

*6. HepNet Symposium  
Hannover, 5. Juni 2009  
Klinische Hepatologie – Aktuelle Aspekte*


# PSC: Pathomechanismen und Therapeutische Konsequenzen

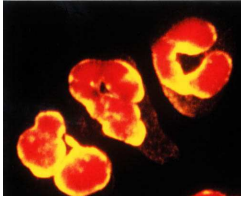
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Univ. Klinik für Innere Medizin



# Herausforderungen bei PSC

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- Pathomechanismen unklar (multifaktoriell?)
  - Heterogenes KH-Bild (Sub-Entitäten?)
  - Keine effektive medikamentöse Therapie
  - Malignomrisiko (Präcancerose)



Immunological Mechanisms

Atypical pANCA  
T-cell Infiltrates  
"Immune Gene" Polymorphisms (HLA, non-HLA)

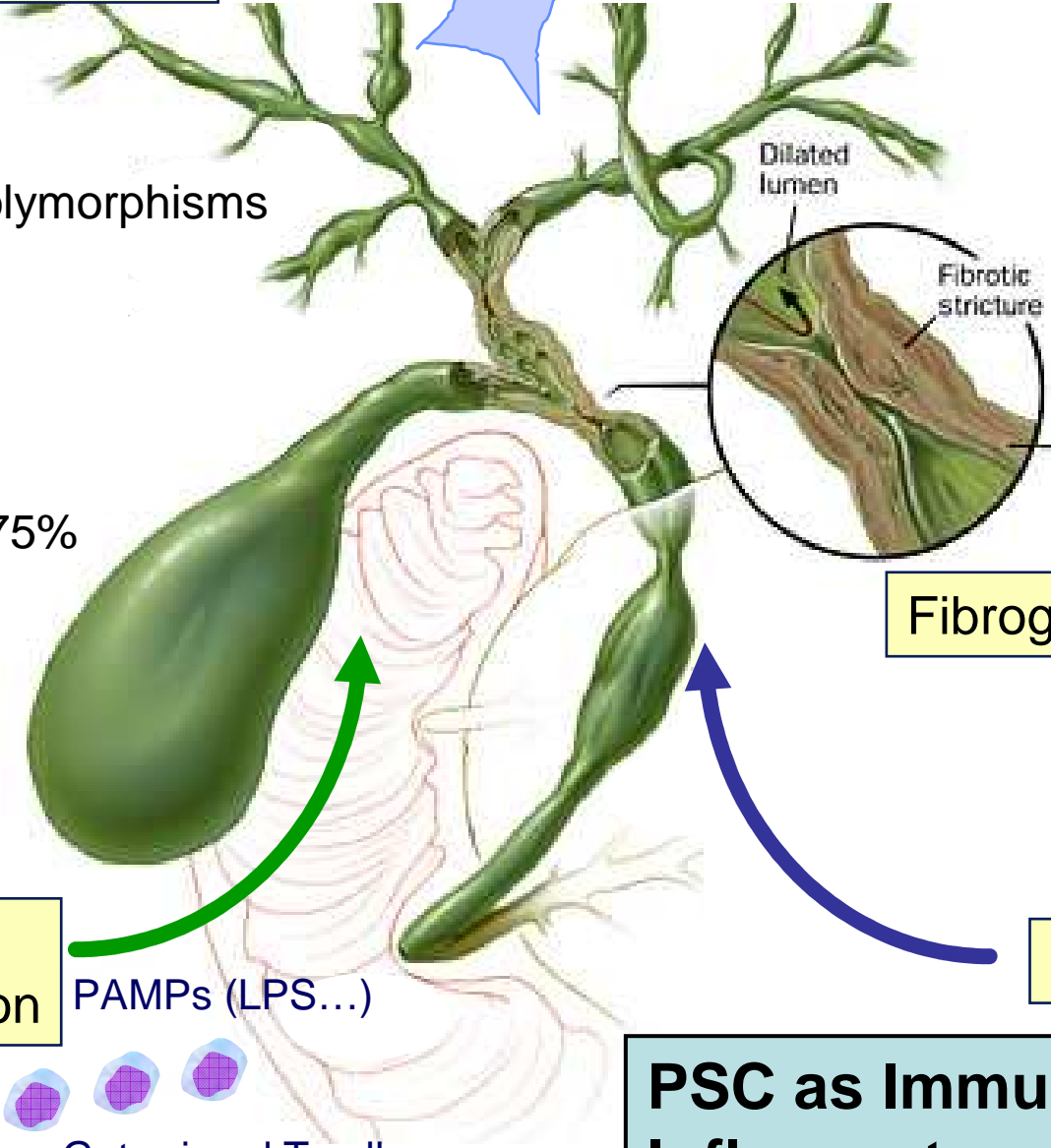


Cytokines

CFTR, MDR3  
PXR/SXR

Transport Defects

Toxic Bile



4-7% ↔  
↔ ~75%



IBD

Intestinal Translocation

PAMPs (LPS...)



