical value of the revised and simplified AIH scoring system is not as reliable.

**Anti-dsDNA *(Muratori, Am J Gastroenterol 2009)*: to be confirmed**

# PBC/AIH Overlap Diagnosis : EASL Proposal

## Standardization of diagnostic criteria not achieved

**Diagnostic criteria of PBC–AIH overlap syndrome.**

***PBC criteria***

1. AP >2× ULN or γGT >5× ULN
2. AMA ⩾1:40
3. Liver biopsy specimen showing florid bile duct lesions

***AIH criteria***

1. ALT >5× ULN
2. IgG >2× ULN or a positive test for anti-smooth muscle antibodies (ASMA)
3. Liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis

Diagnostic criteria of PBC–AIH overlap syndrome of which at least 2 of 3 accepted criteria for PBC and AIH, respectively, should be present (proposed by Chazouilleres et al. [57]). Histologic evidence of moderate to severe lymphocytic piecemeal necrosis (interface hepatitis) is mandatory for the diagnosis.

*(EASL Guidelines, J Hepatol 2009, 2017)*

# PSC/AIH Overlap Diagnosis

**No "official" criteria**

**Presence of at least 2 of the 3 accepted key criteria required for diagnosis of each disease:**

- **PSC (causes of secondary SC excluded):**
  - **1) AP ≥ 2 ULN and/or GGT ≥ 5 ULN,**
  - **2) typical cholangiographic abnormalities**
  - **3) periductal fibrosis (liver biopsy)**

  **NB: some cases of overlap with "small duct" PSC**

- **AIH:**
  - **1) ALT ≥ 5 ULN,**
  - **2) IgG levels ≥ 2 ULN or ASMA ≥ 1/80,**
  - **3) Moderate or severe periportal or periseptal lymphocytic piecemeal necrosis (liver biopsy) (mandatory)**

# PBC- PSC/AIH Variant Syndromes

**Several areas of uncertainty** :

**(i) Cut-offs for IgG/gamma-globulins and transaminases** levels to indicate liver biopsy? (IgG: 20g/L ?)

(ii) **Grade of hepatitis activity** to indicate immunosuppression?

(iii) **A scoring system** to identify patients with PBC and AIH ?

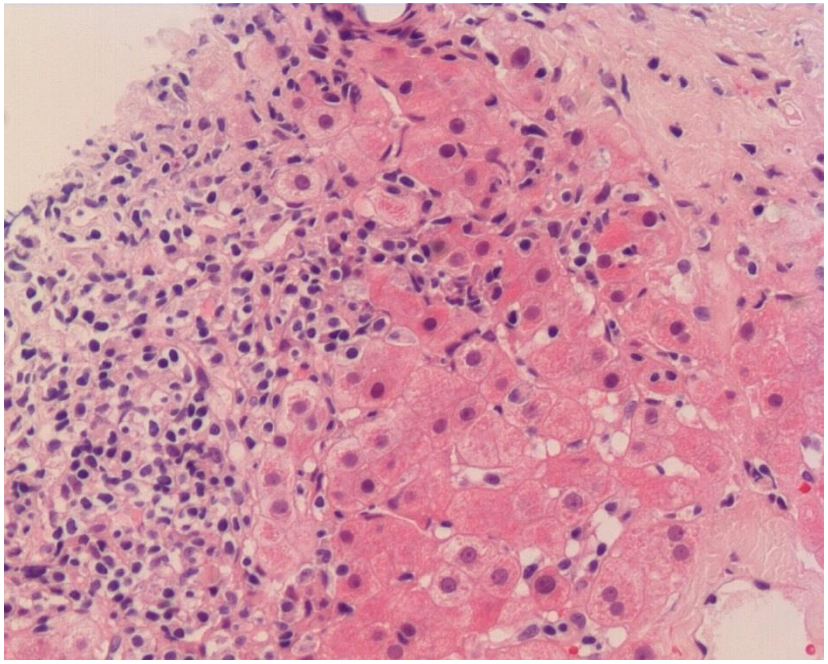
(iv) Degree of histological bile duct damage to define PBC in patients with AIH and to indicate UDCA?

