

# **EFFET DES TRAITEMENTS SUR L'HISTOIRE NATURELLE DES HEPATO-CHOLANGIOPATHIES AUTO-IMMUNES**

**Olivier CHAZOILLERES**

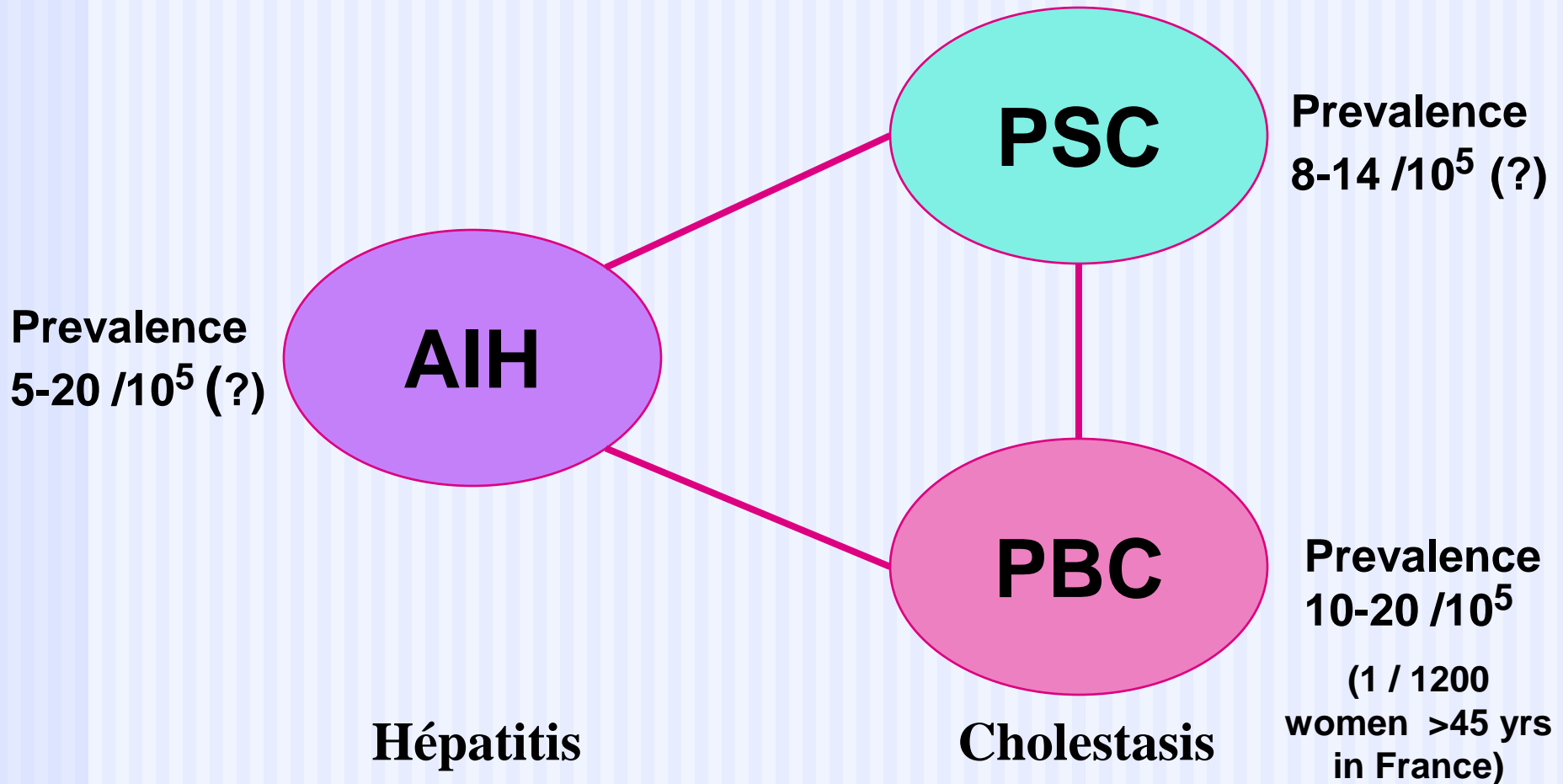
*Service d'Hépatologie*

*Centre de référence des maladies  
inflammatoires des voies biliaires*

*Paris – Saint Antoine*

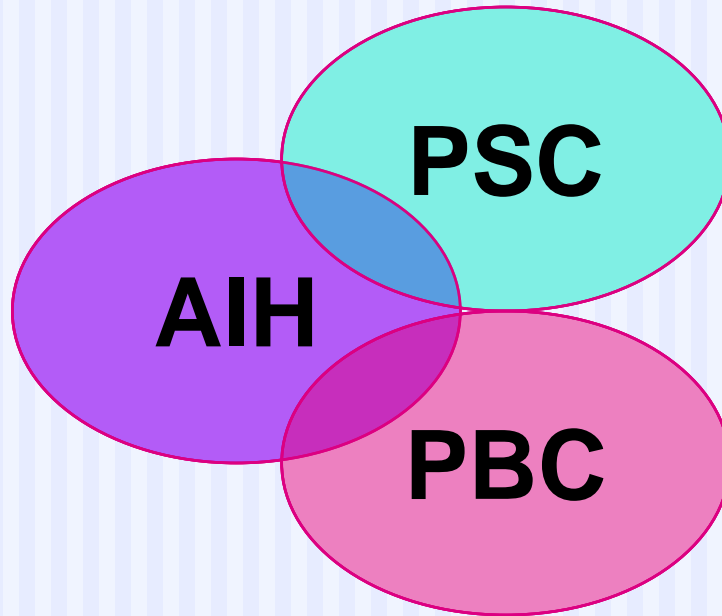


# Autoimmune Liver Diseases



**Numerous variant forms**

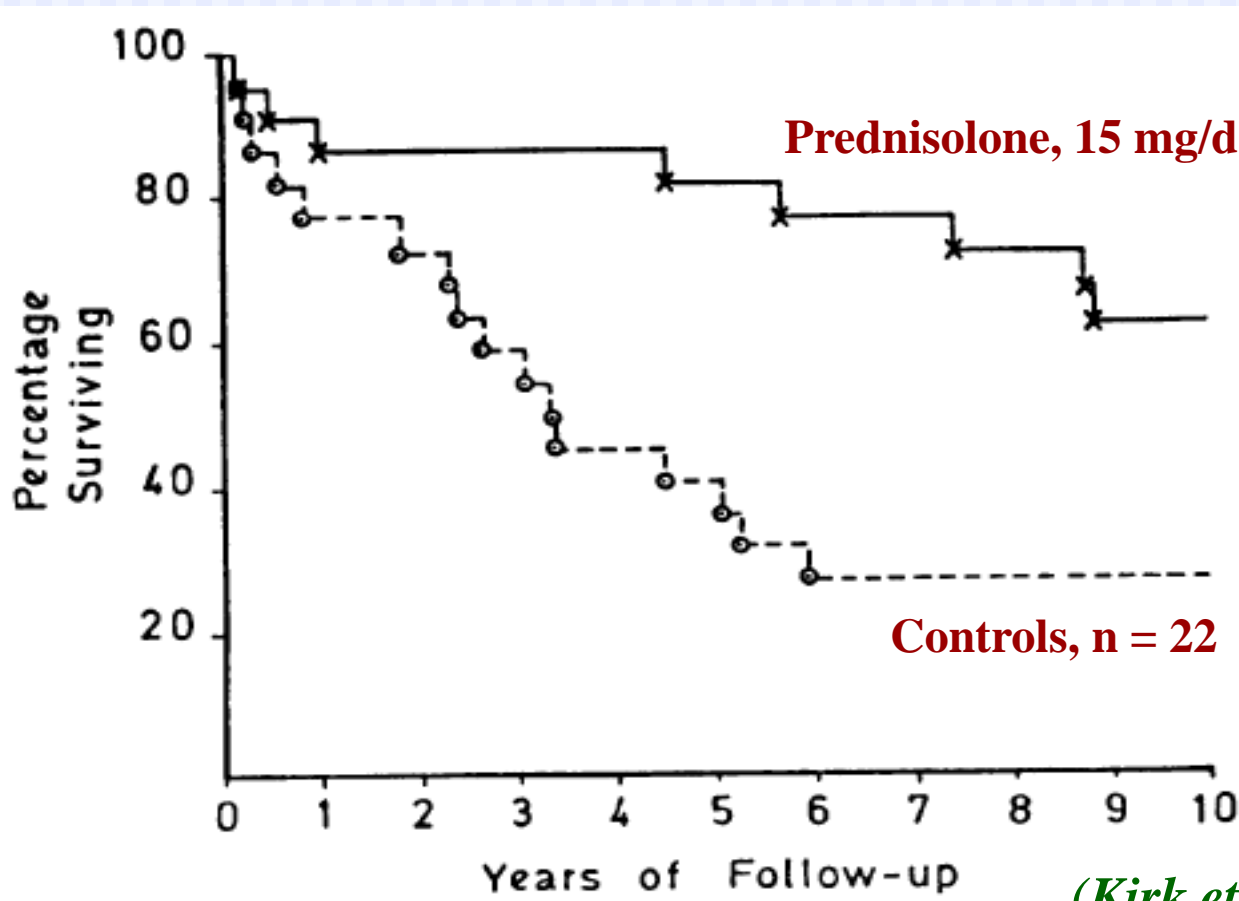
# Autoimmune Overlap Syndromes



# Autoimmune Hepatitis: Main Features

<b>Features</b>	<b>Type 1</b>	<b>Type 2</b>
<b>Characteristic autoantibodies</b>	<b>ANA, ASMA Anti-actin antibody Anti-SLA/LP antibodies</b>	<b>Anti-LKM-1 antibody Anti-LC-1 antibody</b>
<b>Age at presentation</b>	<b>All ages</b>	<b>Children and young adults</b>
<b>Sex</b>	<b>F:M = 3:1</b>	<b>F:M = 10:1</b>
<b>Clinical phenotype</b>	<b>Variable</b>	<b>Generally severe</b>
<b>Histologic features at presentation</b>	<b>Broad range: Mild disease to cirrhosis</b>	<b>Generally advanced inflam/cirrhosis common</b>
<b>Treatment failure</b>	<b>Rare</b>	<b>Common</b>
<b>Relapse</b>	<b>Common</b>	<b>Very Common</b>
<b>Need for long-term maintenance</b>	<b>Common</b>	<b>Approximately 100%</b>