Gut-primed T cells

Fibrogenesis

Ischemia

**PSC as Immune-mediated Inflammatory "Disease"**

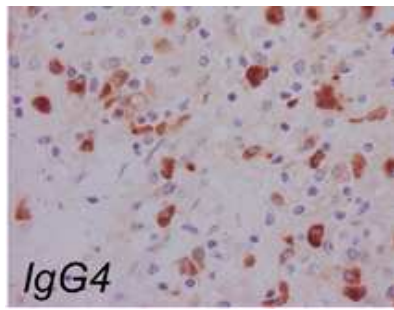
# Small Duct PSC?

Immunological Mechanisms

Cytokines

Transport Defects

Toxic Bile

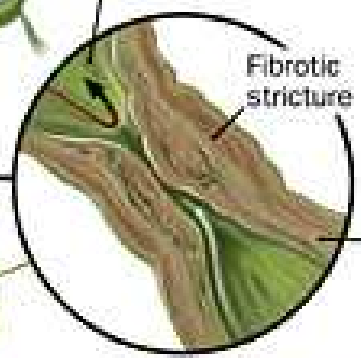


IgG4-assozierte Cholangitis



Intestinal Translocation

PAMPs (LPS...)  
Gut-primed T cells



Fibrogenesis

Ischämische Cholangitis (NAS, Sepsis, ICU...)