***EASL PBC guidelines, J Hepatol, 2017***

# Liver biopsy

**Liver biopsy is mandatory for the diagnosis of overlap syndrome**

> Moderate or severe lymphocytic interface hepatitis



*(PBC patient)*

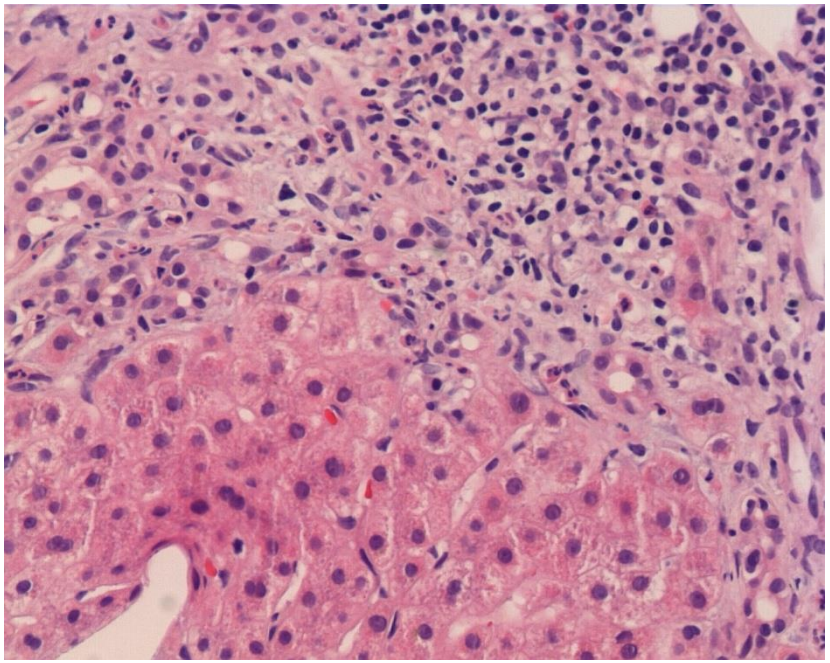
Lymphocytic interface hepatitis

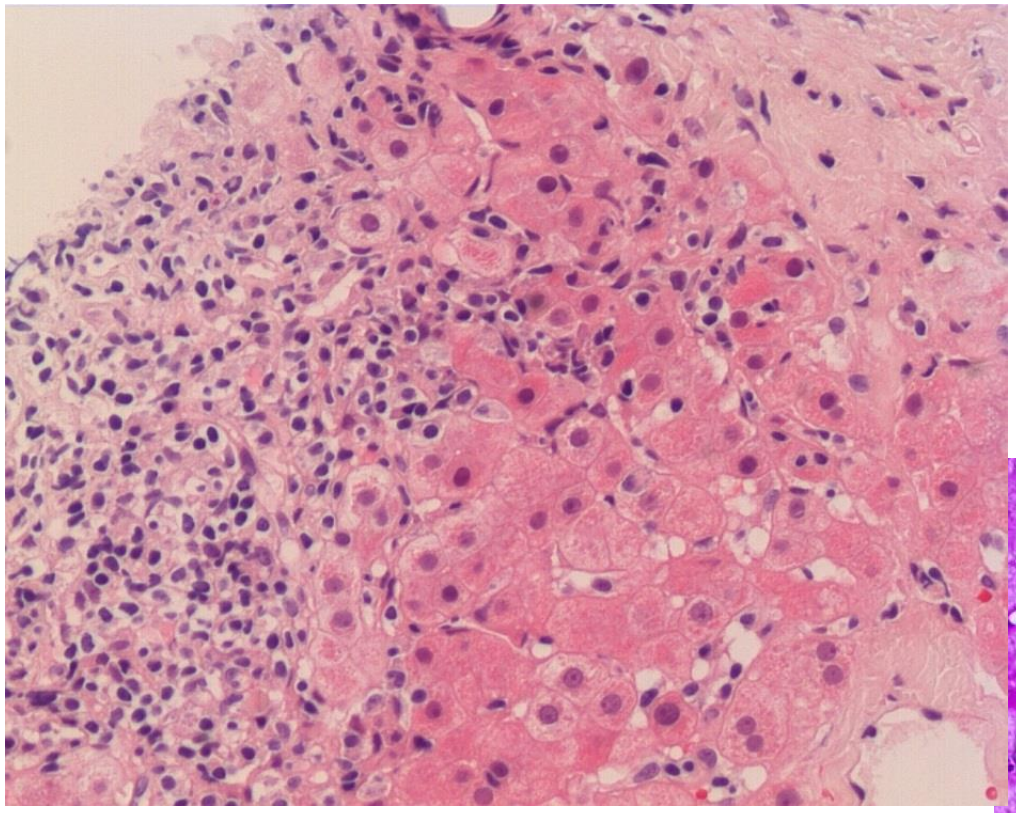
# Liver biopsy

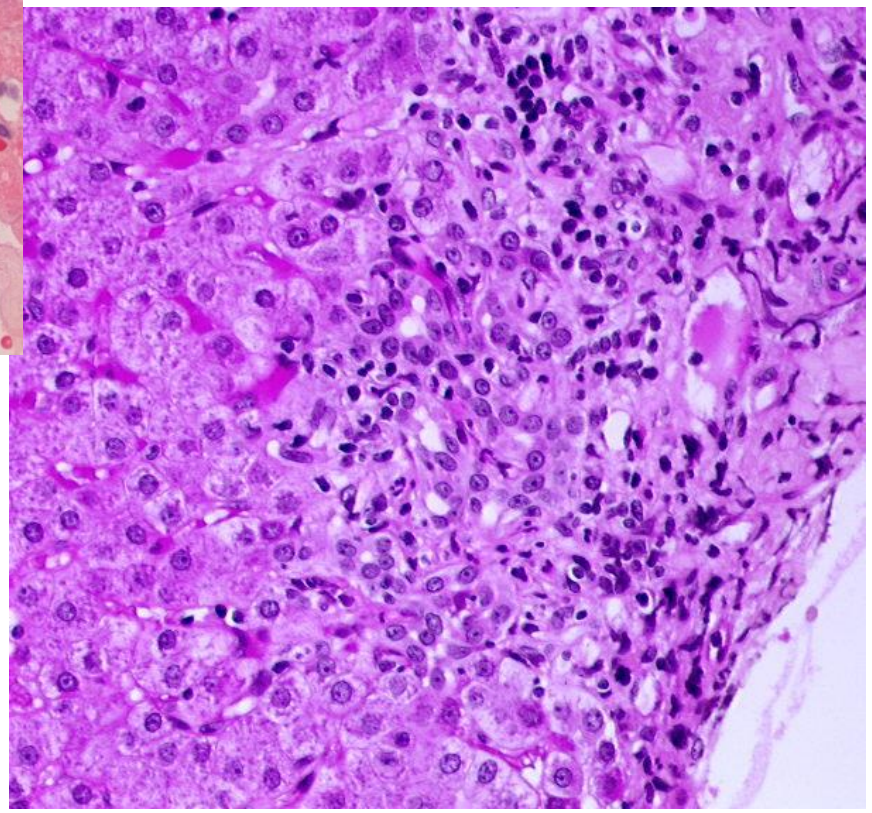
## Areas of uncertainty or difficulties

### 1) lymphocytic interface hepatitis vs biliary interface activity

Biliary interface activity : ductular reaction + inflammatory cells (PMN)
fibrosis +/- cholate stasis