# AIH Treatments: Efficacy



*(Kirk et al, Gut 1980)*

## Reversibility of Hepatic Fibrosis in Autoimmune Hepatitis

*(Dufour et al, Ann Intern Med 1997)*

# Indications for Immunosuppressive Treatment

## ABSOLUTE

- **AST  $\geq$  10 ULN**
- Or
- **AST  $\geq$  5 N and  $\gamma$ globulins  $\geq$  2 ULN**
- Or
- **Bridging necrosis or multiacinar necrosis**

## RELATIVE

- **Symptoms (fatigue, arthralgia, jaundice)**
- Or
- **Elevated AST and/or  $\gamma$ globulins but less than absolute criteria**
- Or
- **Interface hepatitis**

## NONE

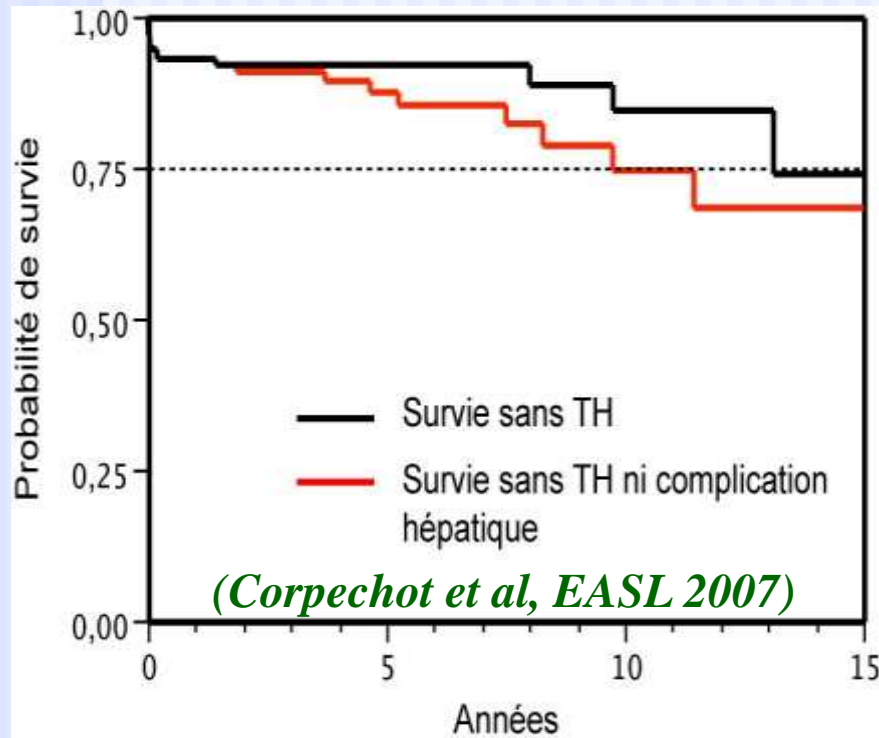
- **Asymptomatic with normal or near normal AST and  $\gamma$ globulins**
- **Inactive cirrhosis or mild portal inflammation (portal hepatitis)**

**Close follow-up +++  
(6 months)**

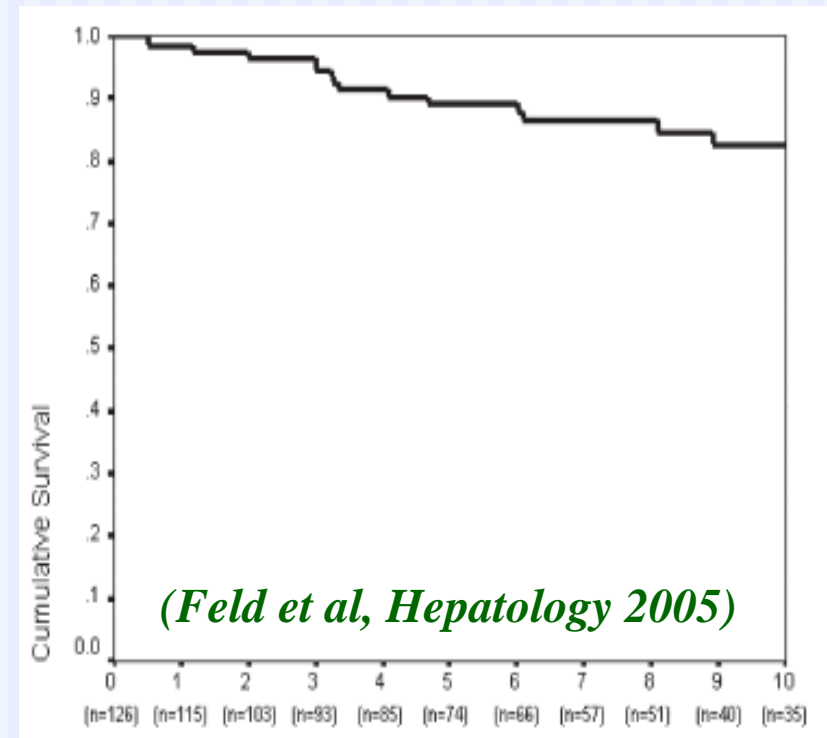
*(AASLD Practice Guidelines, Hepatology 2010)*

# Outcome and Prognostic Factors

## France



## Canada



**Prognostic factors at presentation:  
fibrosis F3-F4  
(sub-fulminant hepatitis excluded)**

**Prognostic factors at presentation:  
cirrhosis (+/- age)**

**Other prognostic factors: African-American men, incomplete biochemical response, inflammation on liver biopsy (on treatment), multiple relapses...**

# HAI – Treatment (AASLD)

	<b>Monotherapy</b>	<b>Combination Therapy</b>	
	<b>Predniso(lo)ne</b>	<b>Predniso(lo)ne</b>	<b>Azathioprine</b>
	<b>(mg/d)</b>	<b>(mg/d)</b>	<b>(mg/d)</b>
<b>Semaine 1</b>	<b>60</b>	<b>30</b>	<b>50*</b>
<b>Semaine 2</b>	<b>40</b>	<b>20</b>	<b>50*</b>
<b>Semaine 3</b>	<b>30</b>	<b>15</b>	<b>50*</b>
<b>Semaine 4</b>	<b>30</b>	<b>15</b>	<b>50*</b>
<b>Maintenance until end point</b>	<b>20 and below</b>	<b>10</b>	<b>50*</b>

**\*: 1-2 mg/kg/d in EU**

*AASLD Practice Guidelines, Hepatology 2010*

**Combination therapy: preferred regimen, unless cytopenia, pregnancy, malignancy, expected short course ( $\leq 6$  months)**

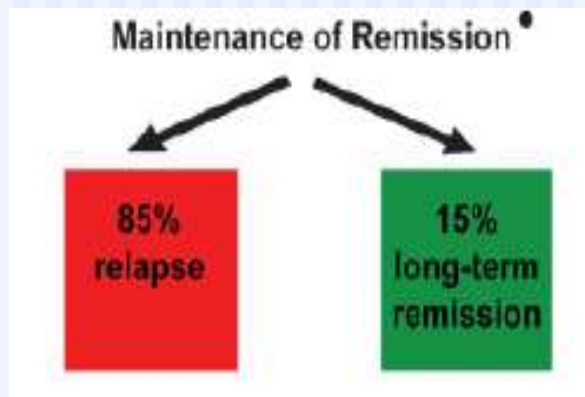
# Outcome of AIH under Therapy

(Manns et al. *Hepatology* 2006)

Standart Treatment

**Remission (clinical  
and biochemical)  
without intolerance**  
**75%**

**Poor Response  
and/or  
intolerance**  
**25%**



• after drug withdrawal

# Treatment Withdrawal

« Liver-biopsy assessment prior to termination of treatment is the only method by which to ensure full resolution of the disease and an optimal end point of therapy ».

*(AASLD Practice Guidelines, Hepatology 2010)*

- Lack of inflammation : 20% relapse
- « Portal hepatitis » : 50% relapse
- Interface hepatitis : 100% relapse

N.B. 1) histological remission lags behind biochemical remission by 3 -12 months

2) interface hepatitis in 55% of patients with normal ALT and  $\gamma$ globulins

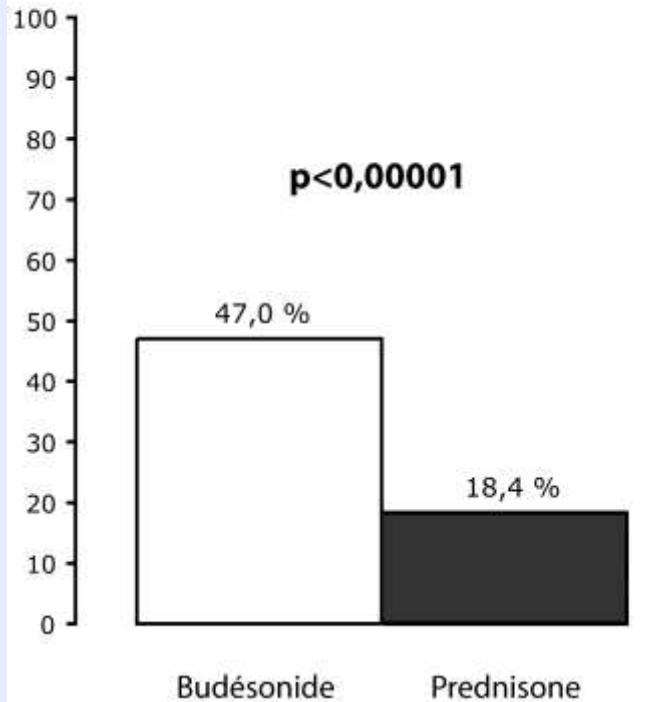
*(Czaja et al. Gastroenterology 1981)*

« Patients should experience a minimum duration of biochemical remission before immunosuppression is terminated after **at least 24 months of therapy** ». *(AASLD Practice Guidelines, Hepatology 2010)*