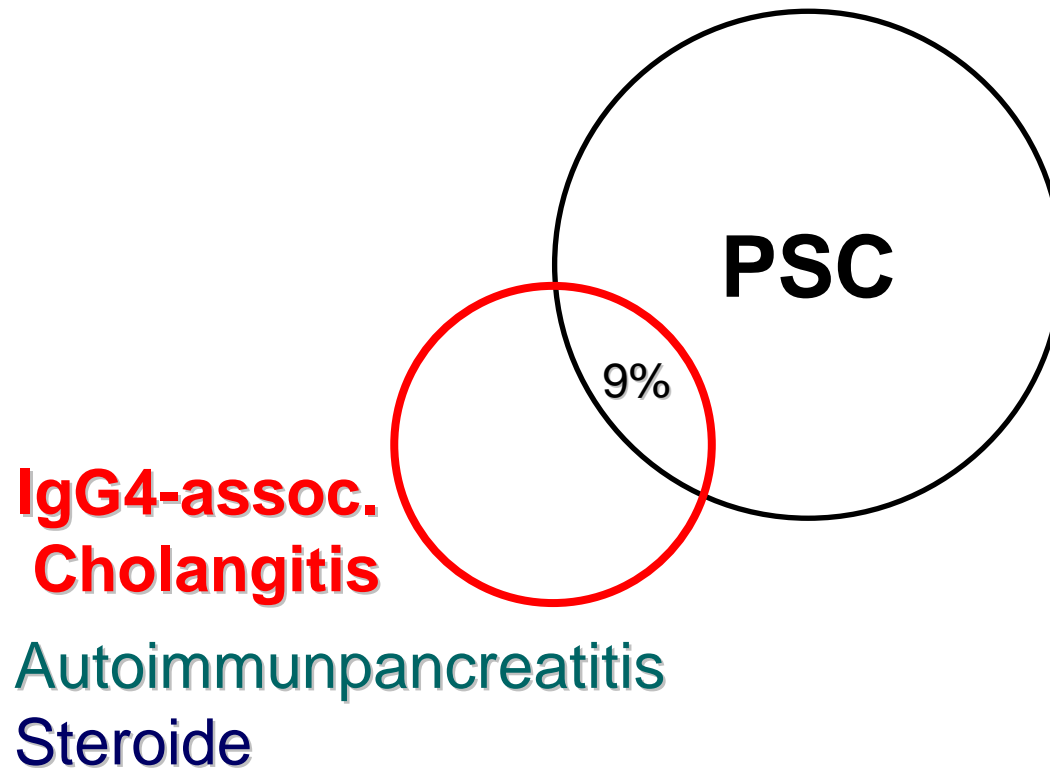
Ischemia

The Many Faces of Sclerosing Cholangitis

# Pathogenese & Verlauf: Neue Aspekte

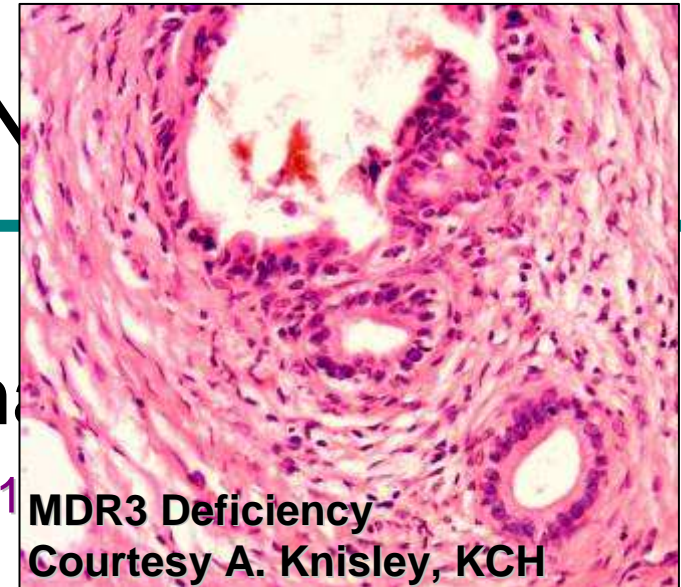
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- IgG4-medierte Immunmechanismen?
  - In bis zu 9% bei PSC erhöht <sup>1</sup>



# Pathogenese & Verlauf: N

- IgG4-medierte Immunmechanismen
  - In bis zu 9% bei PSC erhöht <sup>1</sup>
- Transporter Gen-Polymorphismen?
  - *MDR3*: Suszeptibilität & Progression <sup>2</sup>
  - *CFTR*: sogar Schutz? <sup>3</sup>
- Progression Small Duct → Large Duct PSC
  - Häufiger als vermutet (23% / 7.4 J) <sup>4</sup>



1: Mendes et al., *Am J Gastro* 2006; 101: 2070

2: Melum et al., *Hepatology* 2007; 46: 265A

3: Henckaerts et al., *J Hepatol* 2009; 50 :150

4: Björnsson et al. *Gastro* 2008; 134: 975

# PSC: Pathomechanismen → Rx

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- Immunologisch → ~~Immunsuppressiva~~
- „Gut-derived“ → ~~Rx d. CED, ABx~~
- Vaskulär → Angiogenese?
- Toxische Galle → UDCA?

# Treatment of PSC with UDCA

## Placebo - Controlled Trials

	Beuers (n=14)	Stiehl (n=20)	Lindor (n=105)	Mitchell (n=26)	Olsson (n=110)
Dose (mg/kg/d)	13 -15	10 -12	13 -15	20	17-23
Serum liver tests	+	+	+	+	⊖
Histology	(+)	(+)	⊖	+	
Cholangiography				+	⊖
Survival			⊖		⊖

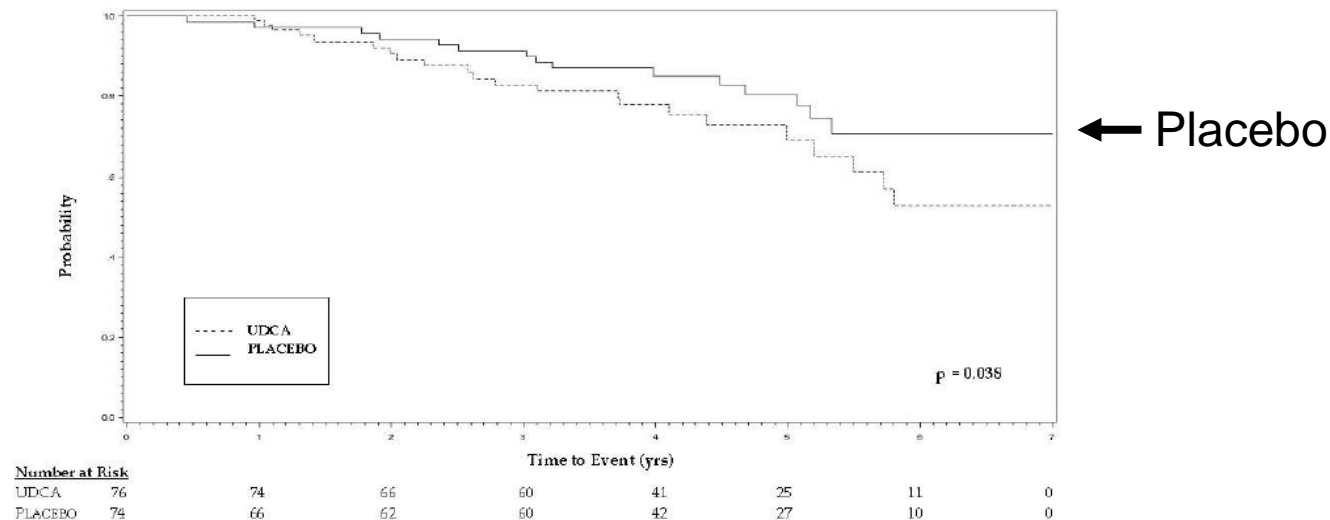
# High-dose UDCA in PSC

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- Pilot study promising (30 mg/kg/d, 2 y)<sup>1</sup>
  - Biochemistry, Mayo risk score improved
- Recent RCT (28-30 mg/kg/d, 3 y) negative<sup>2</sup>
  - 76 vs. 74 pts
  - Biochemistry improved
  - Varices, histological progression RR x 2.2
  - Death, transplant RR x 3.3