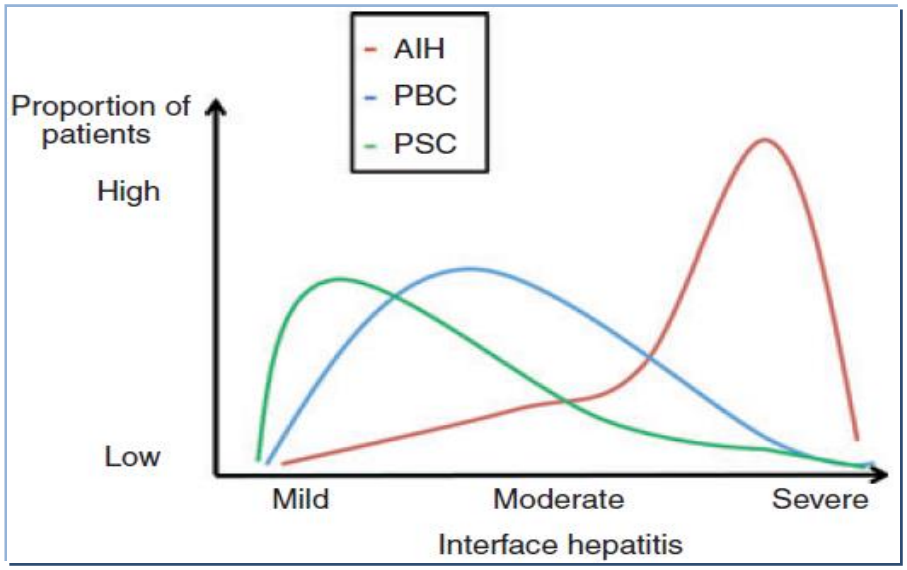




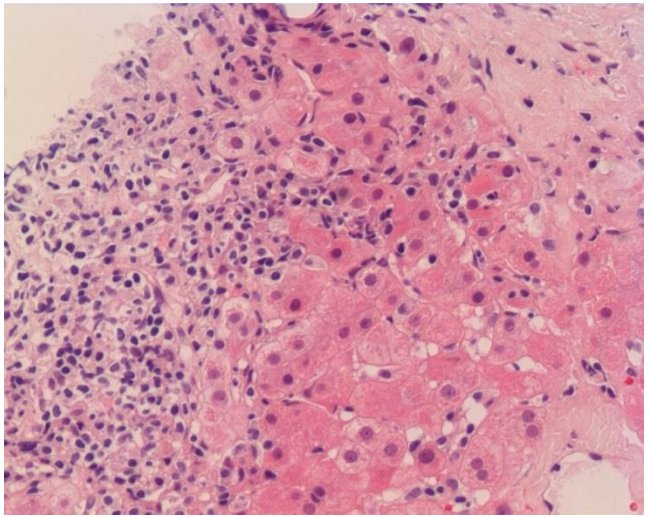
# Liver biopsy

## Areas of uncertainty or difficulties

### 2) Diagnostic criteria for moderate / severe interface hepatitis




*(Trivedi et Hirschfield, Aliment Pharmacol Ther 2012)*



Mild interface hepatitis

*(PBC patient)*

# Liver biopsy

## Areas of uncertainty or difficulties

### 2) Diagnostic criteria for moderate / severe interface hepatitis ?

- No criteria in the EASL guidelines

- Nakanuma Scoring system (PBC) *Histopathology 2006;49: 466*

| | Hepatitis activity |
|---|---|
| (no activity) | No interface hepatitis, and no or minimum lobular hepatitis |
| (mild activity) | Interface hepatitis affecting 10 continuous hepatocytes in one portal tract or fibrous septa, and mild–moderate lobular hepatitis |
| (moderate activity) | Interface hepatitis affecting 10 continuous hepatocytes in more than two portal tracts or fibrous septa, and mild–moderate lobular hepatitis |
| (marked activity) | Interface hepatitis affecting 20 continuous hepatocytes in more than half of the portal tracts, and moderate lobular hepatitis, or bridging or zonal necrosis |

- FBI scoring system (PBC) *Liver Int 2015; 35: 652*

Mild interface hepatitis :focal lymphocytic interface hepatitis in a minority of portal tracts (< 50%)

Severe lymphocytic hepatitis :diffuse or continuous lymphocytic interface hepatitis in a majority of portal tracts (>50%). Diffuse or continuous interface hepatitis lesions could involve more or less than half of the portal tract circumference.

All other features were considered as moderate interface hepatitis.

# Liver biopsy

## Areas of uncertainty or difficulties

### 3) Reproducibility assessing interface hepatitis

- Nakanuma Scoring system (PBC) *Pathology International 2010; 60: 167–174*

*« interobserver agreement for hepatitis activity was slight, less than our expectation (0.2) »*

-FBI scoring system (PBC) *Liver Int 2015; 35: 652*

*interobserver agreement (0.59)*

# Liver biopsy

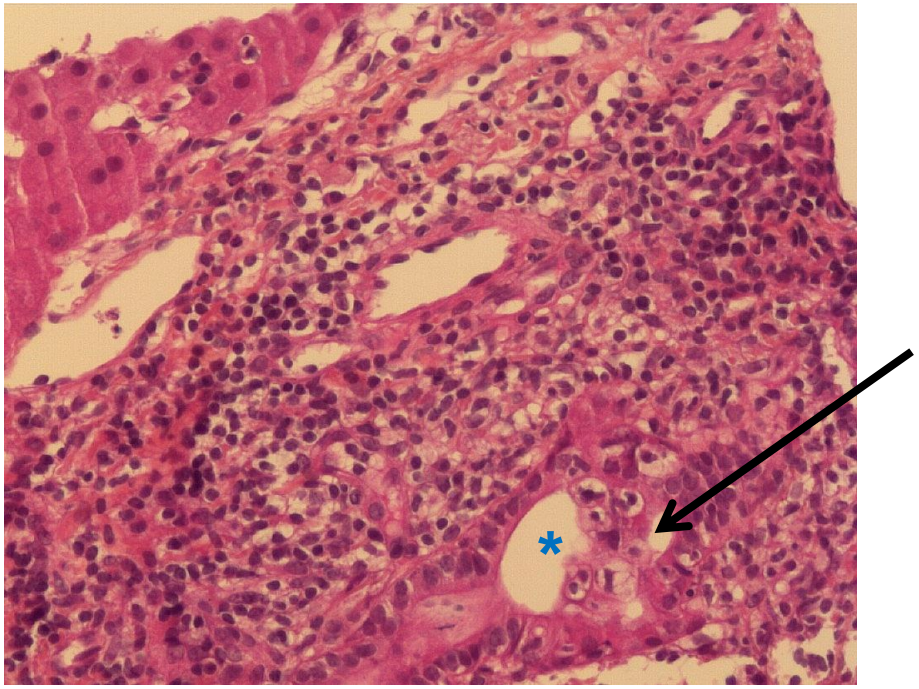
## Areas of uncertainty or difficulties

**4) Biliary lesions can be absent in biopsies of patients with PBC or PSC**

Biliary lesions seen in 20-40%

**5) Biliary lesions can be seen in biopsies of patients with AIH**

Biliary lesions seen in 10-20%



# Liver biopsy

- The pathologist cannot make the diagnosis of overlap syndrome alone

- Role of good-quality liver biopsies

- Role of good-quality liver biopsy interpretation

Histopathology

Any value in a specialist review of liver biopsies ?
Conclusions of a 4-year review

1265 biopsies : diagnostic differences occurred in more than 70% with biliary disease, autoimmune hepatitis or vascular/architectural changes.