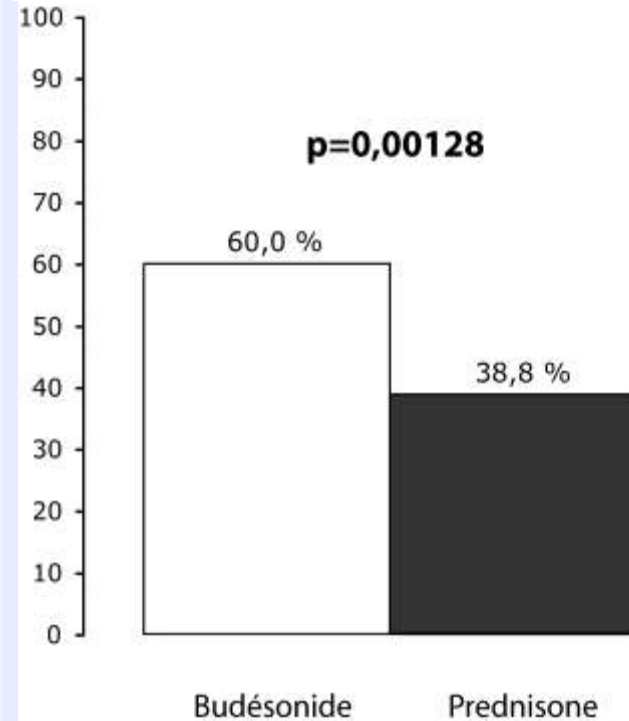
# Budesonide and AIH (1)

Randomized controlled trial Budesonide (9 mg/d) vs Prednisone (40 mg/d), both combined with Azathioprine (1-2 mg/kg/j) (*Manns et al, Gastroenterology 2010*)  
208 non-cirrhotic patients

Normalisation of ALT at 6 months without side effects (intent to treat)



Normalisation of ALT at 6 months (intent to treat)



Sustained remission at 12 months under Budesonide 6 mg/j + AZA  
Switch Prednisone  $\Rightarrow$  Bude M6:  $\downarrow$  40% stéroïds side effects M12

# Budesonide and AIH (2)

- **Negative comments on the trial:**
  - **Bilirubin and IgG: NS**
  - **Low response rate in the Prednisone group**
  - **Long term outcome (histology) ?**
  
- **In clinical practice: Budesonide instead of prednisone**
  - **Initial treatment of non cirrhotic and non severe AIH**
  - **Relative contraindication to steroids**
  - **Steroids side effects (switch)**

**N.B. Cirrhosis - Budesonide: Side effects +++, portal thrombosis(?)**

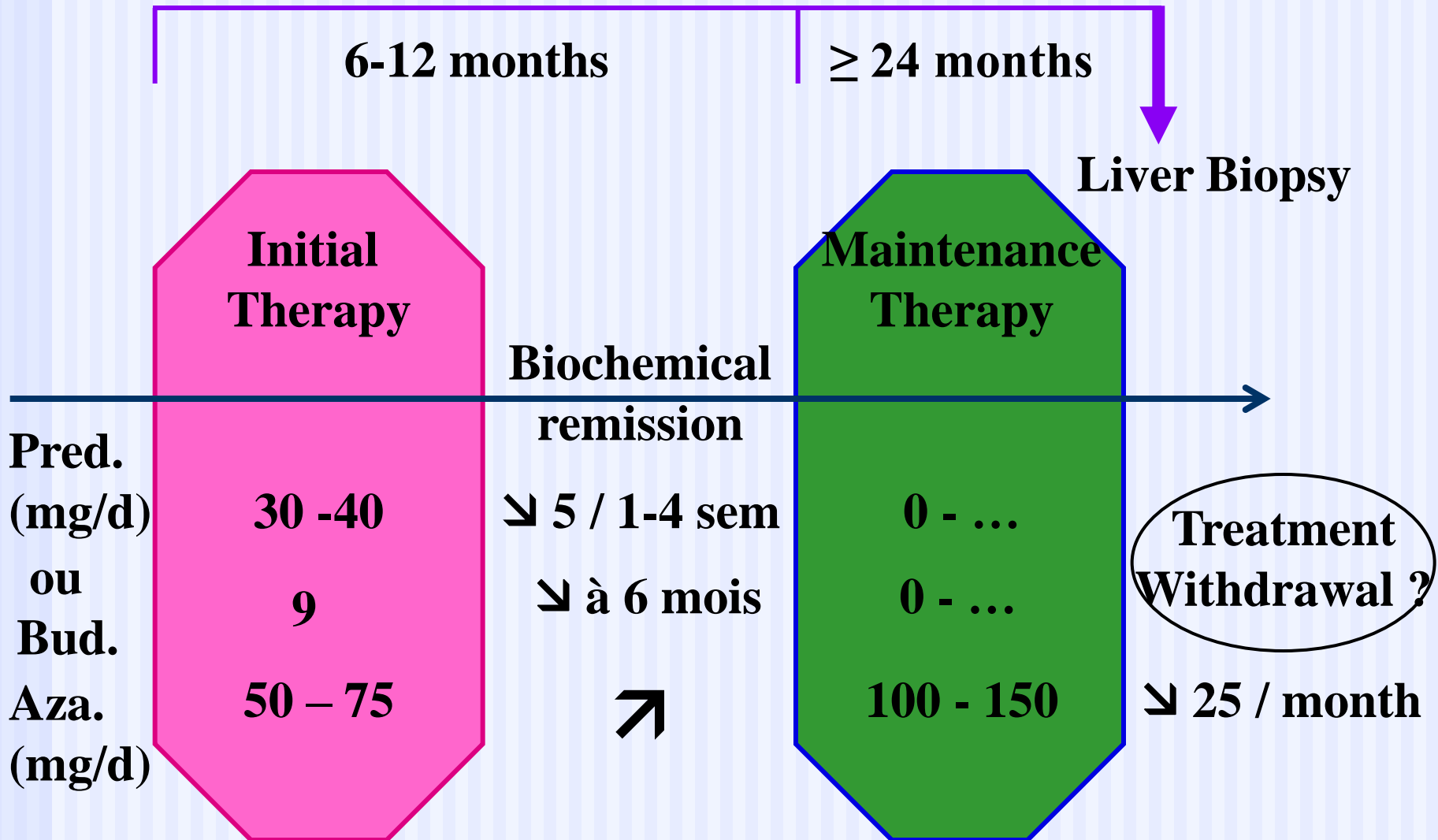
*( Hempfling et al, Hepatology 2003)*

- **Room for Budesonide in maintenance therapy (instead of azathioprine) ?**

# Alternative Treatments (Treatment Failure or Drug Intolerance)

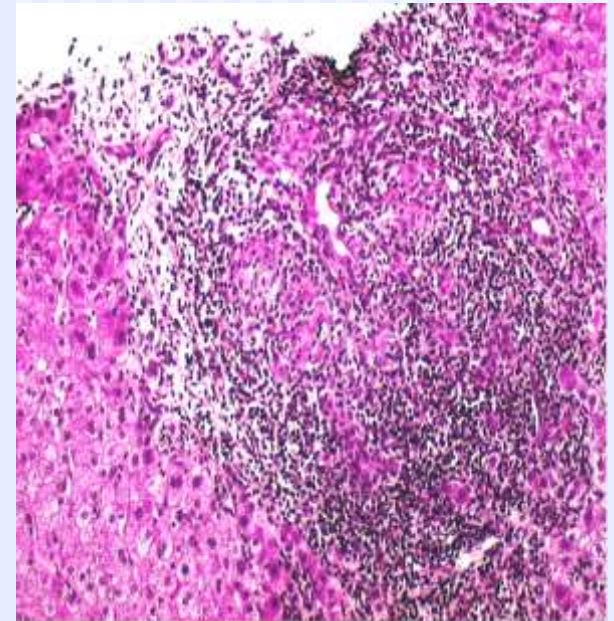
- **Treatment failure:** *AASLD Practice Guidelines, Hepatology 2010*  
High dose prednisone (60 mg/d) or prednisone (30 mg/d)  
in combination with azathioprine (150 mg/d)  
before considering alternative drugs
- **Alternative drugs:**
  - **Cyclosporine:** ++
  - **Mycophenolate mofetil:** mainly in patients intolerant to azathioprine
  - **Others:** tacrolimus, cyclophosphamide, sirolimus, anti-CD20... few data available