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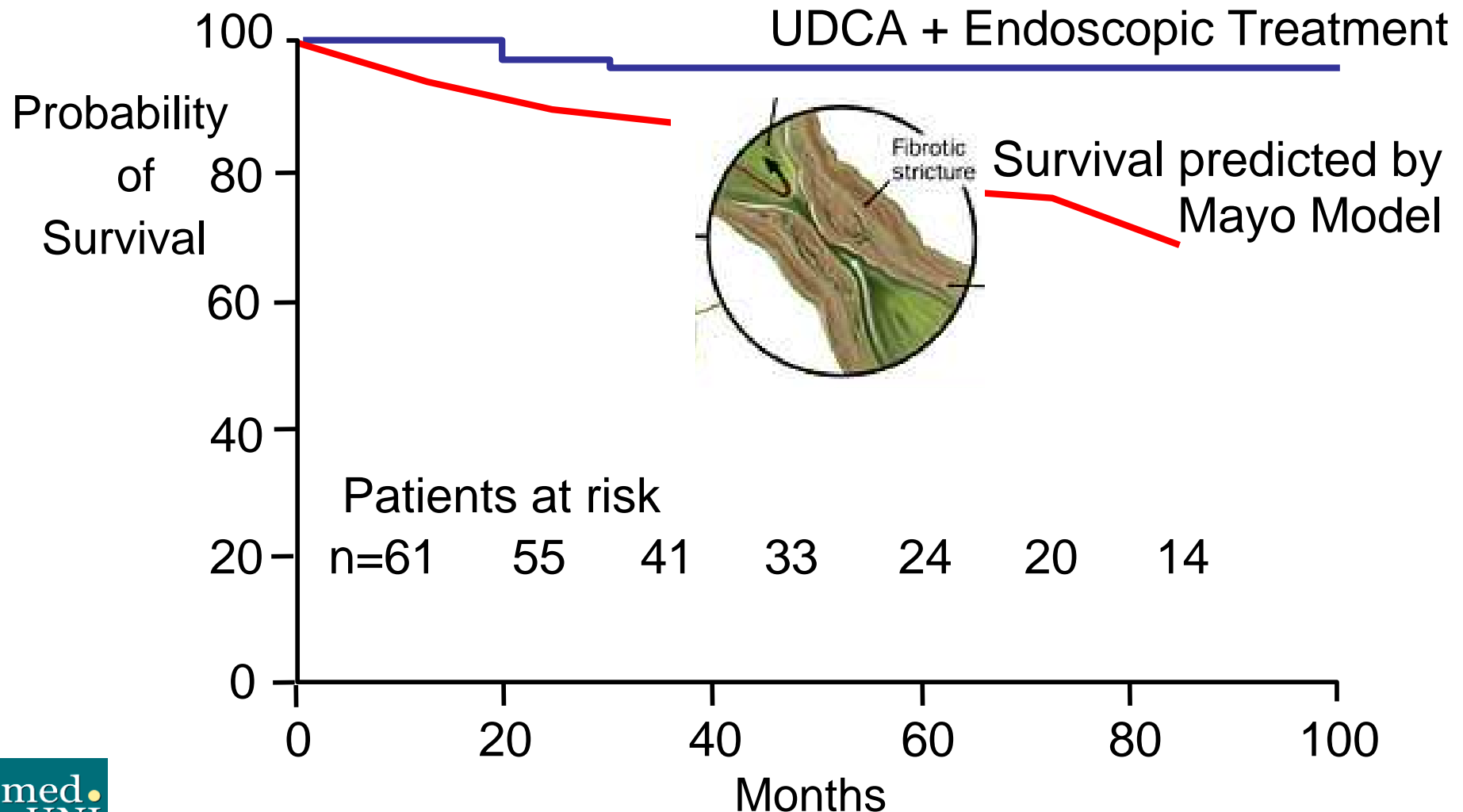
Kaplan Meier curve showing time to death or transplant