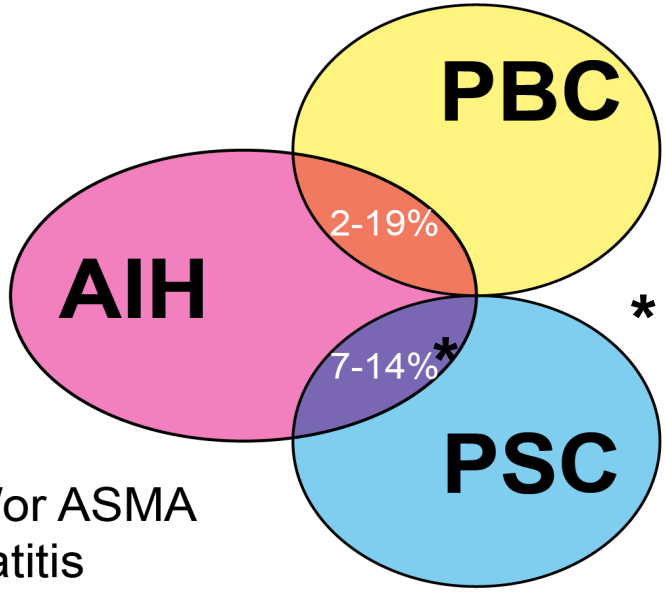
A clinical review of a subset of reports with histopathological differences predicted changes in patient management in 63 of 103 (61%).

*Histopathology 2016; 69:315-321*

# Prevalence and Clinical Presentation

Hepatic features
ALT > 5 ULN

Cholestatic features
ALP > 2 ULN




- Positive AMA
- LB: destructive cholangitis

* **Up to 50% in children**

- Abnormal cholangiogram
- LB: periductal fibrosis
- ± IBD

- IgG ≥ 2 ULN
- Positive ANA and/or ASMA
- LB: interface hepatitis

**Considerable heterogeneity despite the same overlap designation**

**Forms: ◊ Simultaneous: the most frequent**

**◊ Consecutive: changing phenotype or resistance to treatment**

**(PBC then PBC + AIH : 1 - 4 %; AIH then IH +PBC : anecdotal)**

# Autoimmune Overlaps: Presentation

- **One primary disorder (« predominant » disease) often identified: PBC or PSC with AIH features, AIH with PBC or PSC features**

- **Disease with predominating features or occuring first:**
  - **PBC/AIH: usually PBC**

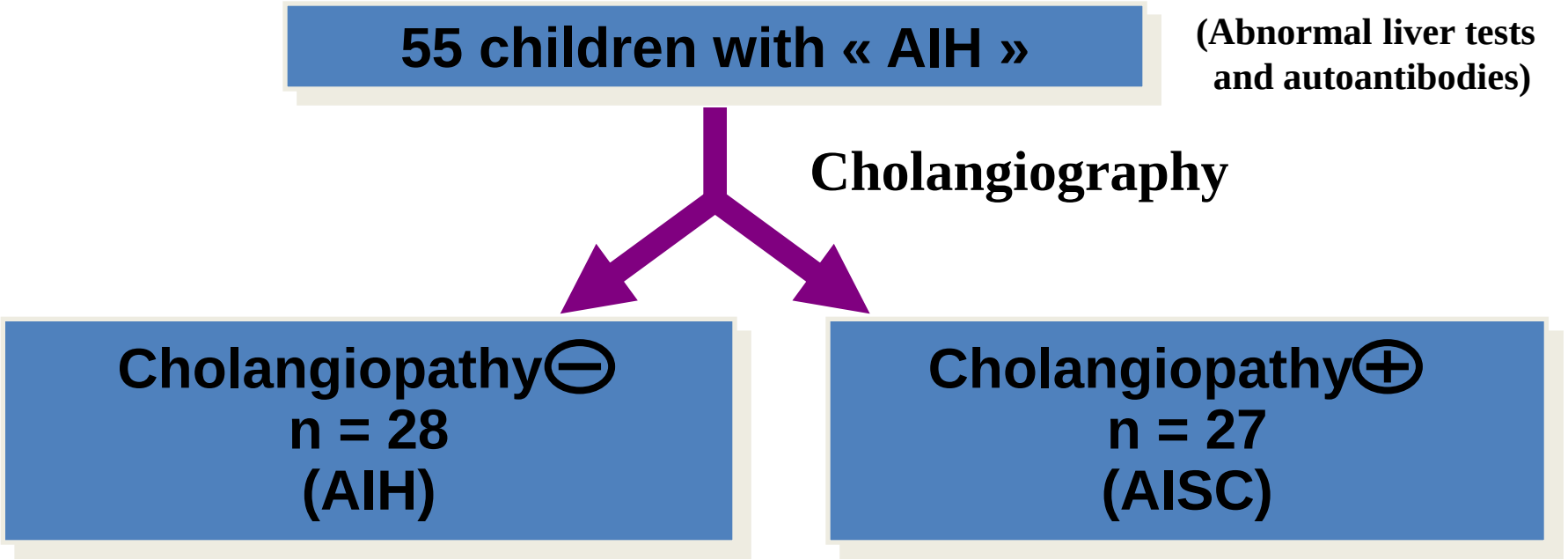
    **(« Hepatitic form of PBC », *Lhose et al, Hepatology 2001*)**

  - **PSC/AIH: usually AIH**

- **A special form: Autoimmune sclerosing cholangitis (AISC)**

  ***(Gregorio et al, Hepatology 2001)***

# Autoimmune Sclerosing Cholangitis (AISC)(1)




**25 % with normal ALP and γGT**

**AISC vs AIH: lower ALT, more IBD and p-ANCA, less LKM1**
**histology: less inflammation, more cholangitis (35%),**
**extensive fibrosis: 65% (NS)**

***(Gregorio et al,, Hepatology 2001)***

# Autoimmune Sclerosing Cholangitis (AISC)(2)

- **Similar biochemical and histological response to immunosuppression**

- **Median follow-up: 7 years**
  - **Increased cholangiorams abnormalities: AISC: 8/17, AIH:1 (with IBD) /17**
  - **Transplant-free survival at 10 years (estimated):**
    - **AISC: 65%**
    - **AIH: 100%**