# AIH – Usual Treatment Regimens in France

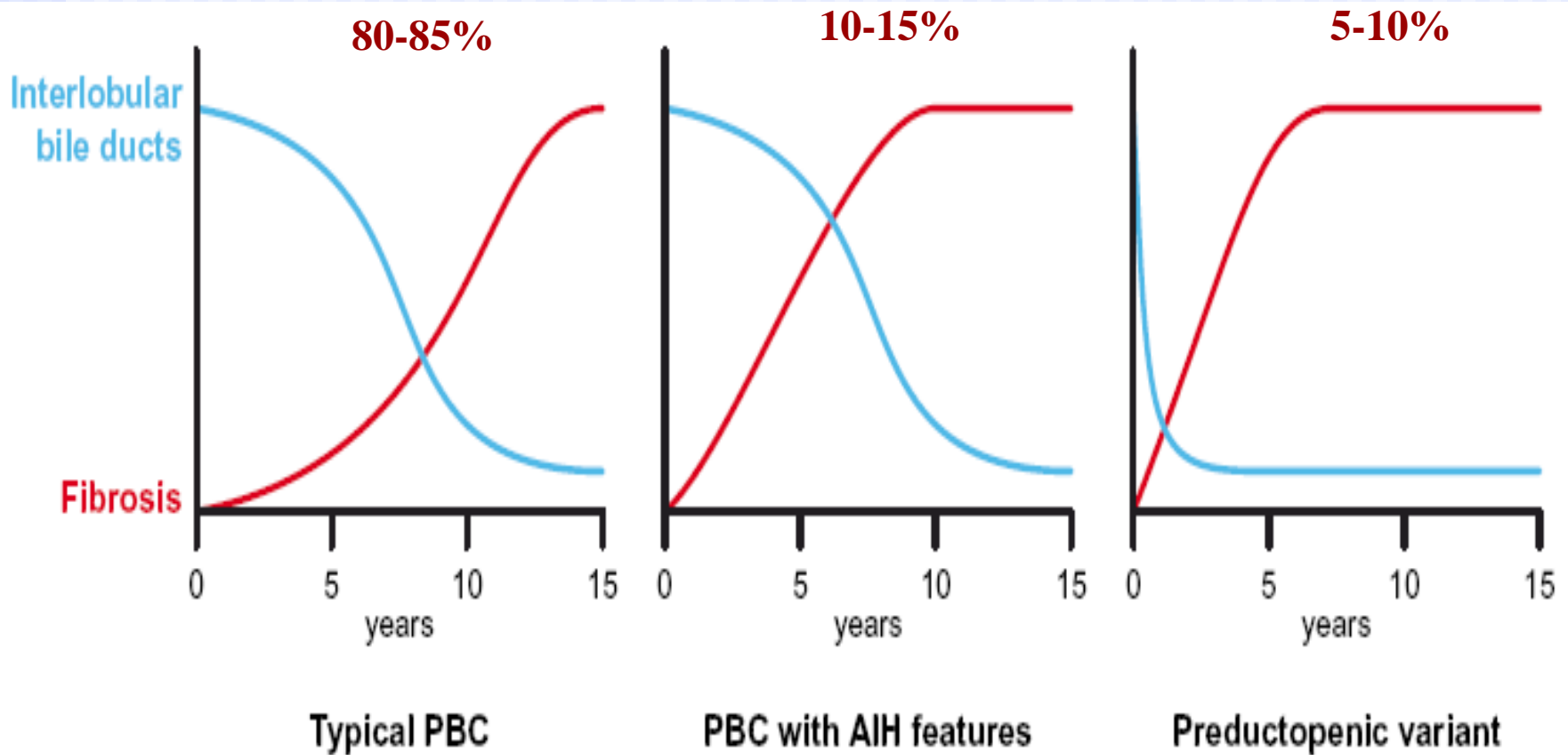


# Primary Biliary Cirrhosis (PBC)

- **Chronic inflammatory autoimmune disease.**
- **Targeting mainly the biliary cells lining the small bile ducts.**
- **Affecting mostly women**



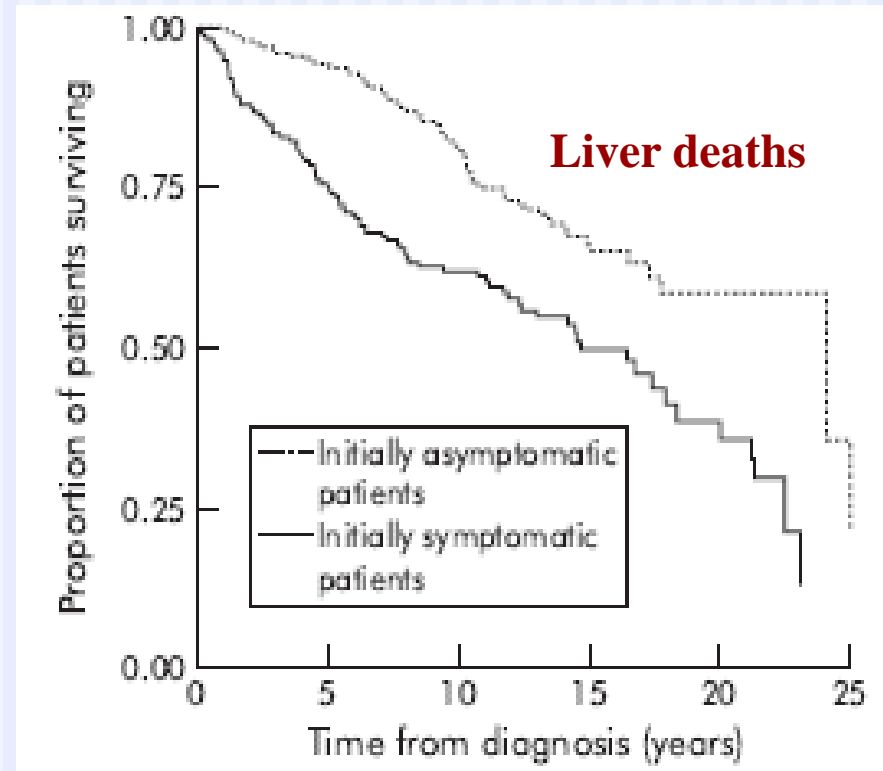
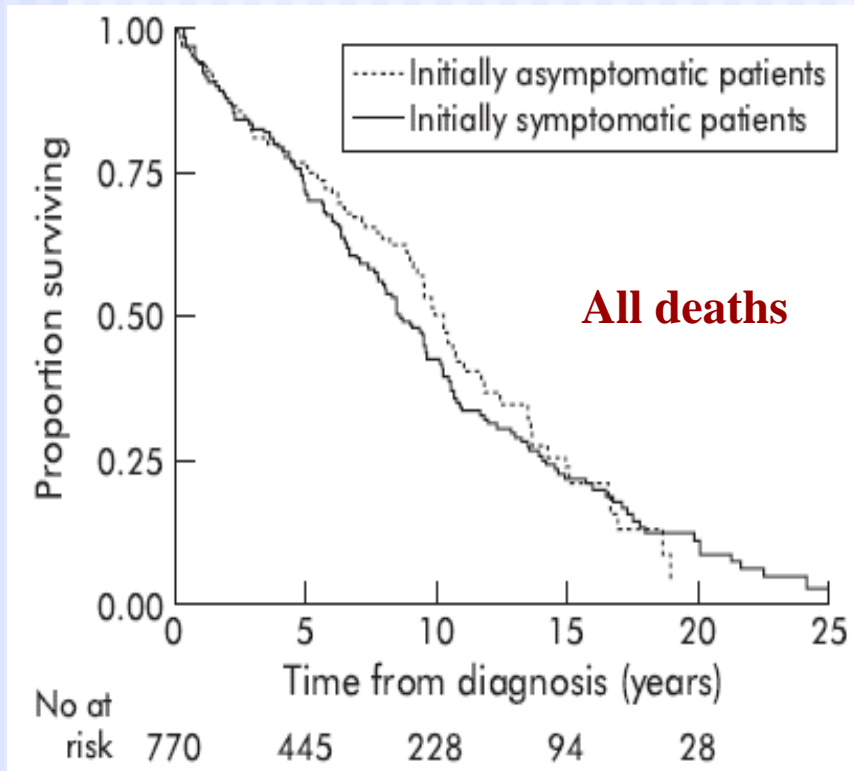
# PBC: 3 Major Forms



*(R Poupon, J Hepatol 2010)*

# PBC: Natural History

Median age at diagnosis: 62 yrs



*(Prince et al, Gut 2004)*

# Natural History of PBC: Prognostic Models

Parameters	Yale	European	Mayo	Glasgow	Oslo	London
Increase in serum bilirubin	+	+	+	+	+	+
Decrease in serum albumin		+	+			+
Increase in PT (INR)			+			
Advanced age	+	+	+	+		+
Hepatomegaly	+					+
Ascites, fluid retention			+	+		+
Esophageal varices						+
Gastrointestinal bleeding				+	+	
Cirrhosis	+	+		+		+
Cholestatic picture at histology		+		+		
Mallory bodies				+		

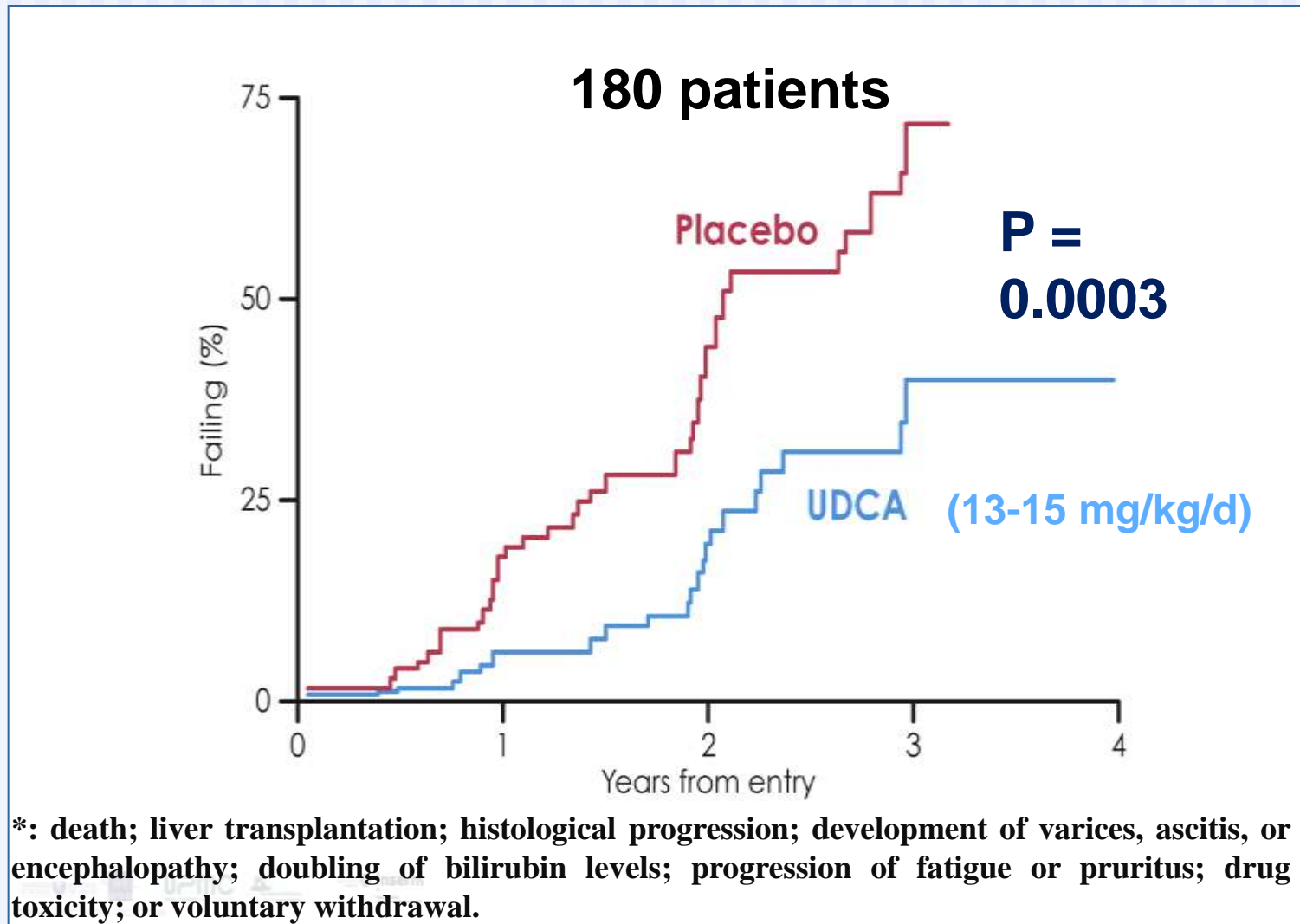
*(Crosignani et al, World J Gastroenterol 2008)*