# EASL Clinical Practice Guidelines

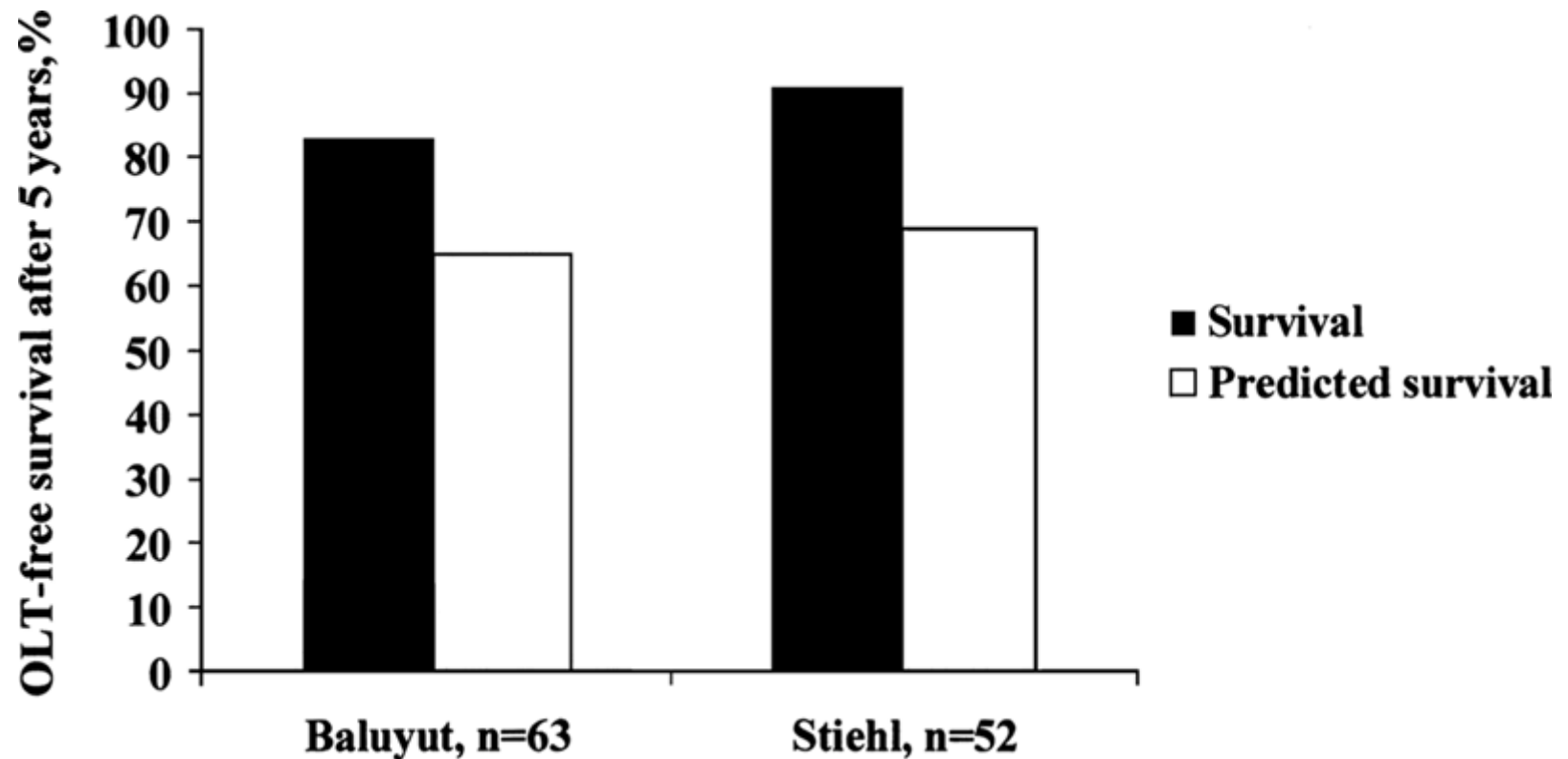
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- The limited data base **does not yet allow** a specific **recommendation for the general use of UDCA** in PSC.
- Currently there is suggestive but limited evidence for the use of **UDCA for chemoprevention** of colorectal cancer in PSC (...particularly **high-risk groups**...).
- **Corticosteroids and other immunosuppressants are not indicated** for treatment of PSC.