***(Gregorio et al,, Hepatology 2001)***

- **PSC in adults: advanced « burnt out » AISC ??**

**MRCP recommended in all children with a diagnosis of AIH**

# Autoimmune Sclerosing Cholangitis (AISC)(3)

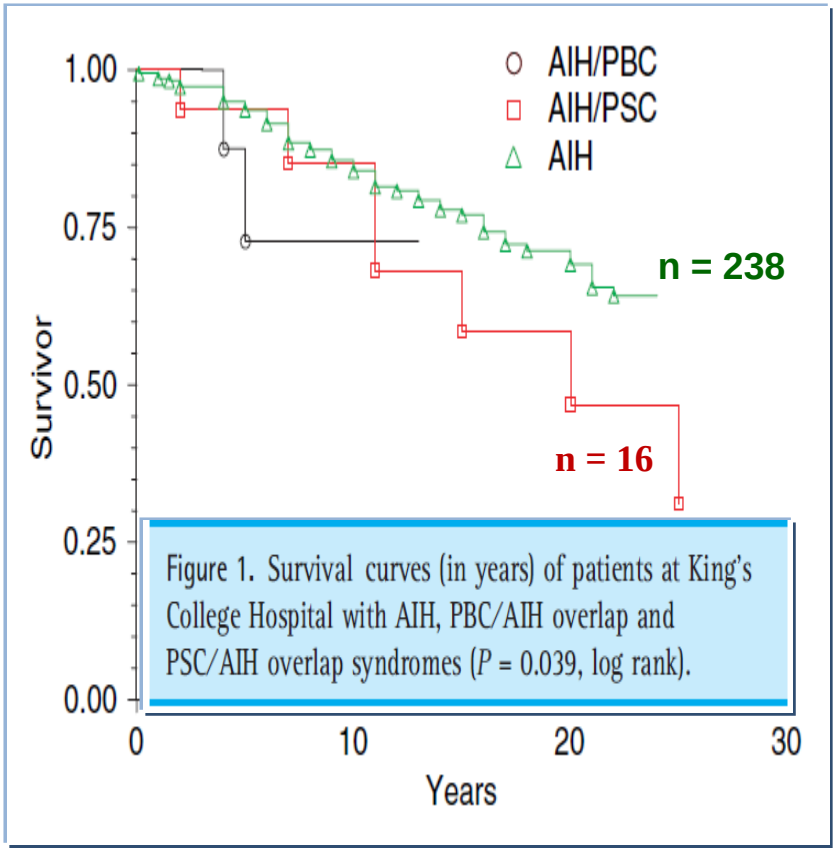
- **781 PSC (UDCA > 75%) :**
  - **Associated AIH: 33%**

TABLE 2. Proportional Hazards Analysis of Phenotypic Characteristics and Event-Free Survival

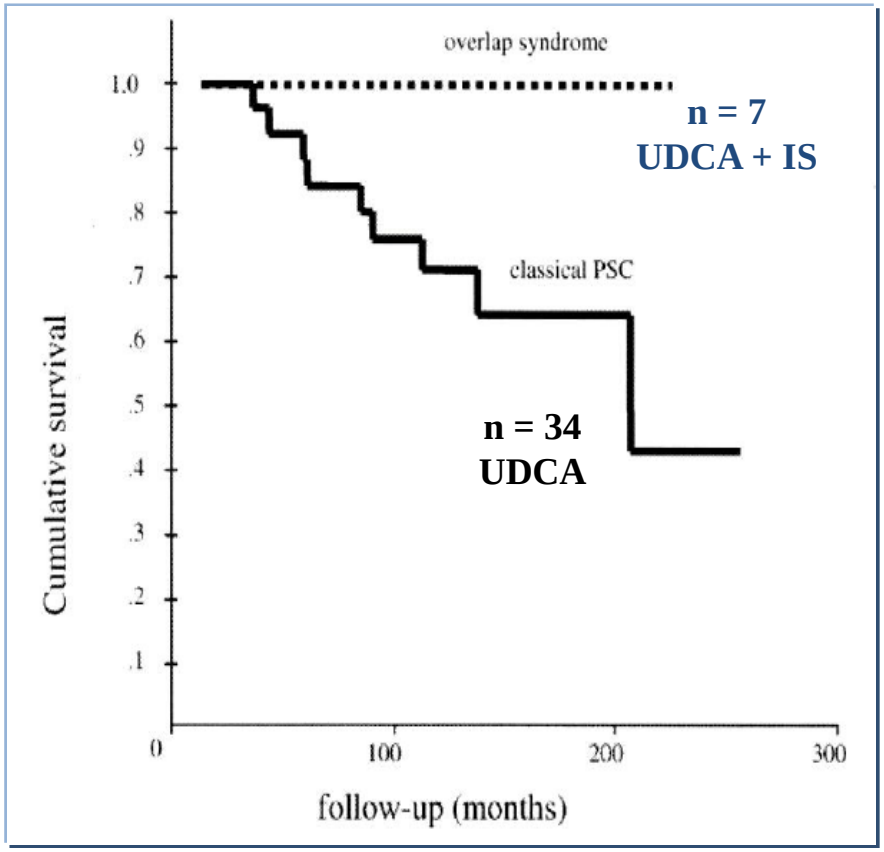
| Predictor | Reference | Univariate Hazard Ratio (95% CI) | *P* | Multivariate Hazard Ratio (95% CI) | *P* |
|---|---|---|---|---|---|
| Male gender | Female gender | 0.88 (0.67-1.15) | 0.342 | 0.90 (0.68-1.18) | 0.450 |
| Age ≥12 years | Age <12 years | 1.02 (0.79-1.34) | 0.857 | 1.04 (0.80-1.36) | 0.778 |
| Small duct PSC | Large duct PSC | **0.71 (0.52-0.99)** | **0.042** | **0.69 (0.50-0.96)** | **0.028** |
| AIH | No AIH | 1.00 (0.75-1.32) | 0.990 | 0.89 (0.67-1.2) | 0.461 |
| IBD | No IBD | **0.66 (0.49-0.89)** | **0.006** | **0.63 (0.47-0.86)** | **0.004** |

