

*XXV Congresso Brasileiro de Hepatologia*

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# **Primary sclerosing cholangitis**

## **From diagnosis to treatment**

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**Colangite Esclerosante Primária: Do diagnóstico ao tratamento**

**São Paulo**

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Tytgat Institute of Liver and Intestinal Research

# Disclosures

2010-2019

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## **Grant support**

German, Norwegian, American and South-African PSC patient foundations  
Netherlands Foundation of Gastroenterology and Hepatology (MLDS)  
EU project LIVERHOPE

## **Support for investigator-initiated studies**

Dr. Falk, Intercept

## **Consulting fees / Consulting without fees**

Intercept, Novartis, Shire / NGM

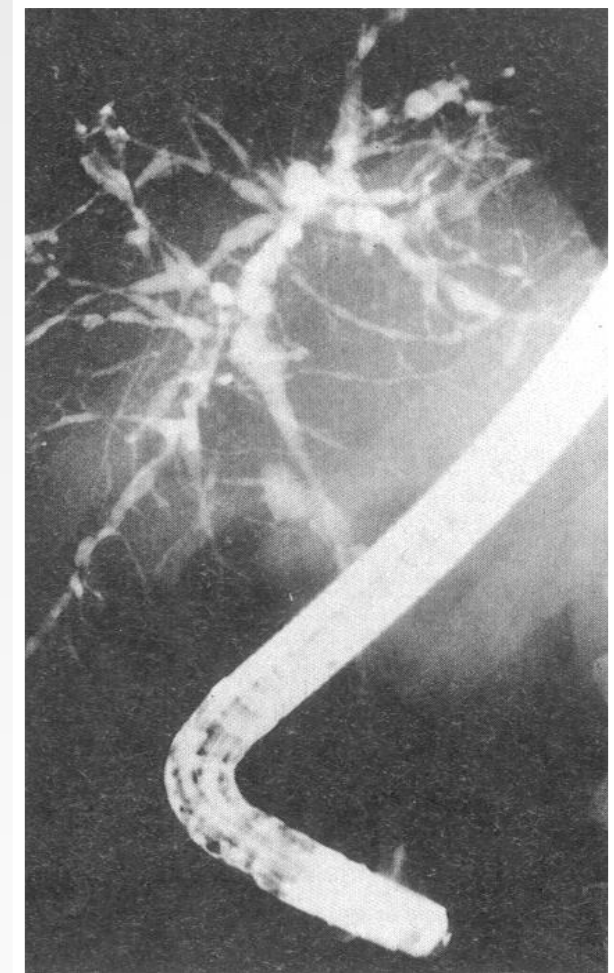
## **Lecture fees**

Abbvie, Falk Foundation, Gilead, Intercept, MSD, Novartis, Roche, Shire, Zambon

# Primary sclerosing cholangitis

## The typical patient in the Netherlands

Point prevalence (per 100.000)	6.0
Incidence (per 100.000/year)	0.5
Age at manifestation (yrs, mean)	38.9
Male gender	64%
Inflammatory bowel disease	68%
UDCA treatment	92%
LTx-free survival (yrs, mean)	<b>21.2</b>
(LTx-free survival of 450 patients at 3 LTx centres	13.2)
Cholangiocarcinoma	7%
Colorectal carcinoma	3%



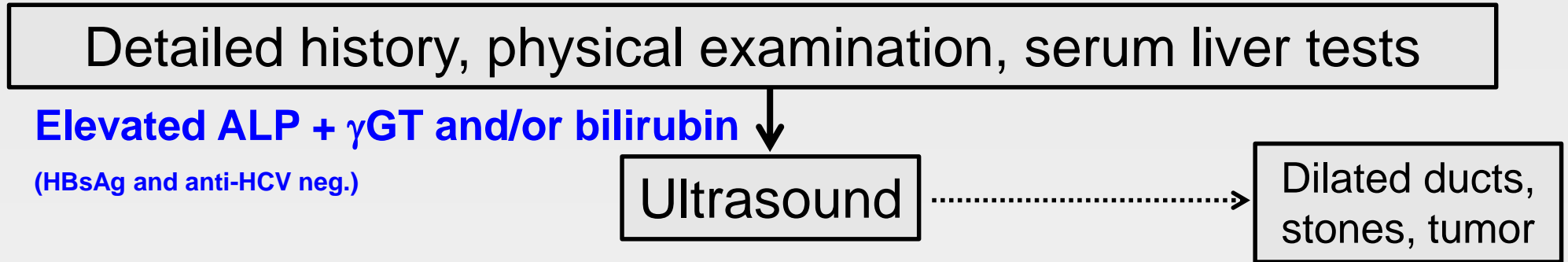
m, 42 years

# Primary sclerosing cholangitis

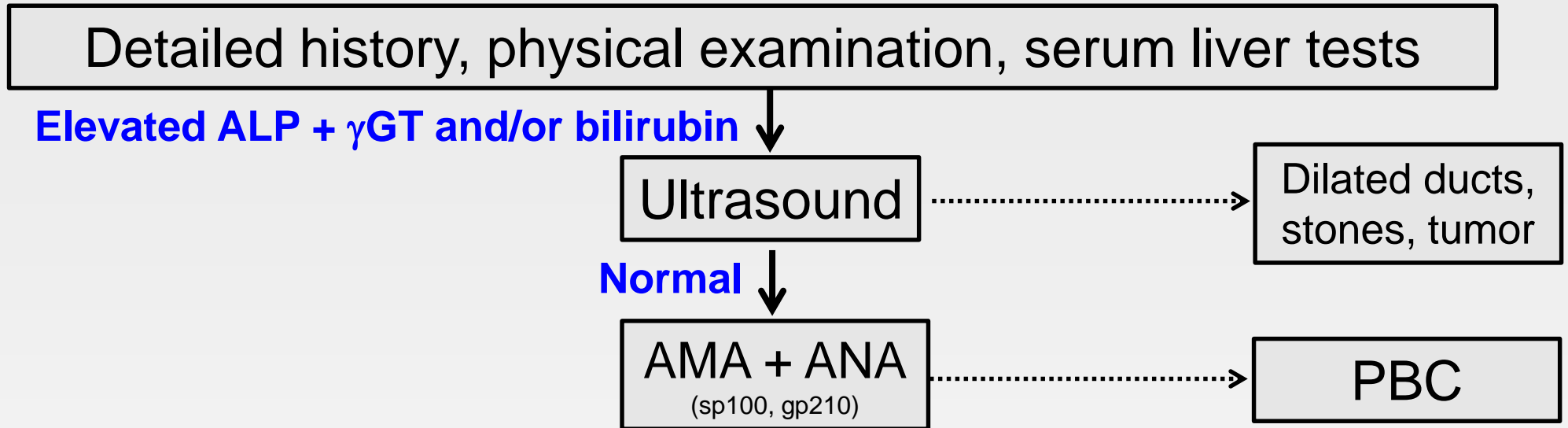
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- **Diagnosis**
- Pathogenesis
- Therapy