# UDCA Combined with Endoscopic Treatment of Strictures Improves Survival of Patients with PSC



# Endoscopic Treatment (Combined with UDCA) Improves Survival of Patients with PSC

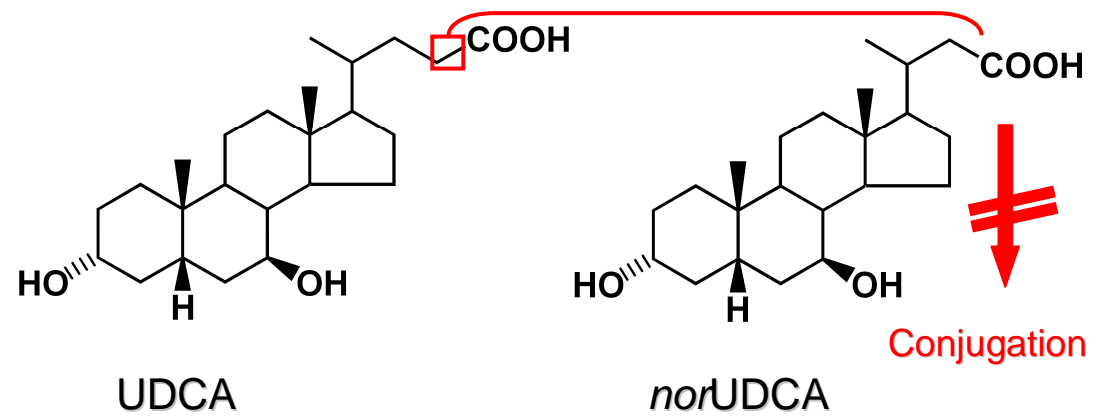
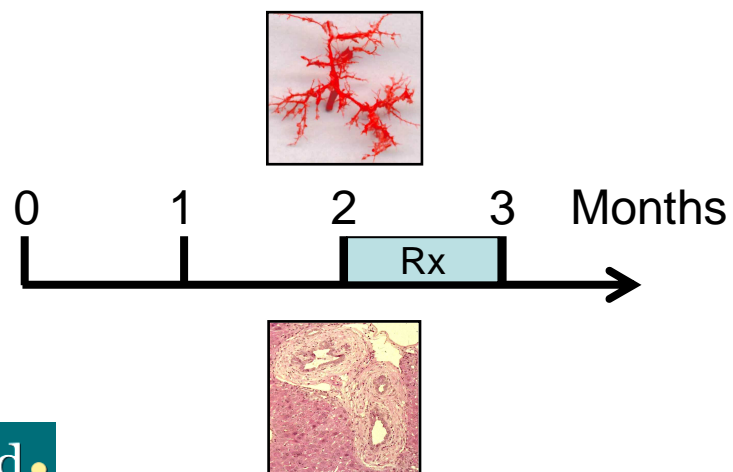
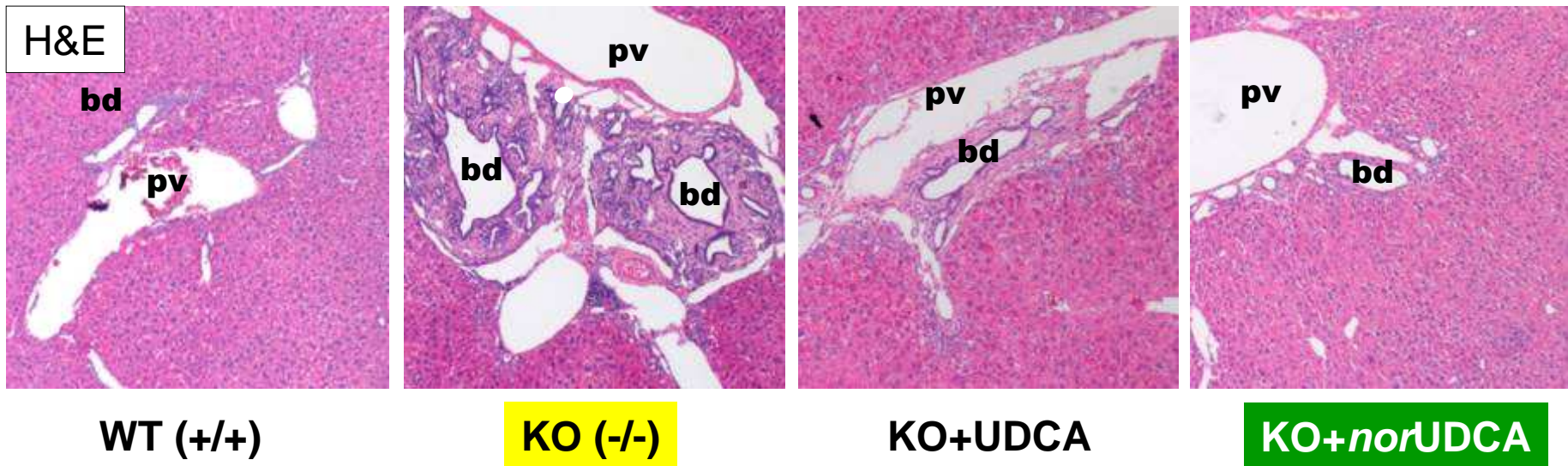