***(Deneau et al, Hepatology 2017)***

# PSC/AIH Overlap : Outcome in Adults




*(Al-Chalabi et al, Aliment Pharmacol Ther 2008)*



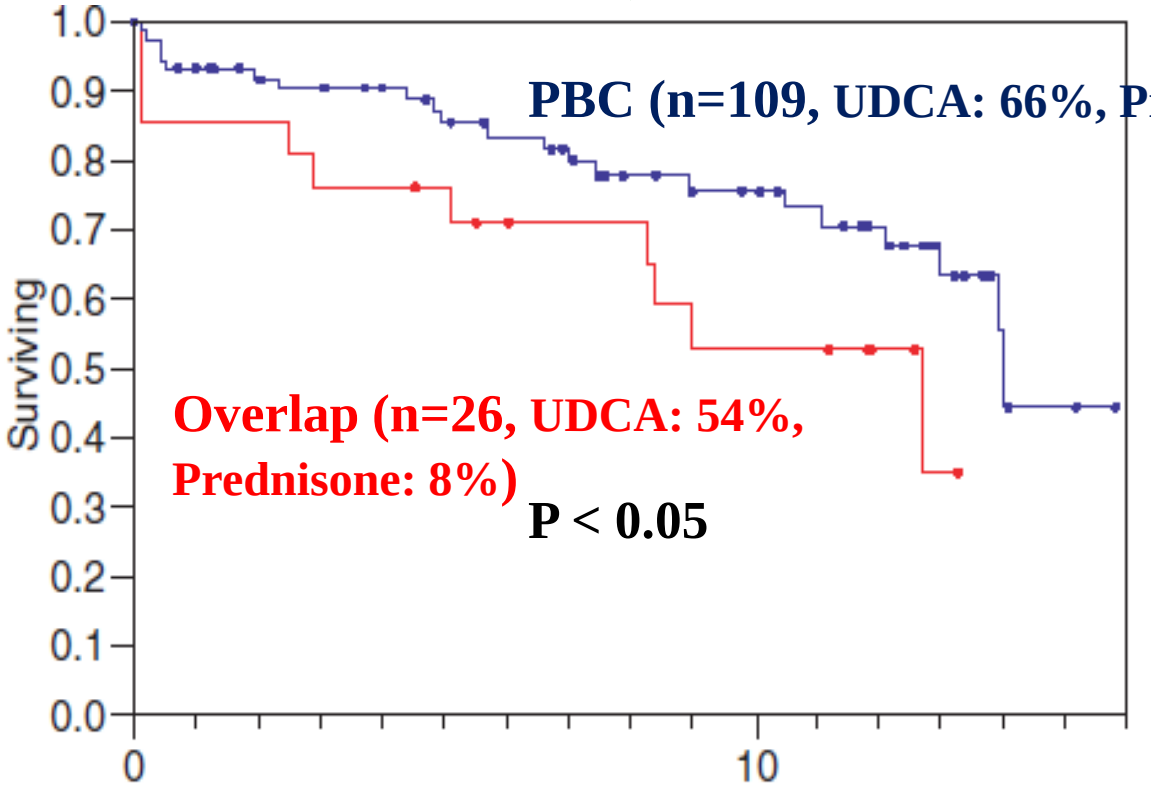

*(Floreani et al, AM J Gastroenterol 2005)*

**Development of cirrhosis: 12/16 (median follow-up: 12 years)**

*( Luth S et al, J Clin Gastroenterol 2009)*

# PBC/AIH Overlap : Outcome

*(Silveira et al, Am J Gastroenterol 2007)*




**Overlap vs PBC:**
**- younger: 44 vs 59 yrs**
**- F3-F4 = 57 vs 39%**

*(Heurgué et al, Gastroenterol Clin Biol 2007)*

# Autoimmune Overlaps: : Treatment

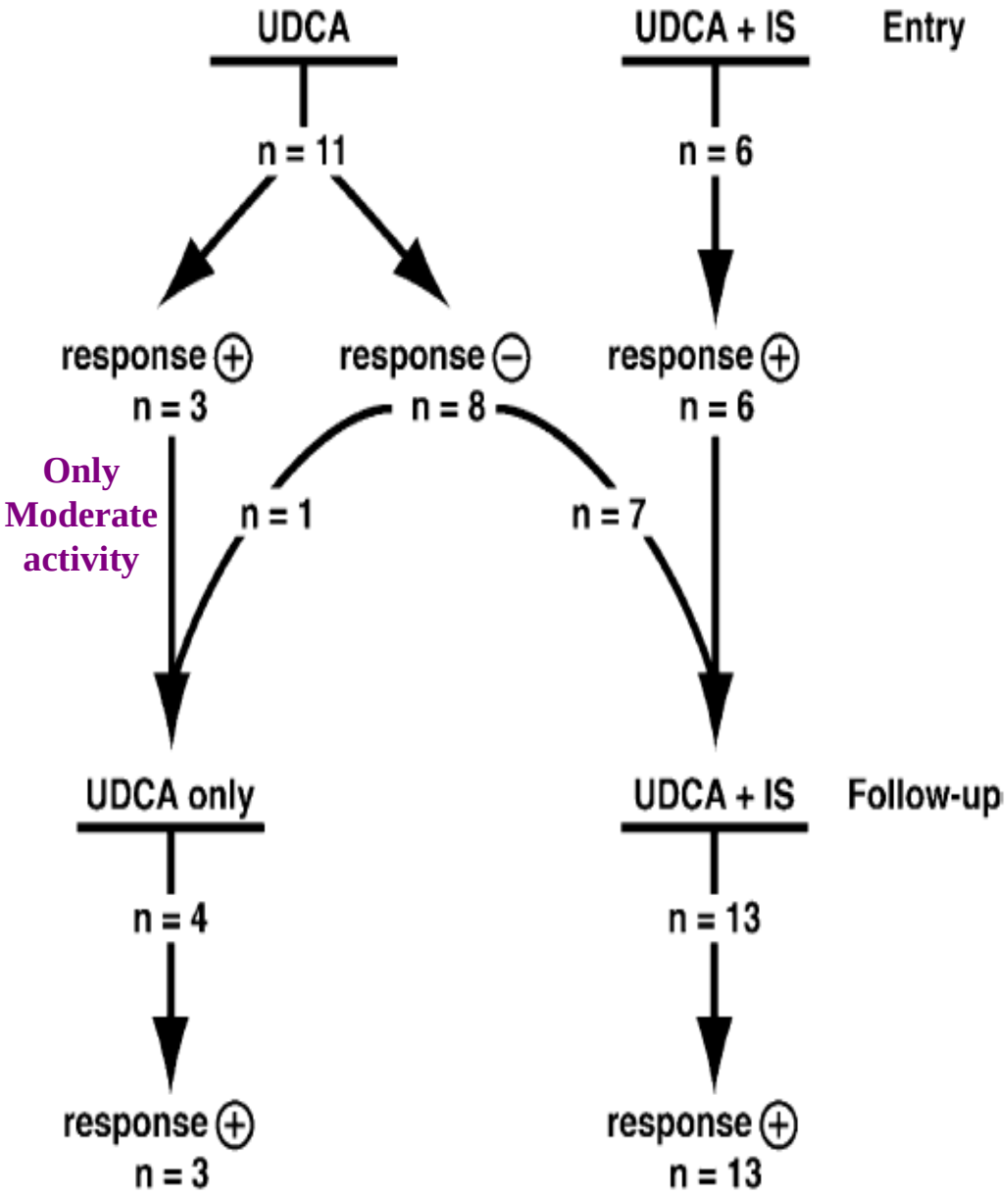
**Question:**

**Immunosuppressive therapy, UDCA, both ?**

- **No controlled therapeutic trials (low prevalence)**
- **Only small retrospective non-randomized studies**

**Treatment is largely empiric**

# PBC/AIH Overlap : The Paris Experience



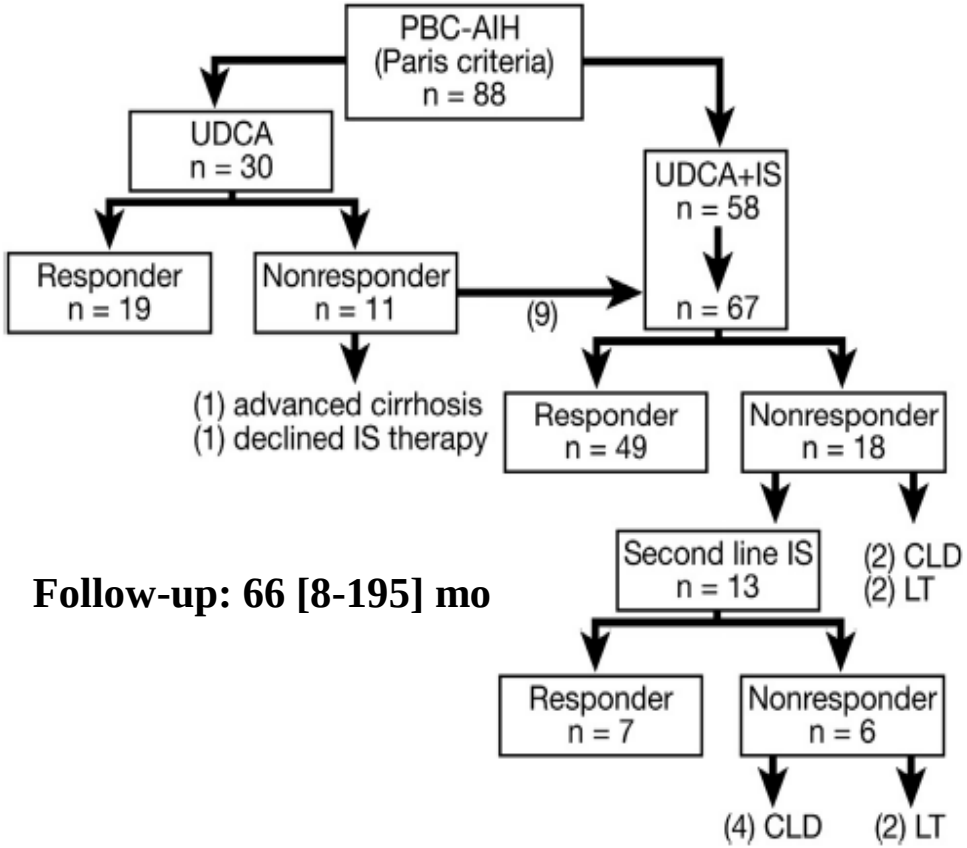