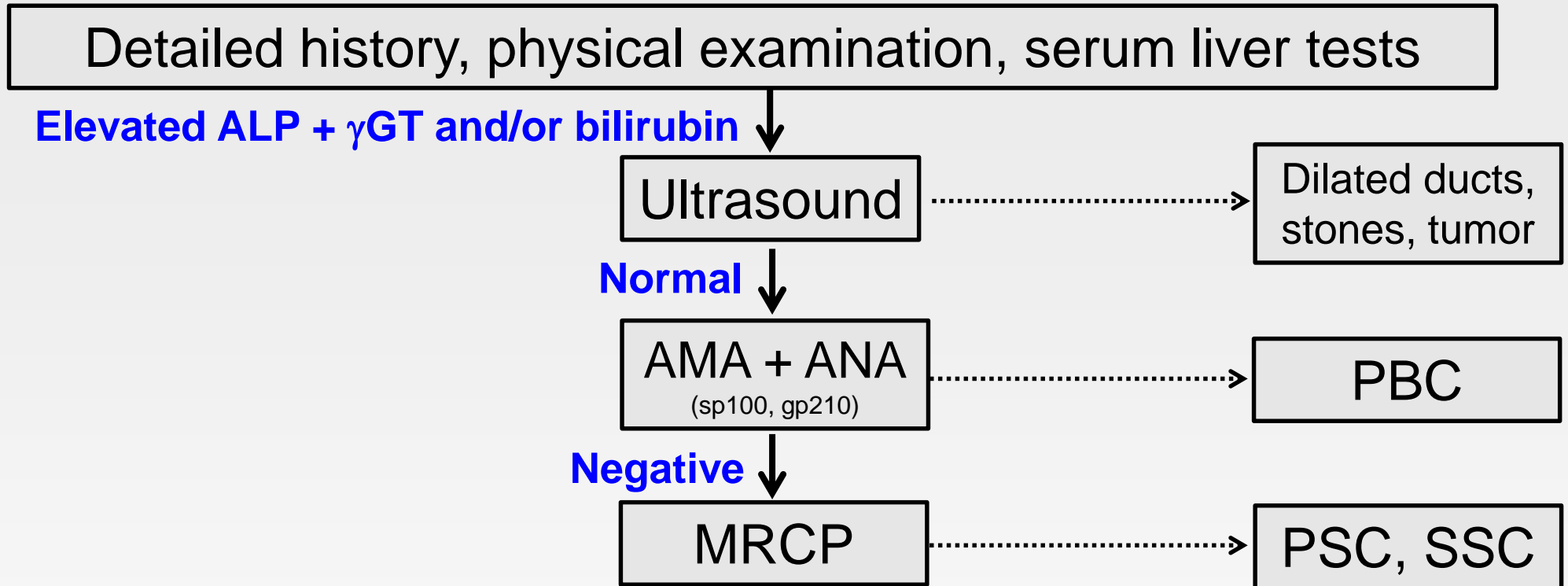
# Diagnostic approach to cholestasis



# Diagnostic approach to cholestasis



# Diagnostic approach to cholestasis



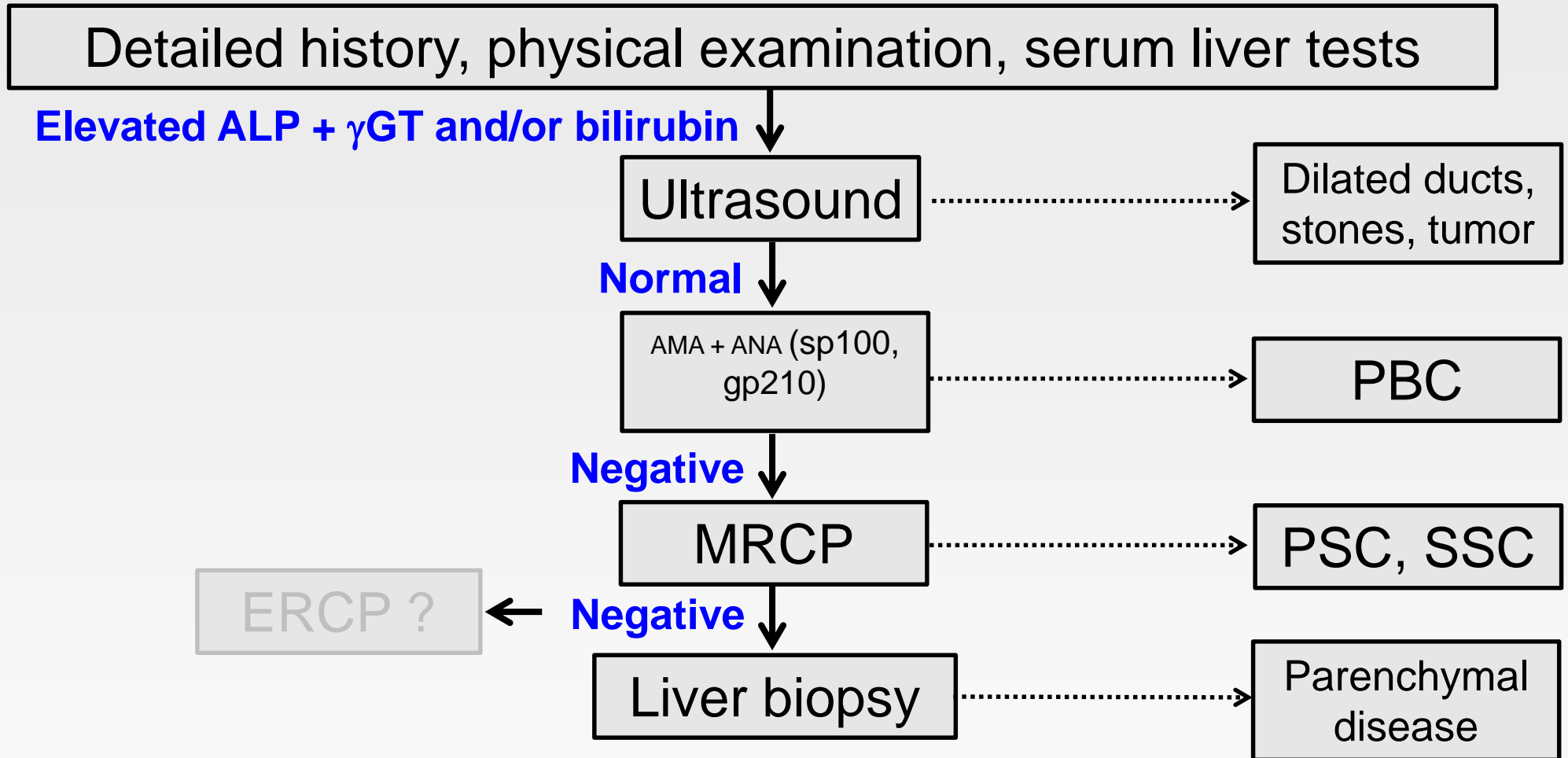
# Sclerosing cholangitis

## MRCP



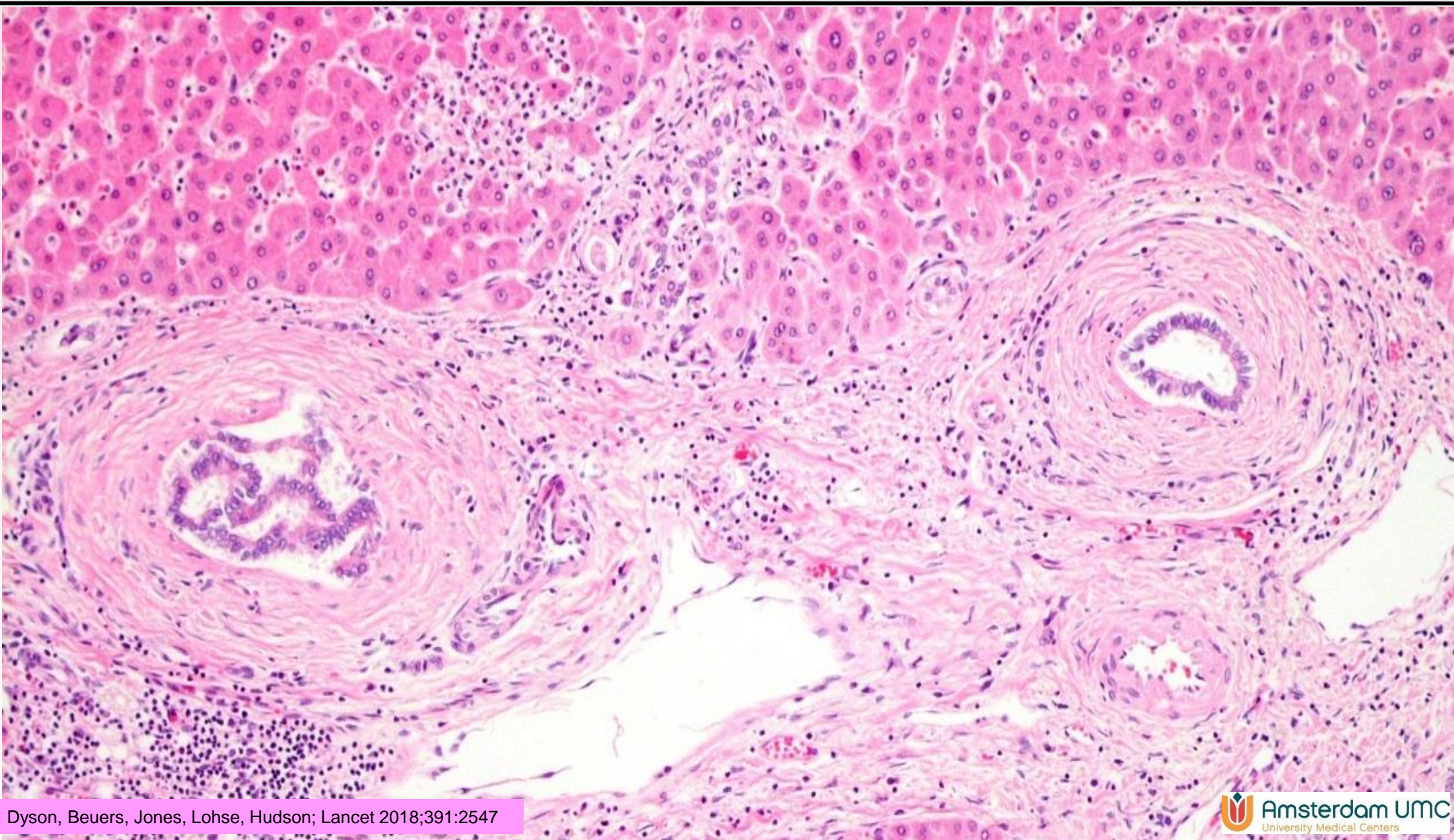


# Diagnostic approach to cholestasis



# Sclerosing cholangitis

## Histology





# The patient with sclerosing cholangitis

## History, additional diagnostic procedures:

Causes of secondary sclerosing cholangitis ?

no

**Primary sclerosing cholangitis**

yes

- AIDS-related cholangiopathy
- Cholangiocarcinoma
- Choledocholithiasis
- Chronic biliary infestation (liver fluke, ascaris)
- Congenital (choledochal cysts, Caroli's s., biliary atresia)
- Cystic fibrosis
- Eosinophilic cholangitis
- Histiocytosis X
- IgG4-related cholangitis
- Ischaemic cholangitis
- Mast cell cholangiopathy
- Portal hypertensive biliopathy
- Recurrent pyogenic cholangitis
- Sarcoidosis
- Sclerosing cholangitis of the critically ill patient
- Surgical trauma

**Secondary sclerosing cholangitis**

# The patient with sclerosing cholangitis

## History, additional diagnostic procedures:

Causes of secondary sclerosing cholangitis ?

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**Primary sclerosing cholangitis**