# EASL Clinical Practice Guidelines

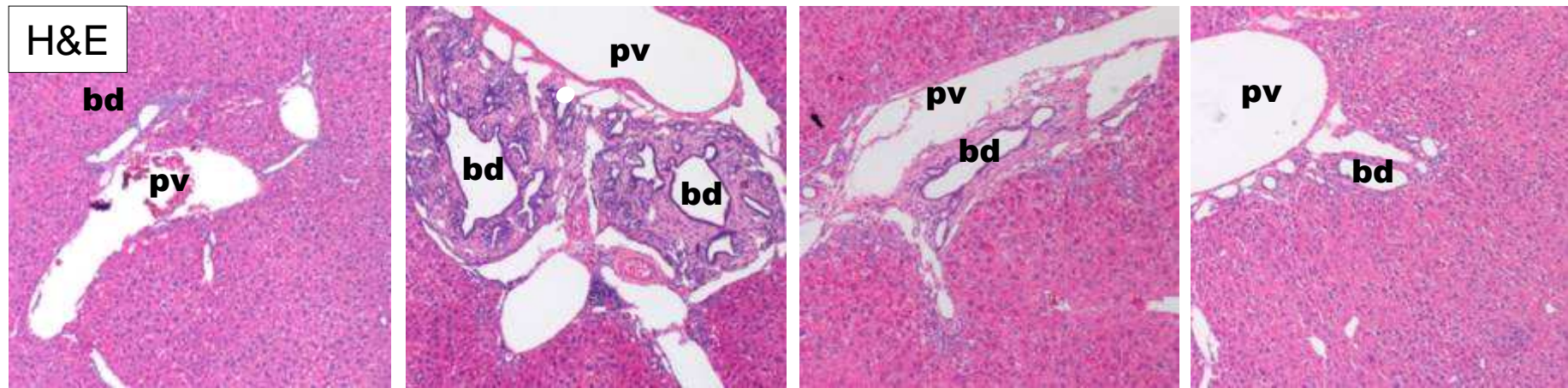
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- **Dominant bile duct strictures** with significant cholestasis should be treated with **biliary dilatation**.
- Biliary **stent insertion** should be **reserved** for cases where stricture dilatation is unsatisfactory.
- **Prophylactic antibiotic** coverage is recommended.
- **Liver transplantation** is recommended in patients with **late-stage PSC**.
- May be considered in patients with evidence of **cholangiocyte dysplasia** or severe **recurrent bacterial cholangitis**.

# *nor*UDCA Reverses Sclerosing Cholangitis in *Mdr2*<sup>-/-</sup> (KO) Mice



# *nor*UDCA Reverses Sclerosing Cholangitis in *Mdr2*<sup>-/-</sup> (KO) Mice

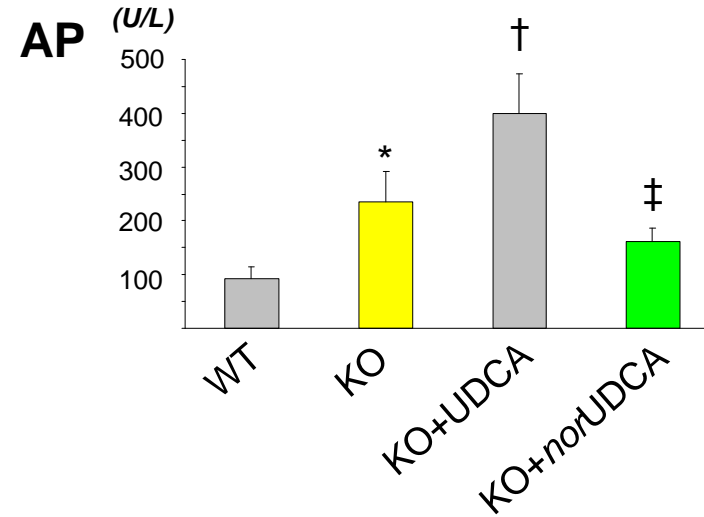
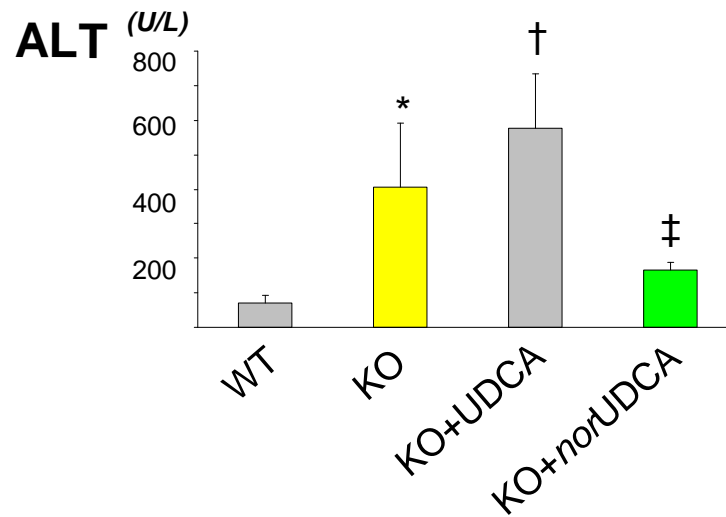