# PBC Treatment

*UDCA in a dose of 13-15 mg/kg/day orally is recommended for patients with PBC who have abnormal liver enzyme values regardless of histologic stage (Class I, Level A).*

*(AASLD Guidelines, Hepatology 2009)*

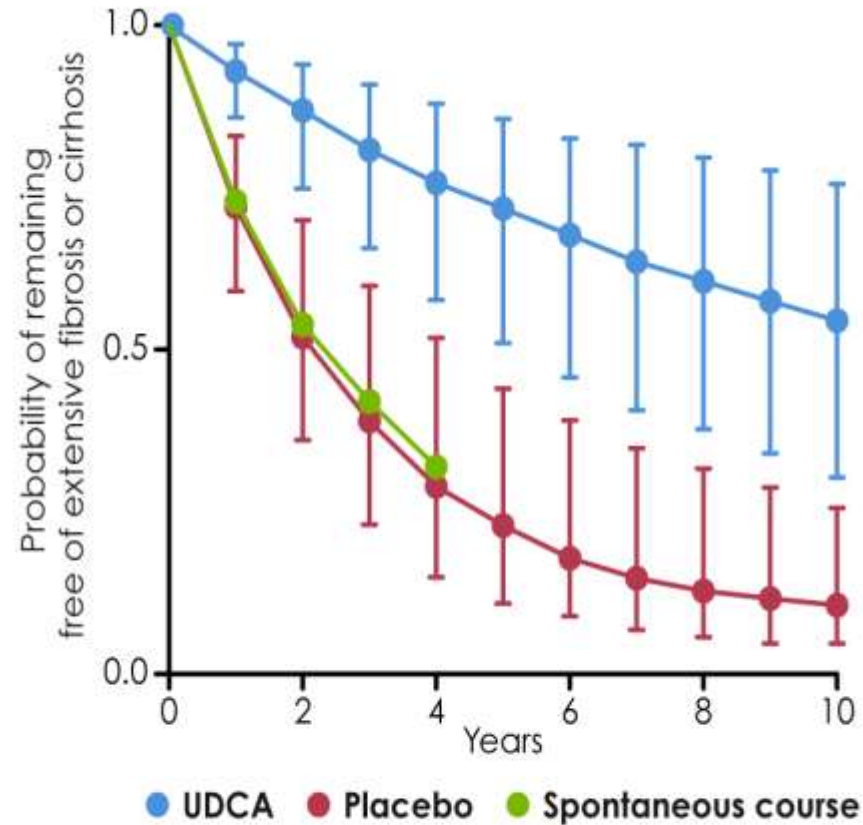
# Mayo UDCA–PBC Trial: Treatment Failure\*



*(Lindor et al, Gastroenterology 1994)*

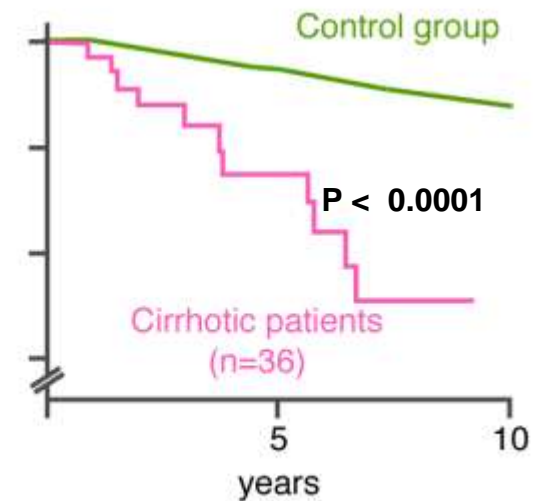
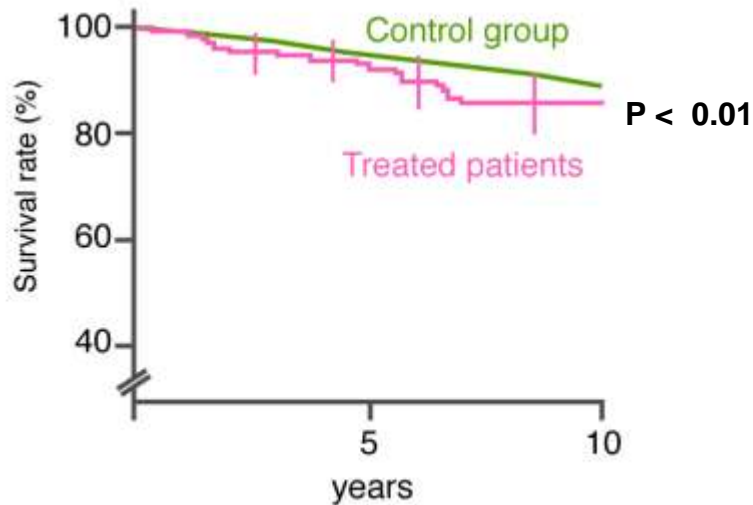
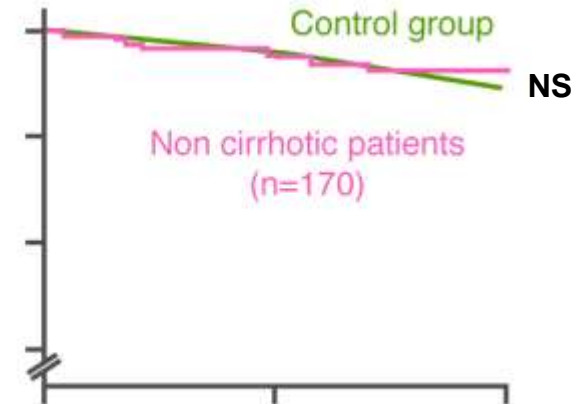
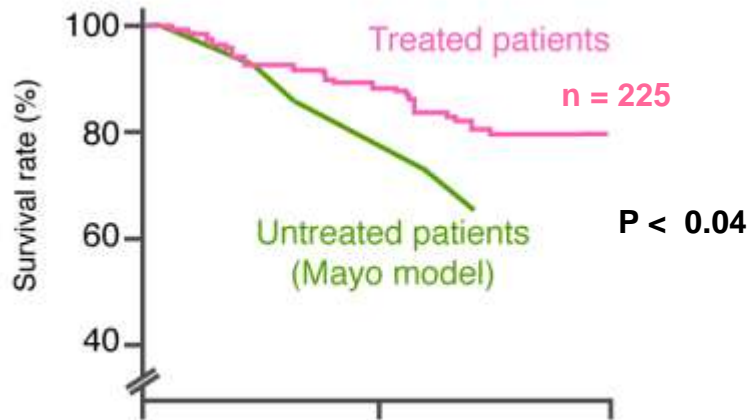
# UDCA and Histological Progression

Markov model, 162 pairs of liver biopsy specimen



*(Corpechot et al, Hepatology 2000)*

# Long-Term Survival in UDCA Treated PBC



*(Poupon et al, Hepatology 1999)*

# Prognostic Factors under UDCA

**Table 5. Multivariate Analysis of Predictive Factors for Death or Liver Transplantation in UDCA-Treated Patients**

Variable	P	Relative Risk (95% CI)
Total serum bilirubin >1 mg/dL*	0.0131	1.7 (1.1-2.6)
Histological stage 3-4*	0.0445	1.5 (1.0-2.2)
Moderate to severe interface hepatitis*	0.0022	1.9 (1.2-2.9)
Absence of biochemical response at 1 year according to the present study's criteria†	<0.0001	2.3 (1.5-3.7)

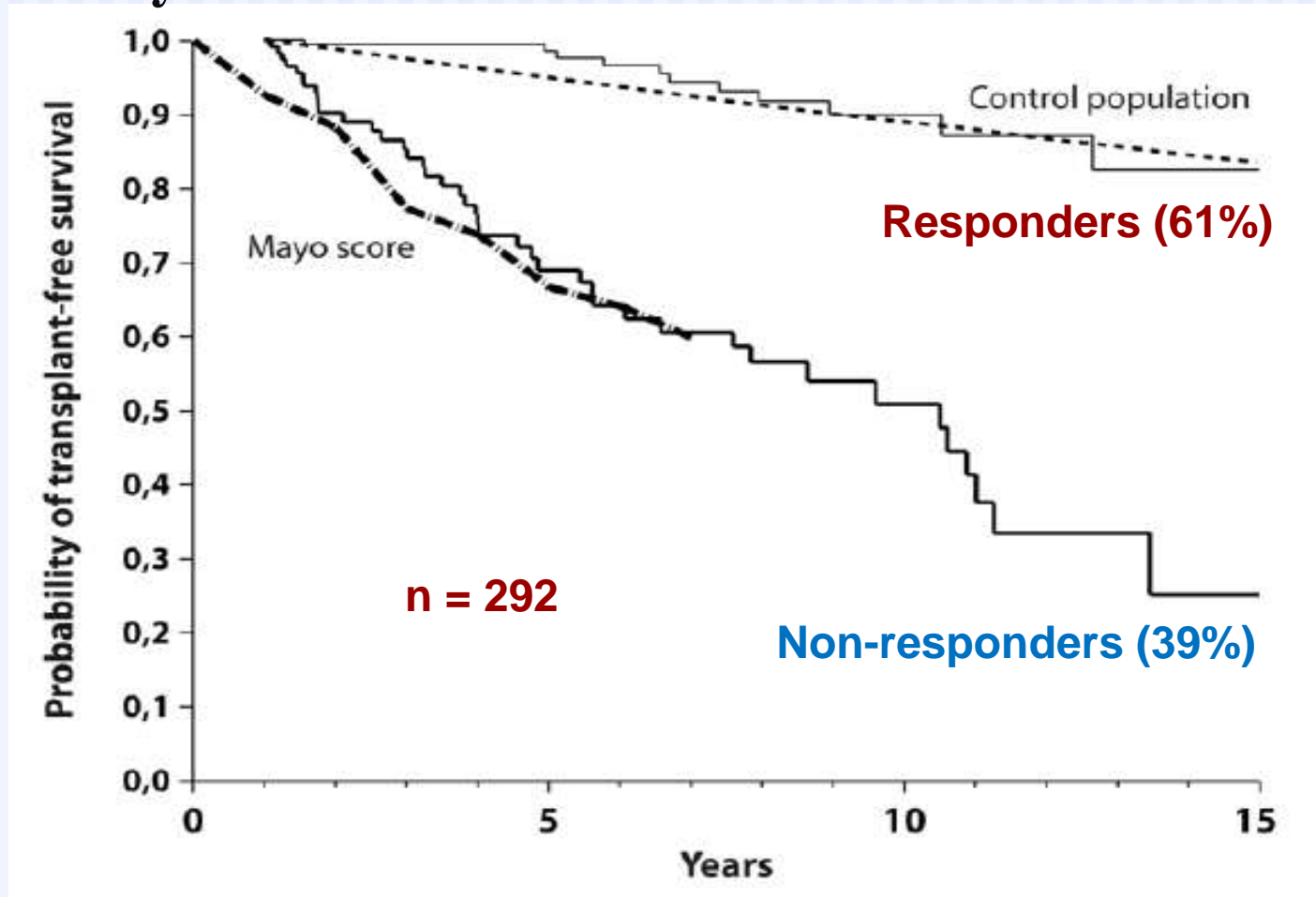
\*At the onset of treatment. †Total serum bilirubin >1 mg/dL, or ALP >3 ULN, or AST >2 ULN.