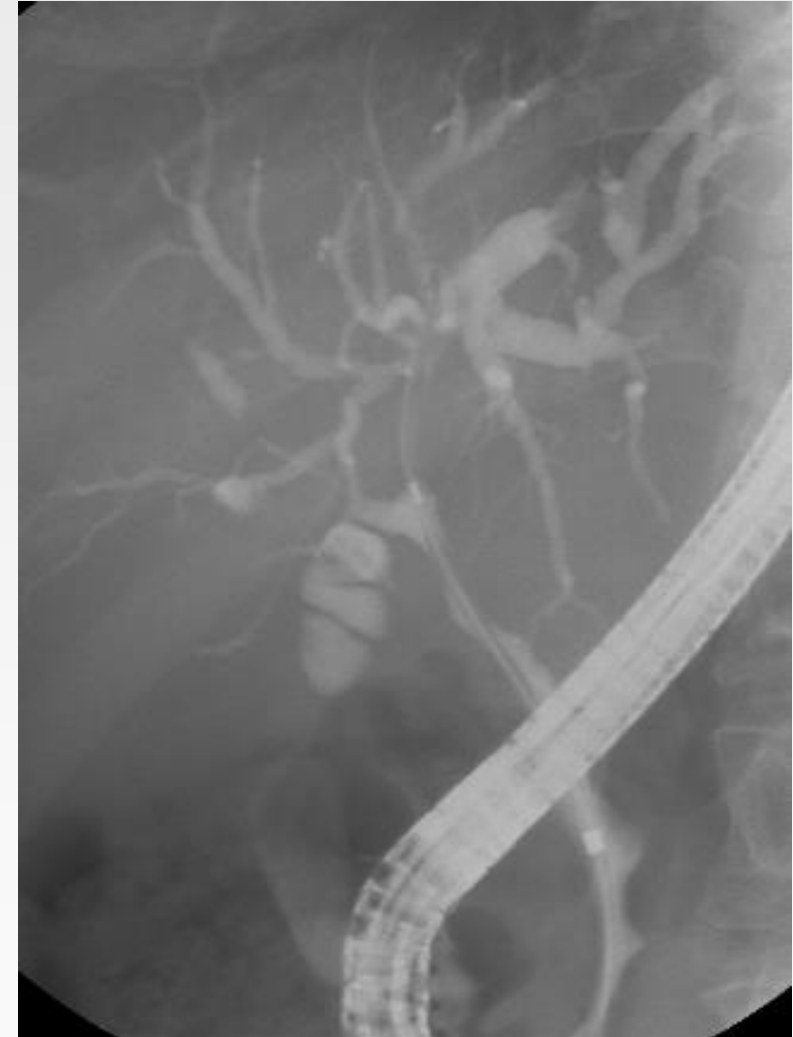
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**Secondary sclerosing cholangitis**

# IgG4-related cholangitis

- Male (>80%)
- Middle aged / elderly (> 50 yrs)
- **Jaundice**, weight loss, abdominal pain
- Localized organ swelling / tumor
- Elevated serum / tissue IgG4
- Other organ manifestations of IgG4-RD



# Diagnosis of PSC

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A diagnosis of PSC is made in patients with biochemical markers of cholestasis ... when MRCP shows typical findings and causes of secondary sclerosing cholangitis are excluded (II-2/B1).

II-2: Cohort or case-control analytic studies

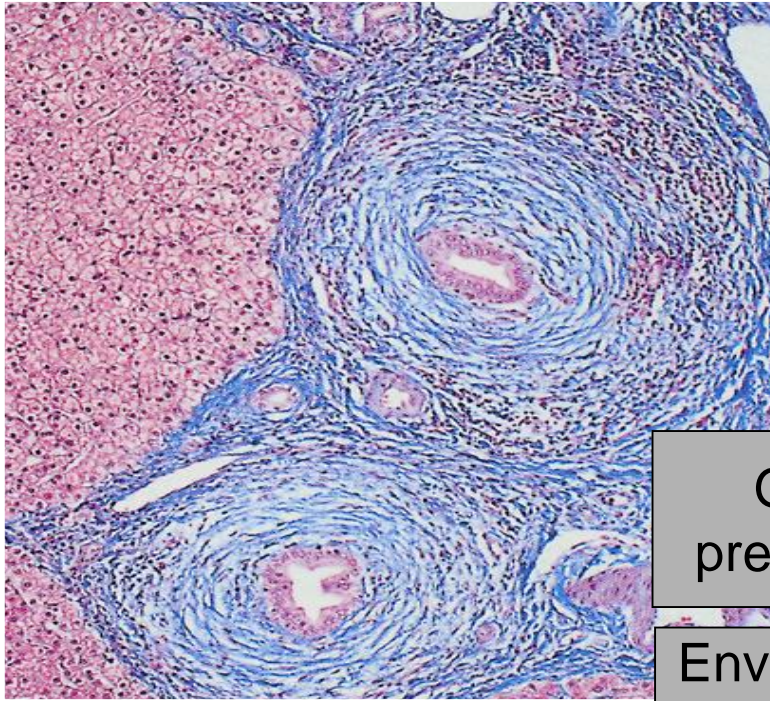
B1 : Moderate quality / strong recommendation (GRADE)

# Primary sclerosing cholangitis

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- Diagnosis
- **Pathogenesis**
- Therapy

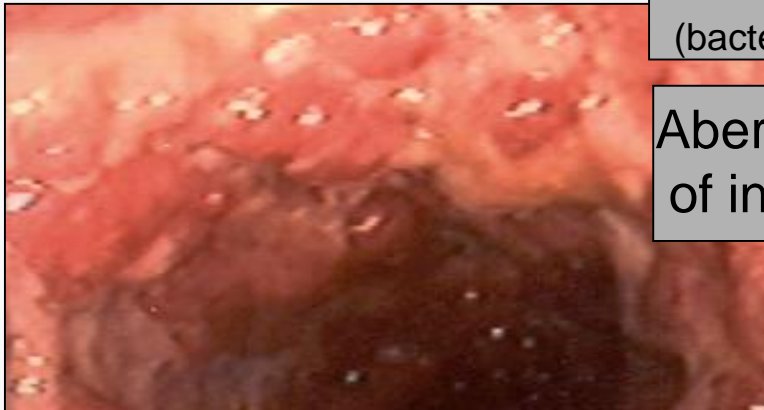
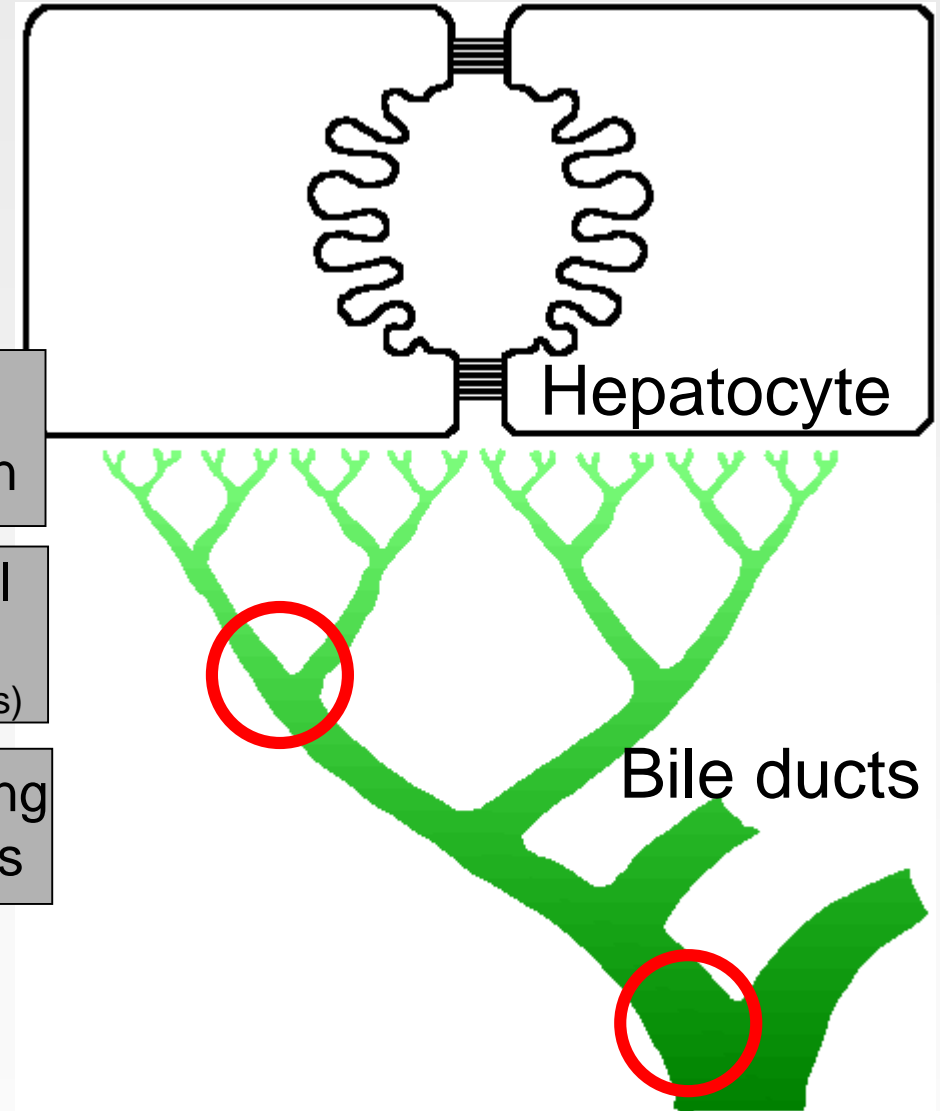
# Pathogenesis of primary sclerosing cholangitis