WT (+/+)

KO (-/-)

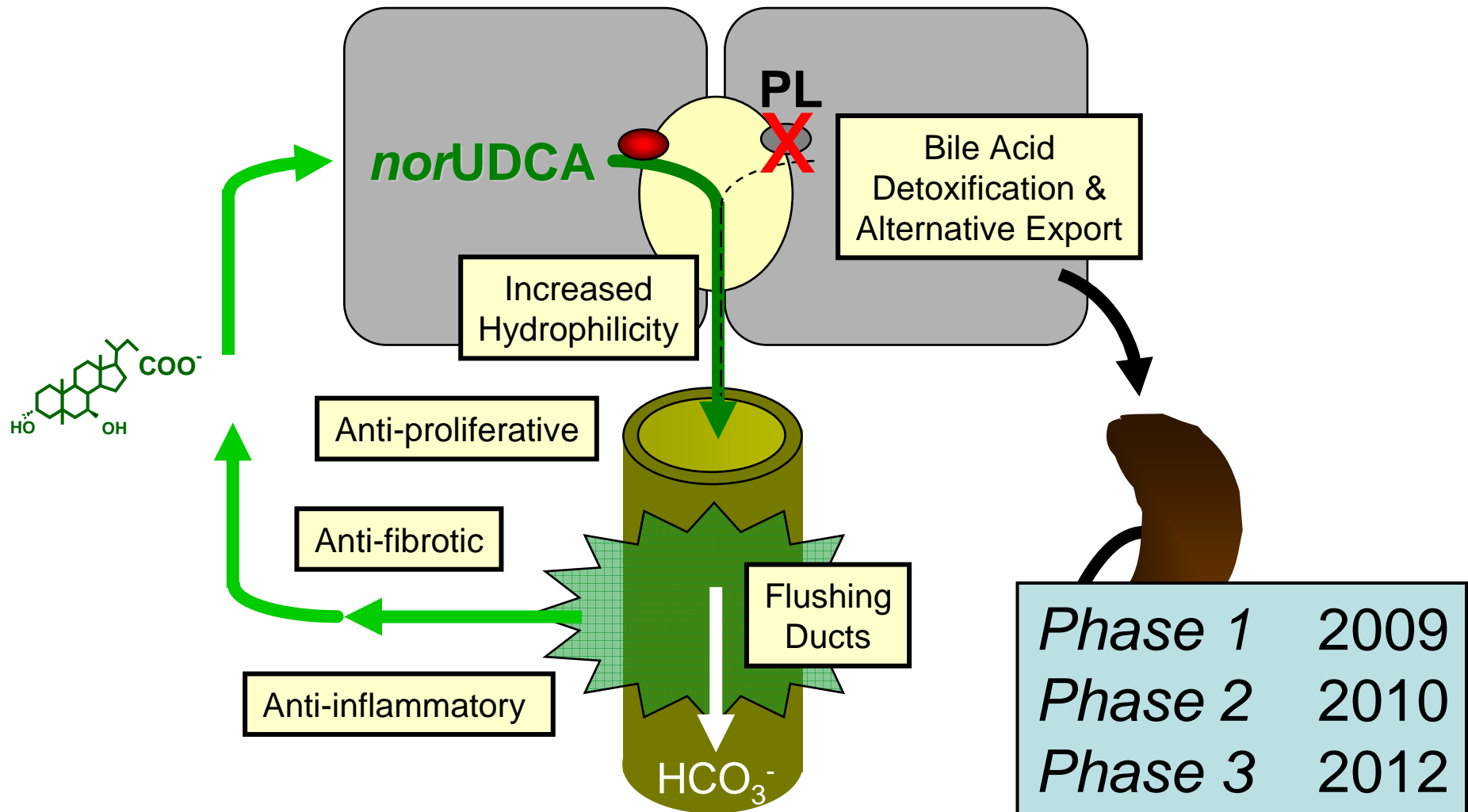
KO+UDCA

KO+*nor*UDCA



p<0.05  
 \* vs. WT  
 † vs. KO  
 ‡ vs. KO

# *nor*UDCA: Multi-targeted Therapy for Complex Multi-factorial Disorders?



# Zsfg.: Herausforderungen bei (P)SC

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- Pathomechanismen unklar
  - Multifaktoriell oder verschiedene Entitäten?
- Heterogenes KH-Bild
  - „Zerfall“ in (teils behandelbare) Subgruppen
- Keine effektive medikamentöse Therapie
  - UDCA: „höher  $\neq$  besser“
  - Hoffnungsschimmer *nor*UDCA
  - LTx; interventionelle Endoskopie (Studien?)
- Malignomrisiko (Präcancerose)

**Danke für Ihre  
Aufmerksamkeit!**

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