*(Corpechot et al, Hepatology 2008)*

# Biochemical Response to UDCA

Definition of biochemical response:

$ALP \leq 3 \text{ ULN}$ ,  $AST \leq 2 \text{ ULN}$  and  $bilirubin \leq 1 \text{ mg/dL}$   
after 1 year of treatment



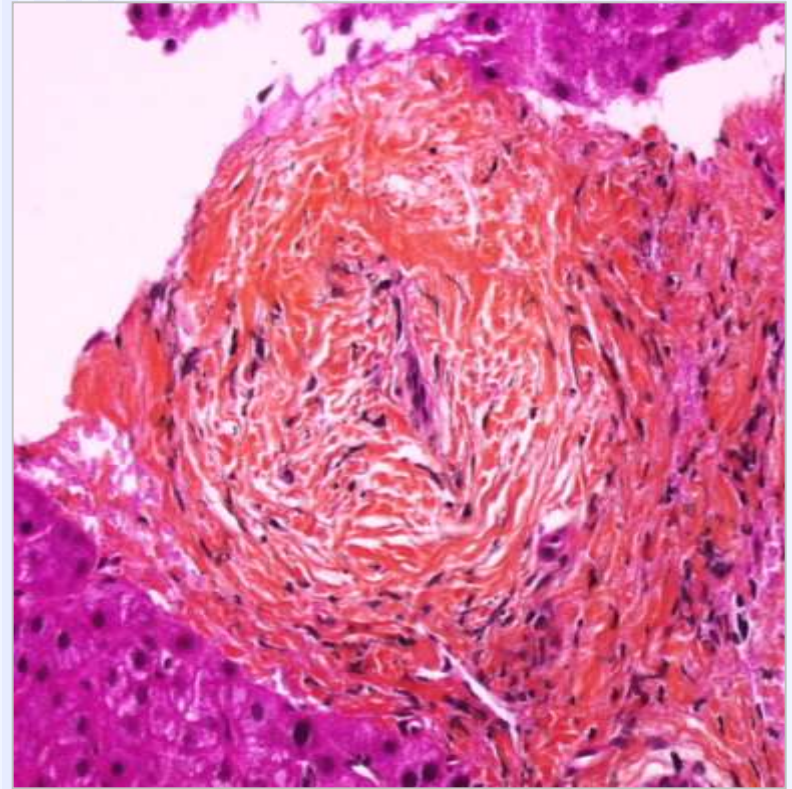
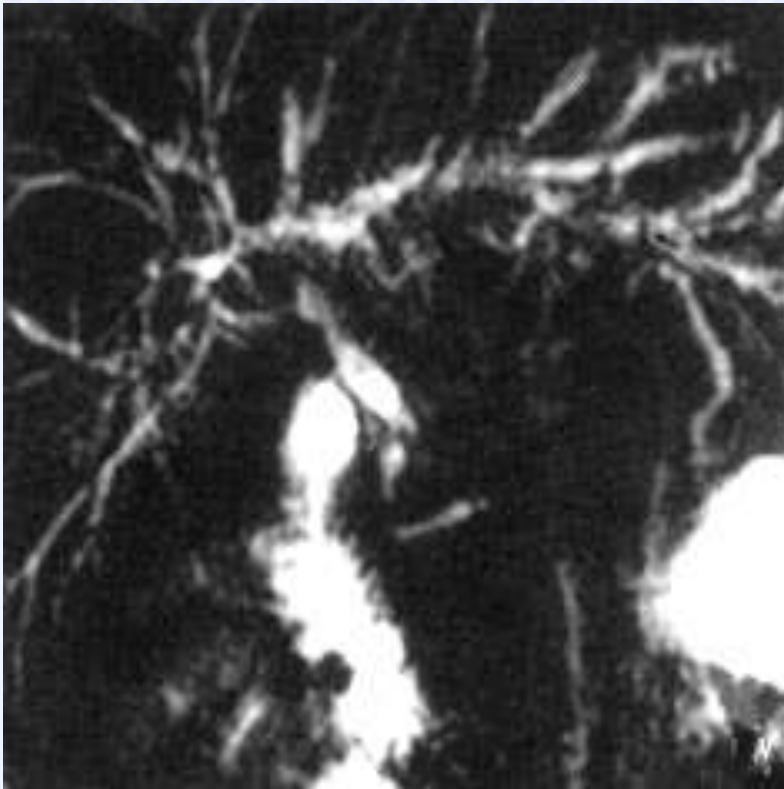
*(Corpechot et al, Hepatology 2008)*

# Patients with Incomplete Response to UDCA: Propositions

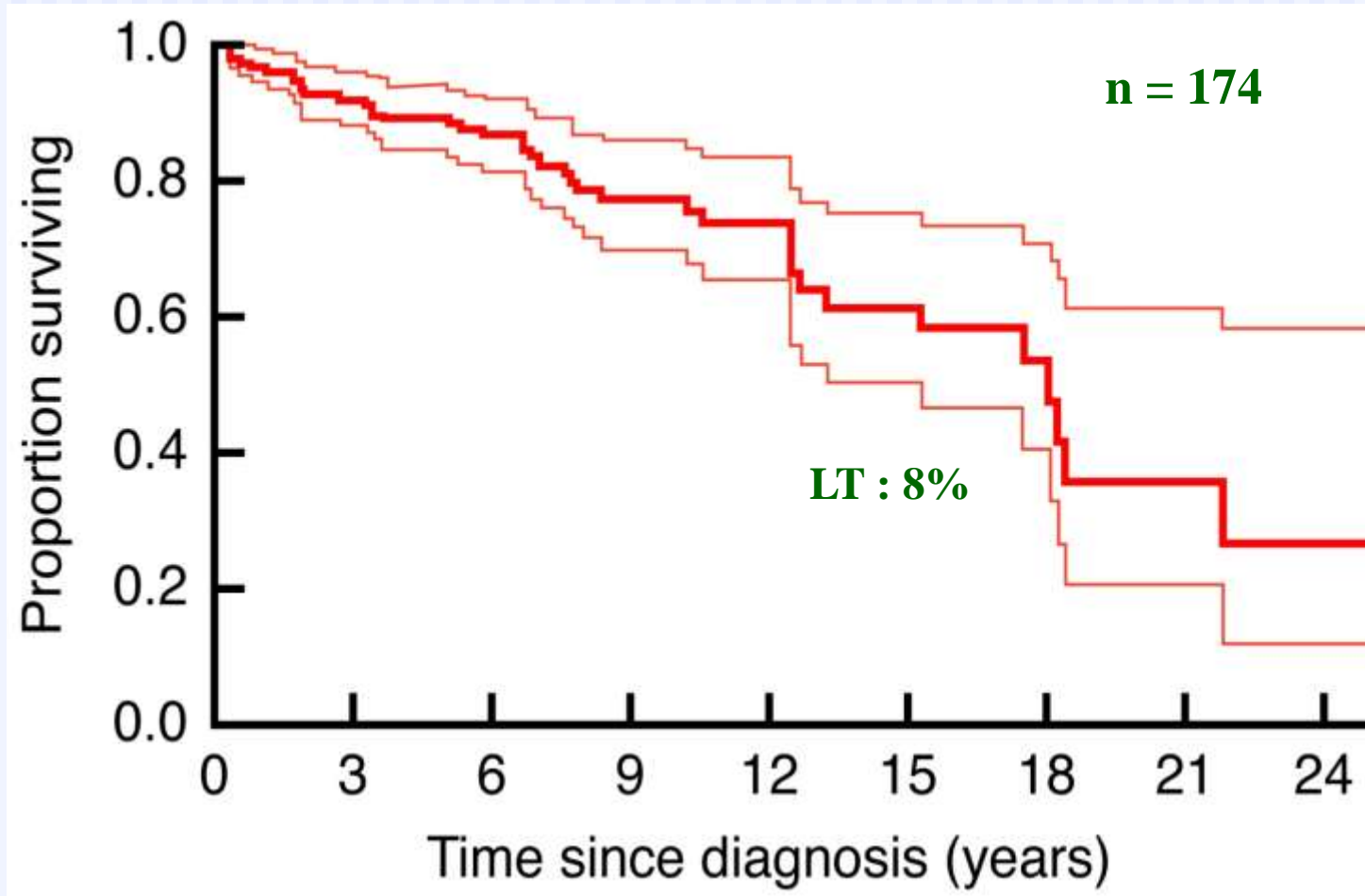
- **No validated recommendations**
- **↑ UDCA dosage ? (if UDCA < 40% total serum bile acids)**
- **Saint-Antoine policy in patients with significant interface hepatitis (not fulfilling overlap criteria):**
  - Budesonide (3-6 mg/day) (in non-cirrhotic patients)**
  - ± Mycophenolate mofetil (1-1.5 g/day)**
- **Emerging treatments:**
  - **FXR agonists: obeticholic acid**
  - **PPAR $\alpha$  agonists: fibrates**