**17 patients, follow-up: 7.5 yrs**

**Fibrosis ↑:**
**UDCA: 4/8**
**UDCA + IS: 0/6**
**P = 0.04**

**IS:**
**Pred (0.5 mg/kg/d, then ↓) + Aza**
**Side effects: 6/13**
**IS free patients: 4/13**

***(Chazouillères et al, J Hepatol 2006)***

# PBC/AIH Overlap : an International Experience




***(Ozaslan et al, Clin Gastroenterol Hepatol 2014)***

**Follow-up: 66 [8-195] mo**

**Successful withdrawal of IS: 15/20**

**In terms of ALT response:**

- **moderate interface hepatitis: UDCA vs UDCA+IS: similar efficacy (≈ 80%)**
- **Severe interface hepatitis: UDCA (14%) vs UDCA+IS (71%)**

# PBC/AIH Variant Syndromes
# EASL Treatment Guidelines

- **Combined therapy with UDCA and corticosteroids is the recommended therapeutic option (especially if severe interface hepatitis) (Budesonide is an option)**

- **Alternative approach (especially if moderate interface hepatitis) : start with UDCA only and add corticosteroids if biochemical response to UDCA is inadequate at 3 months**

- **In UDCA-treated PBC patients developping sequential overlap, use of immunosuppressive treatment is mandatory**