Genetic predisposition

Environmental factors  
(bacterial pathogens)

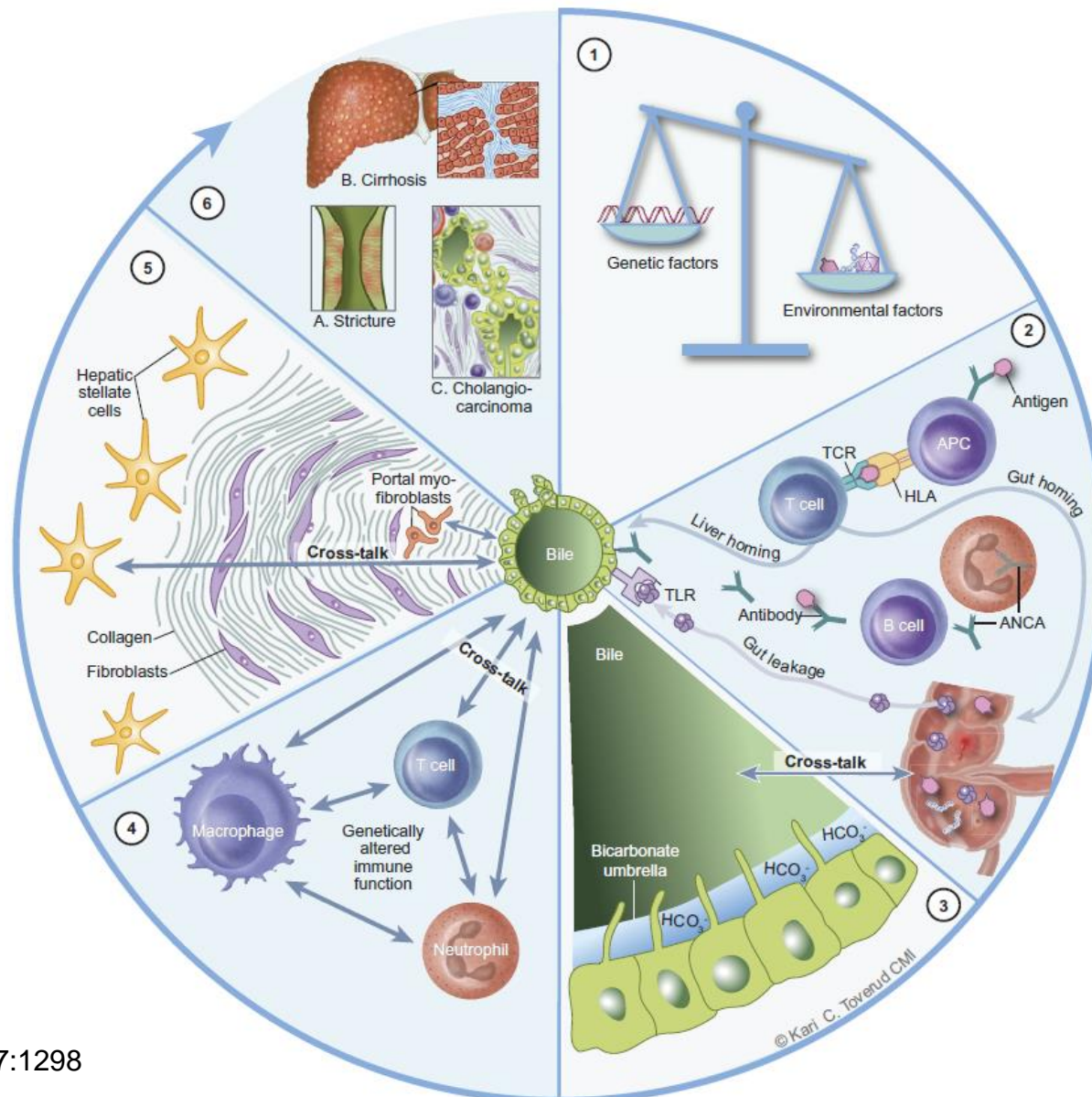
Aberrant homing of intest.T-cells



Association with IBD  $\geq 70\%$

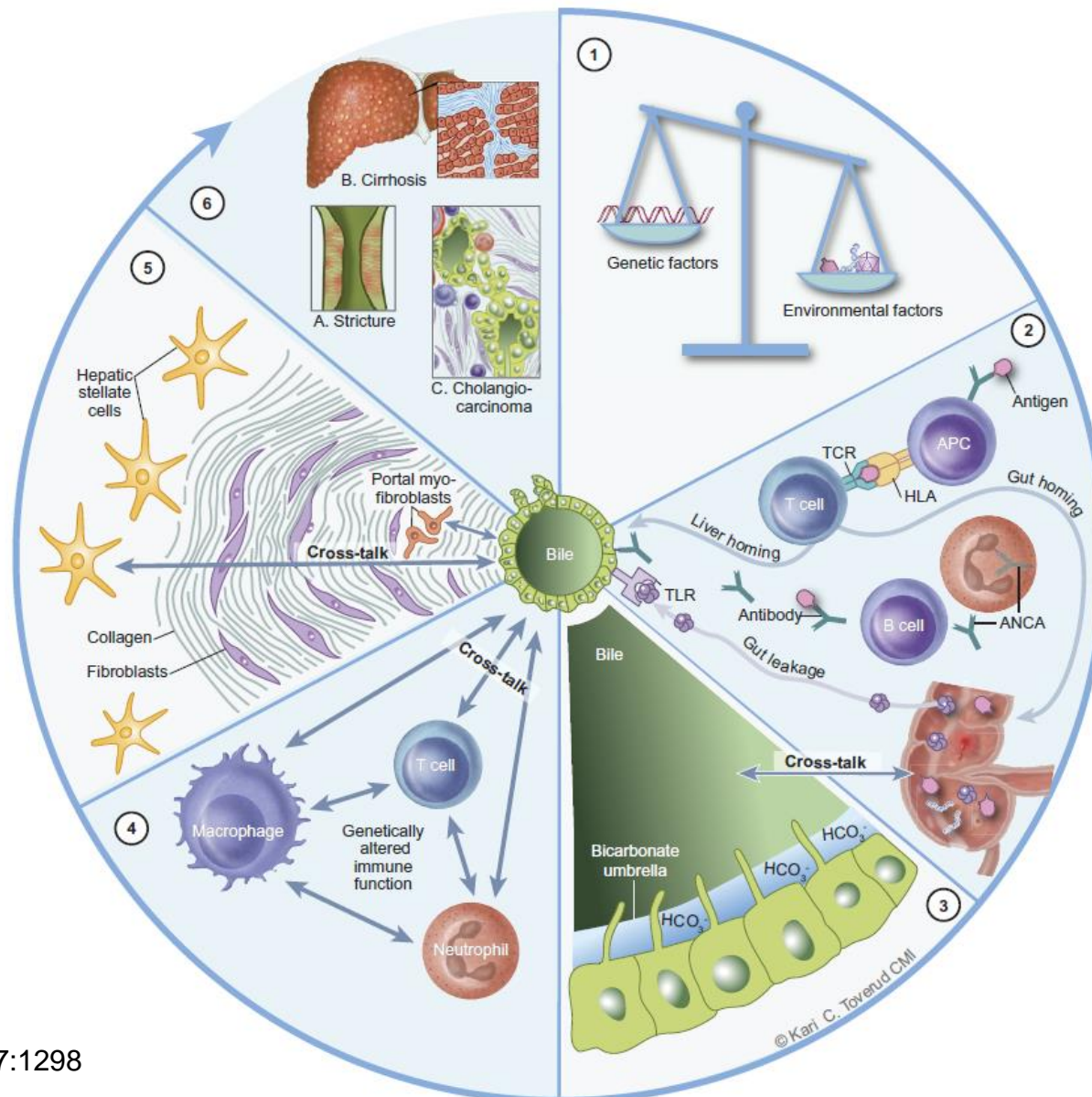


# Integrated overview of the pathophysiology of PSC



# Integrated overview of the pathophysiology