# Primary Sclerosing Cholangitis (PSC)

**Inflammation and fibrosis of both intra and extrahepatic bile ducts**

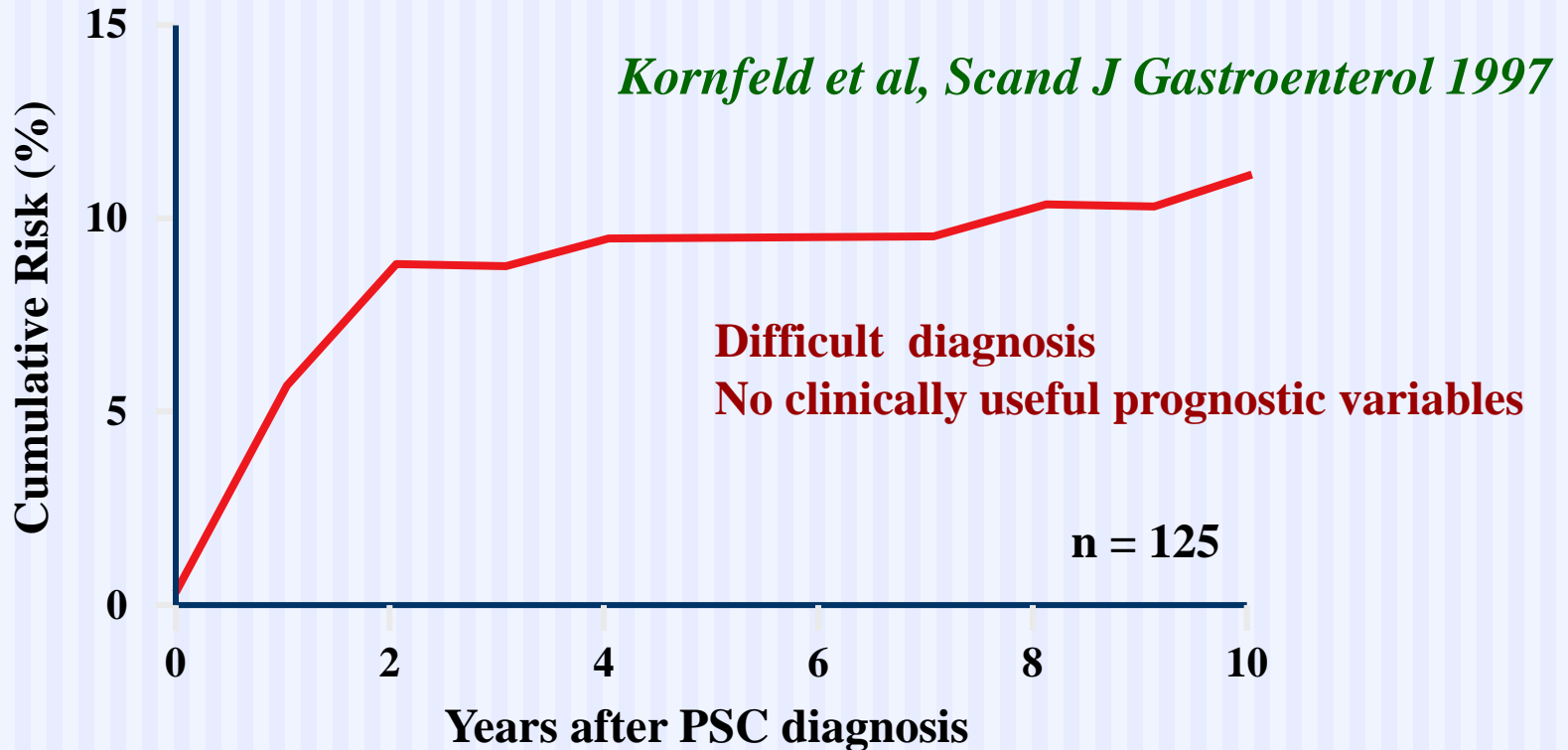


# PSC: Natural History



*(Ponsioen et al, Gut 2002)*

# PSC and Cholangiocarcinoma



**1 yr after diagnosis of PSC:**

- hepatobiliary malignancy: 1,5% /yr (n = 604) (*Bergquist et al, J Hepatol 2002*)
- cholangiocarcinoma: 0,6% /yr (n = 161) (*Burak K et al, Am J Gastroenterol 2004*)

# Prognostic Models

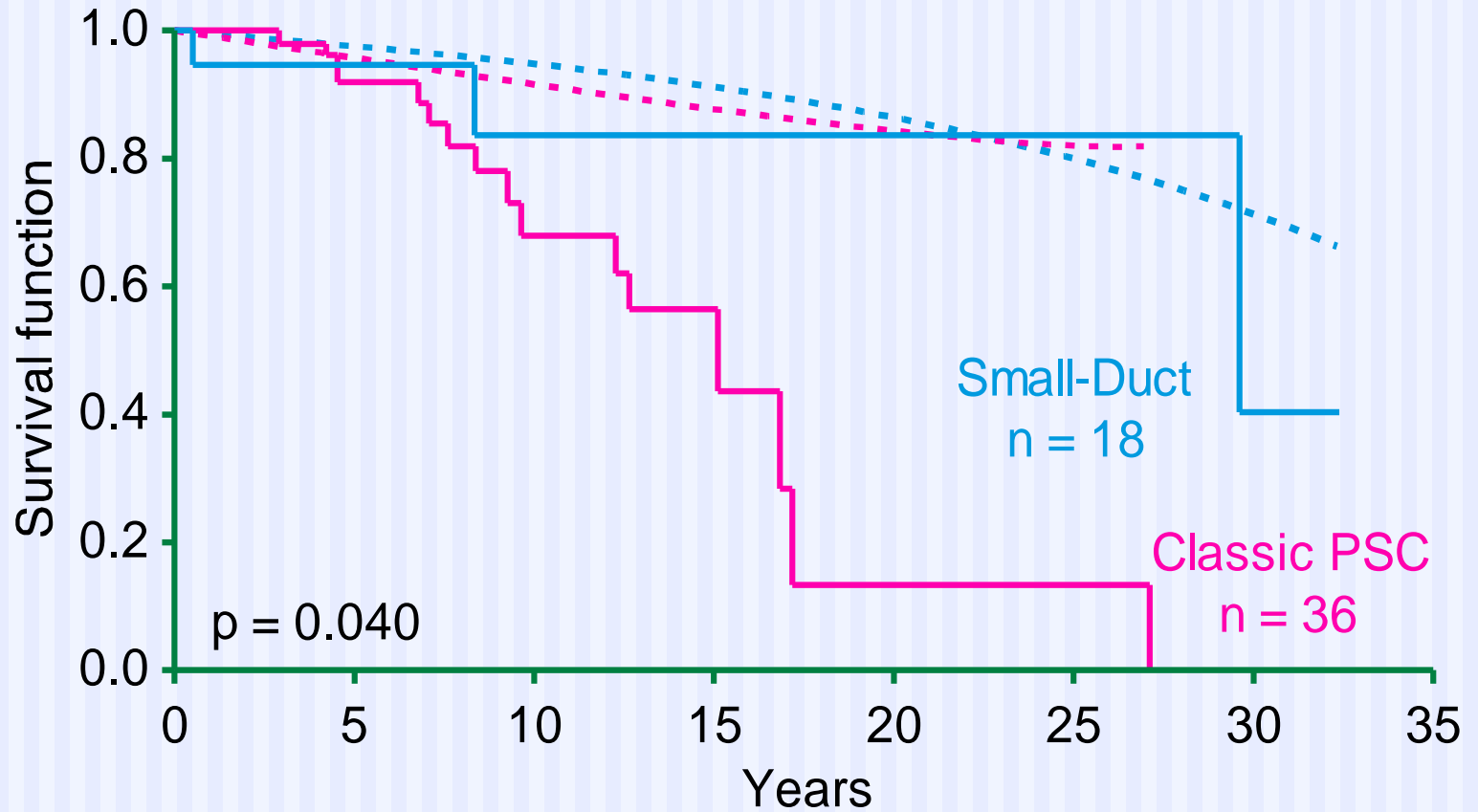
**Main prognostic factors:**

- ♠ age, serum bilirubin,
- ♠ histological staging +/- cholangiographic scoring

*27. In patients with PSC, we recommend against the use of prognostic models for predicting clinical outcomes in an individual patient as no consensus exists regarding the optimal model (1B).*

*(AASLD Guidelines, Hepatology 2010)*

# Small Duct PSC (5 - 10%)



*(Angulo et al, Hepatology 2002)*

→ **25% large duct PSC at 10 yrs**

**No cholangiocarcinoma**

# Immunoglobulin G4 Associated Cholangitis: Description of an Emerging Clinical Entity Based on Review of the Literature

Einar Björnsson,<sup>1</sup> Suresh T. Chari,<sup>2</sup> Thomas C. Smyrk,<sup>2</sup> and Keith Lindor<sup>2</sup>

*(Hepatology 2007)*

## ■ Main characteristics :

- Pancreatic involvement (inconstant)
- Abrupt jaundice, Age > 50 yrs
- IBD unfrequent
- ↑ IgG4 (not always !)
- Steroid responsiveness +++



# Treatment of PSC

- **Liver transplantation is the only therapy of proven efficacy**
- **Specific therapy:**
  - **UDCA ?**
  - **Endoscopic therapy ?**

# PSC and Endoscopic Therapy

**No randomized controlled studies**

*7. In patients with dominant strictures from PSC, we recommend initial management with endoscopic dilatation with or without stenting (1B).*