***EASL guidelines, J Hepatol, 2009***
***EASL guidelines, J Hepatol, 2017***

# PSC/AIH Overlap: EASL and AASLD Guidelines

- **EASL cholestasis guidelines: combined therapy (UDCA +IS)**

***(J Hepatol 2009)***

- **AASLD PSC guidelines: immunossuppressants**

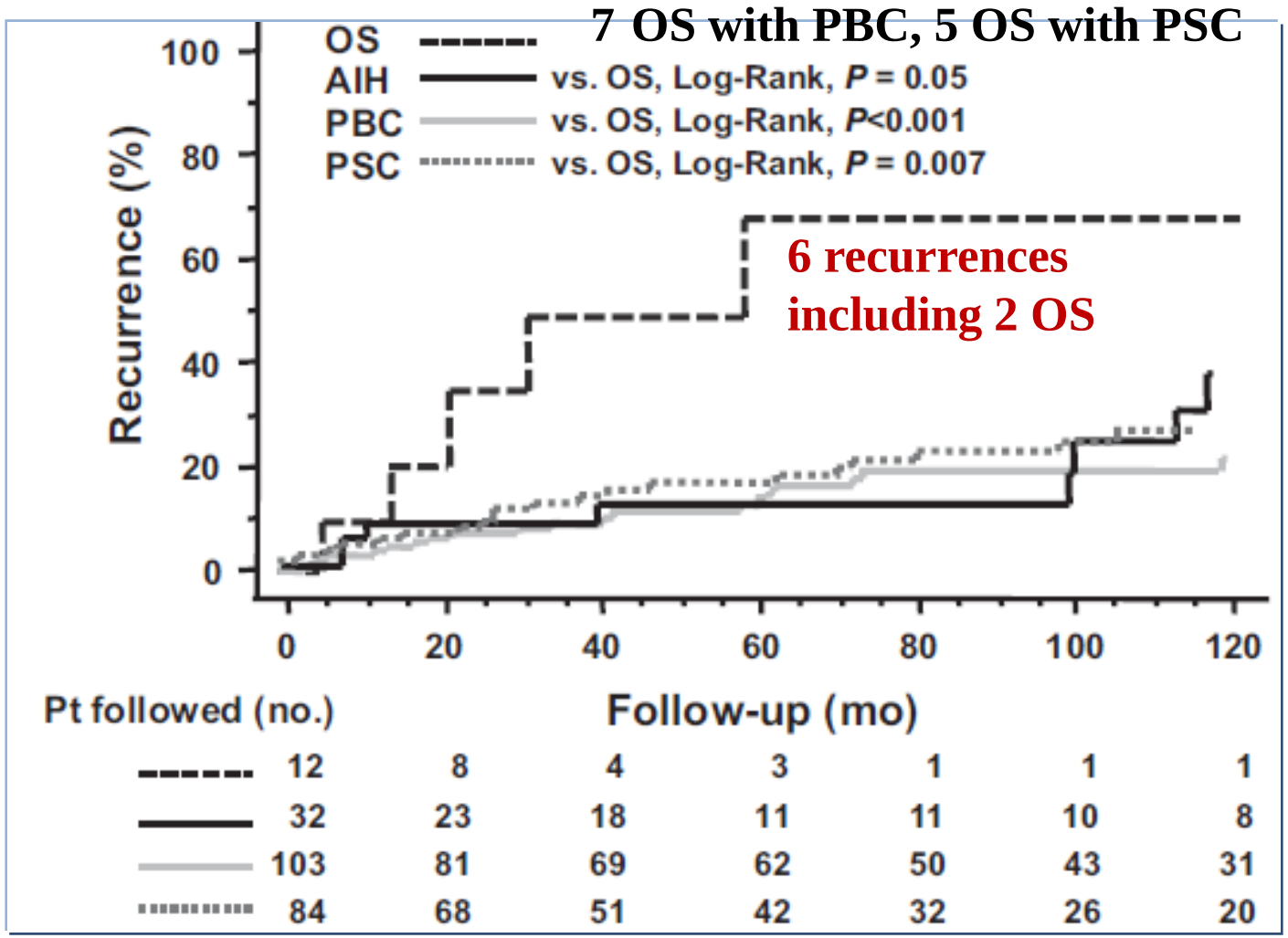
***(Hepatology 2010)***

- **EASL AIH guidelines: combined therapy but**

**In patients with dominant AIH features, an alternative approach is to start with immunosuppressants only and then add UDCA if response is insufficient (III).**

***(J Hepatol 2015)***

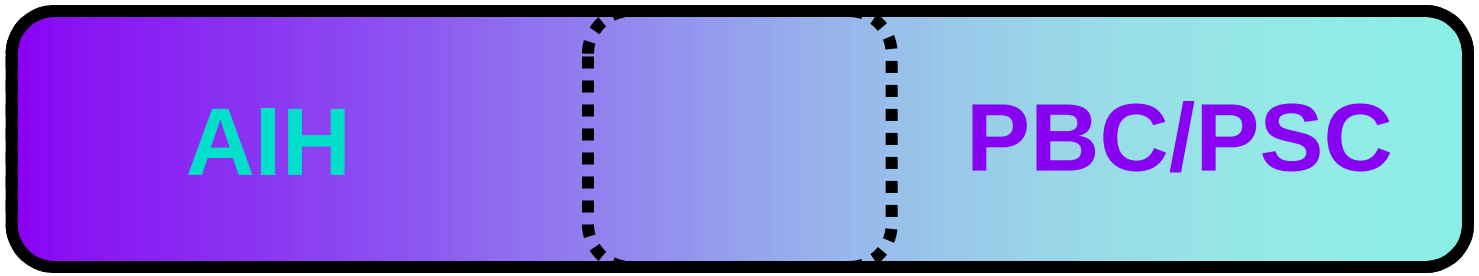
# Overlaps and Liver Transplantation




*(Bhanji et al, Liver Int 2013)*

# How to Deal with Overlaps ? Key Points

- **Critical approach**
- **« Strict » diagnostic criteria (don't over-diagnose !)**
- **Tailor-made treatments based on disease phenotype:**
  - **in case of « dominant » disease: treat it first**




**Hépatitis** ⇄ **Cholestasis**

**Immunosuppressants** **UDCA**

- **Adjust according to the response (close follow-up)**

**(don't over-treat but don't miss an opportunity of IS !)**

# Overlaps: Conclusions

- **Overlap syndrome is ill-defined and "heterogeneous but it constitutes a clinical reality that must be accepted, refined, treated and studied"** ***(Czaja, Dig Dis Sci 2013)***

- **"Overlap" (strongly suggests the presence of 2 distinct diseases):**

  **potential misnomer but**

  - **very popular**
  - **draws physician's attention to particular features with clinical consequences**

- **How to go further ?**
  - **Large data base (international)**
  - **Interface hepatitis: reproducible grading and characterization**
  - **Specific molecular signatures (genomics, proteomics…)**