of PSC

## Potential future therapeutic targets



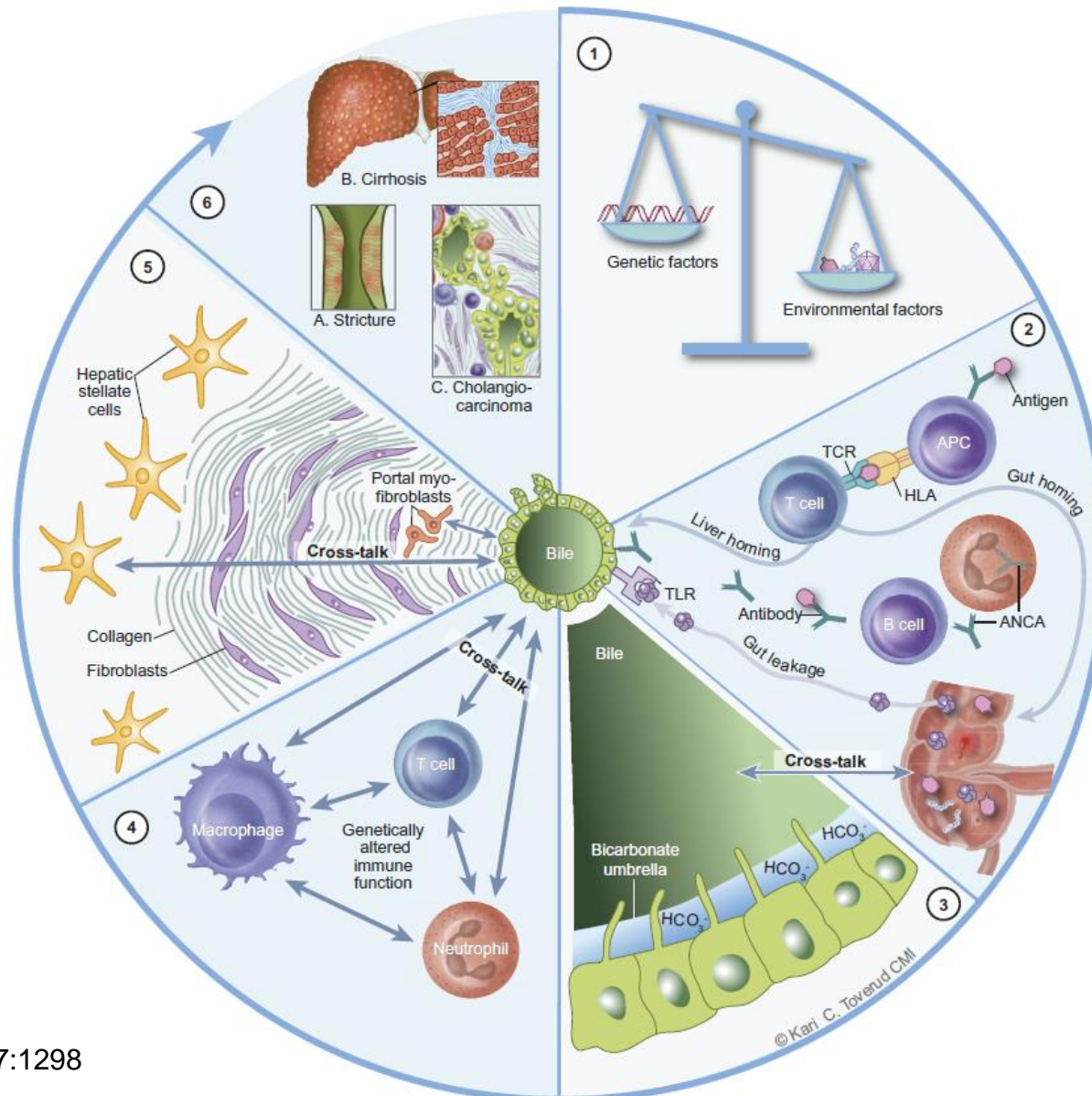
Epigenetic factors

Microbiota



# Integrated overview of the pathophysiology of PSC

## Potential future therapeutic targets



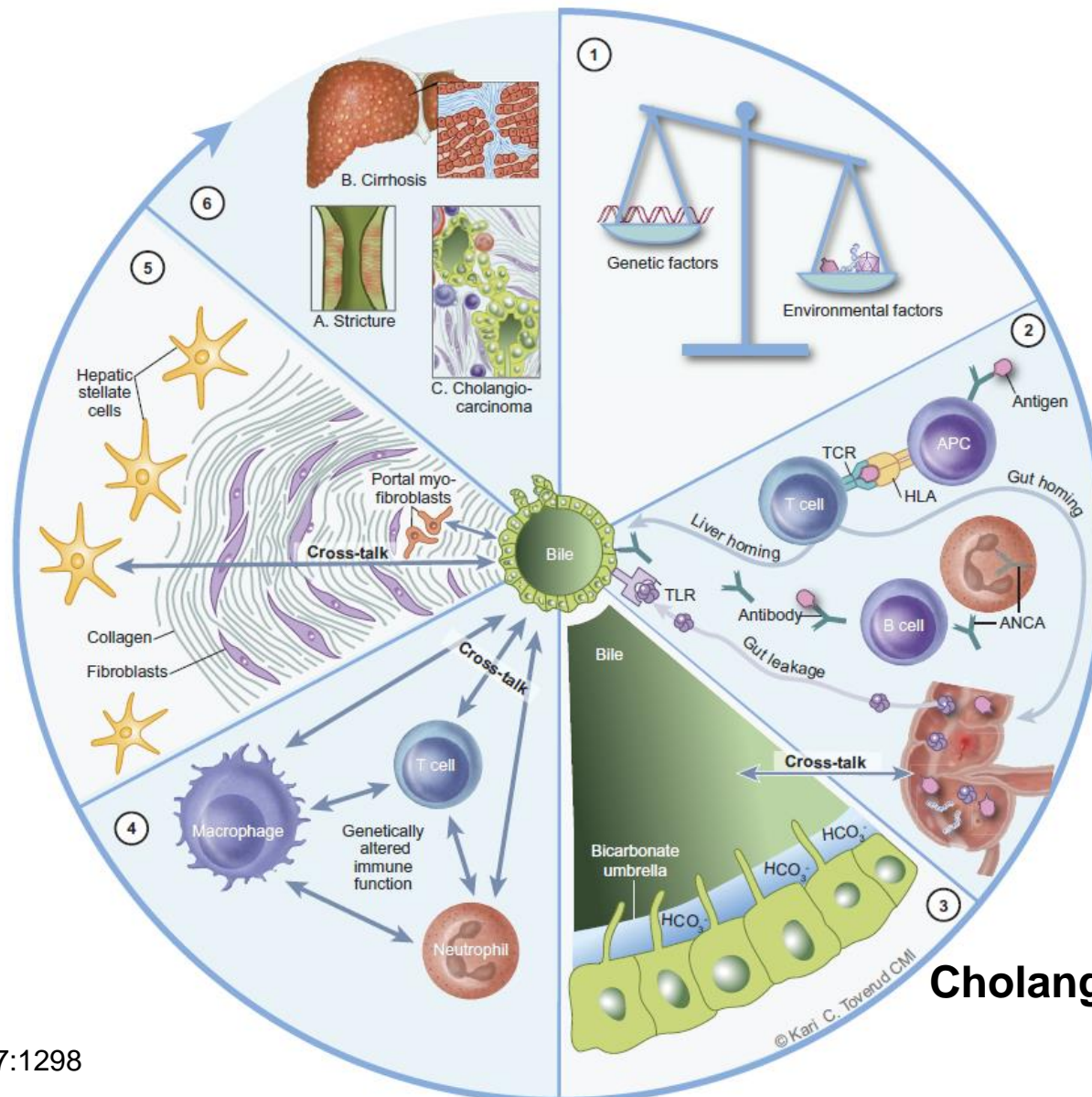
Epigenetic factors

Microbiota