*(AASLD Guidelines, Hepatology 2010)*

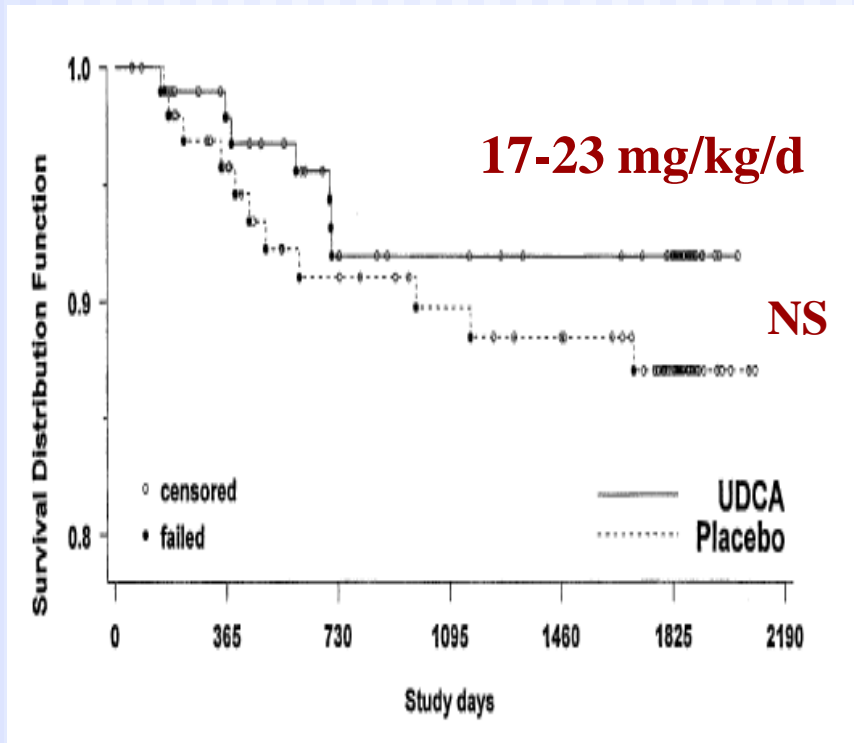
Cholestasis in patients with PSC does not seem to be related to the presence of DS. Endoscopic therapy of DS should not be routinely undertaken and randomized studies are needed to clarify its potential benefits.

*(Björnsson et al, Am J Gastroenterol 2004)*

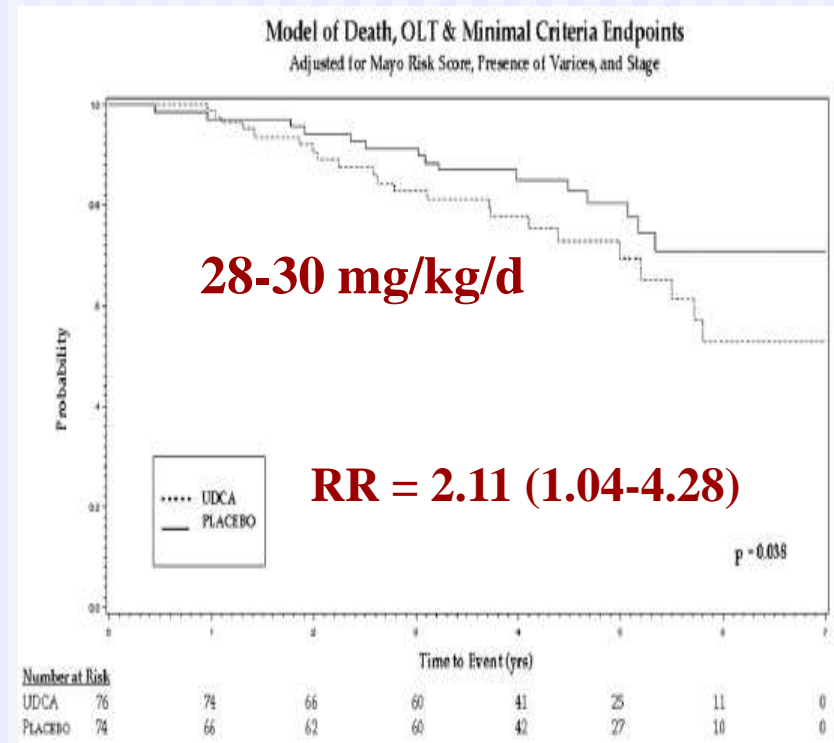
**⇒ Current policy: careful selection  
(no disseminated intrahepatic changes)**

# UDCA and PSC (1)

- Role for slowing PSC progression unclear



*(Olsson et al, Gastroenterology 2005)*



*(Lindor et al, Hepatology 2009)*

## UDCA and PSC (2)

The available data base shows that UDCA (15–20 mg/d) improves serum liver tests and surrogate markers of prognosis (I/B1), but does not reveal a proven benefit on survival (III/C2). **The limited data base does not yet allow a specific recommendation for the general use of UDCA in PSC.**

*(EASL Guidelines, J Hepatol 2009)*

*28. In adult patients with PSC, we recommend against the use of UDCA as medical therapy (1A).*

*(AASLD Guidelines, Hepatology 2010)*

**Current policy in France:**

- ♣ portal hypertension or extensive fibrosis: UDCA 8-15 mg/kg/d
- ♣ other cases: UDCA 20 mg/kg/d

**very high doses (28–30 mg/kg/d) should not be used**

# PBC/PSC-AIH Overlap Syndrome (PBC/PSC with AIH Features)

**Standardization of diagnostic criteria not achieved**

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

---

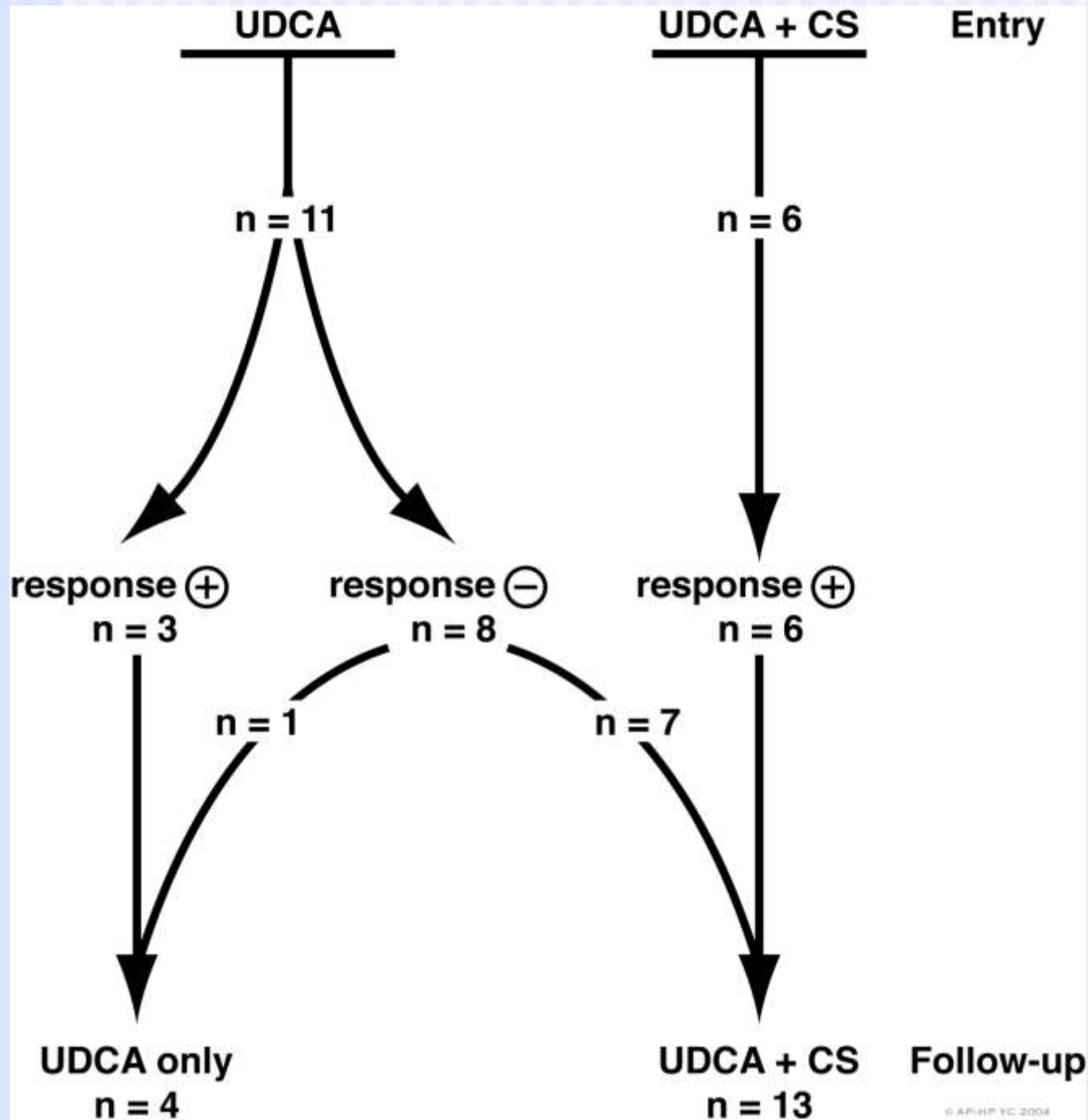
*PBC criteria*

1. AP  $>2\times$  ULN or  $\gamma$ GT  $>5\times$  ULN
2. AMA  $\geq 1:40$
3. Liver biopsy specimen showing florid bile duct lesions

*AIH criteria*

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

*(EASL Guidelines, J Hepatol 2009)*



Suivi: 7,5 ans

F ↑:

UDCA: 4/8

UDCA + CS: 0/6

P = 0.04

*(Chazouillères et al,  
J Hepatol 2006)*

# Treatment of Overlap Syndromes

Combined therapy with UDCA and corticosteroids is the recommended therapeutic option in patients with **PBC–AIH overlap syndrome** (III/C2).

*(EASL Guidelines, J Hepatol 2009)*

*29. In adult patients with **PSC and overlap syndrome**, we recommend the use of corticosteroids and other immunosuppressive agents for medical therapy (1C).*

*(AASLD Guidelines, Hepatology 2010)*

# Conclusions

## Specific Treatments:

- **High efficacy:**
  - **AIH (steroids, immunosuppressors)**
  - **Early PBC (UDCA)**
  
- **Poor efficacy:**
  - **PSC (UDCA, endoscopy)**
  - **Advanced PBC (UDCA)**

**Liver transplantation (non specific):**

**High efficacy**

**Potential recurrence**