Aberrant homing of intestinal T cells

# Integrated overview of the pathophysiology of PSC

## Potential future therapeutic targets



Epigenetic factors

Microbiota

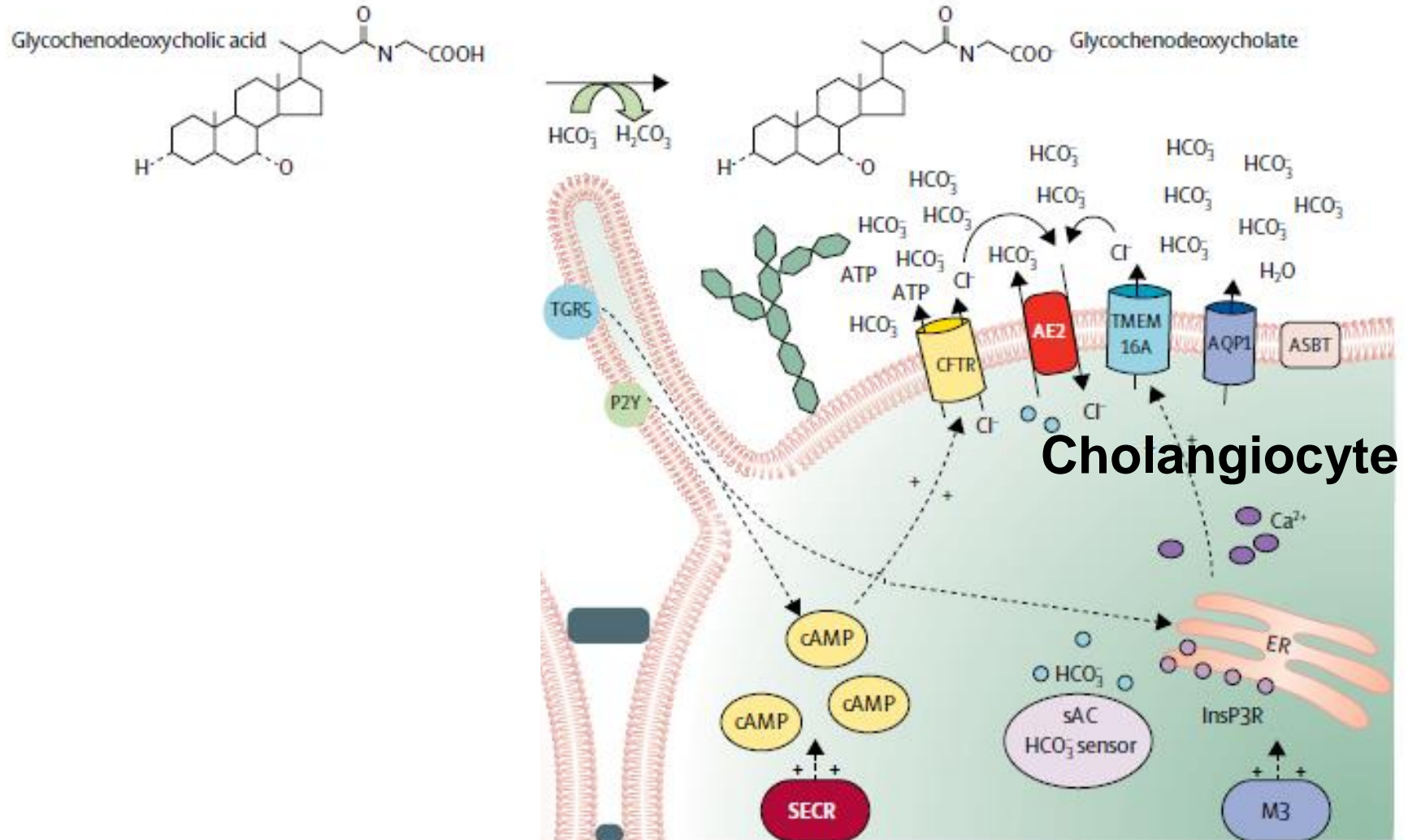
Aberrant homing of intestinal T cells

Cholangiocyte vulnerability

# The 'Biliary $\text{HCO}_3^-$ Umbrella' Hypothesis

---> Activation

Bile



Cholangiocyte

Beuers et al., Hepatology 2010;52:1489  
 Hohenester, Wenniger et al., Hepatology 2012; 55: 173  
 Chang et al., Hepatology 2016;64:522

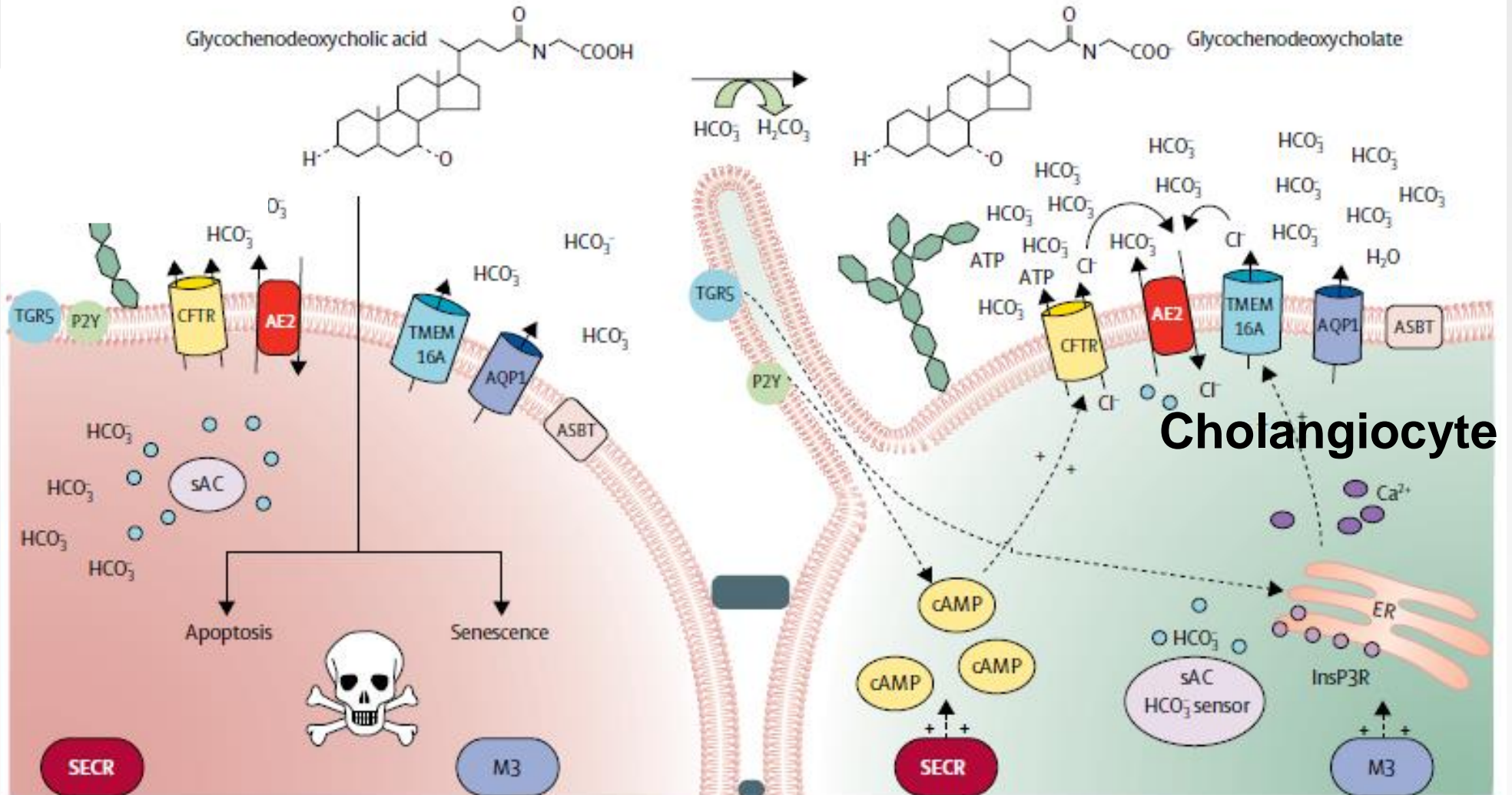
[Lancet 2018;391:2547]



# The 'Biliary HCO<sub>3</sub><sup>-</sup> Umbrella' Hypothesis

⚡ → Activation

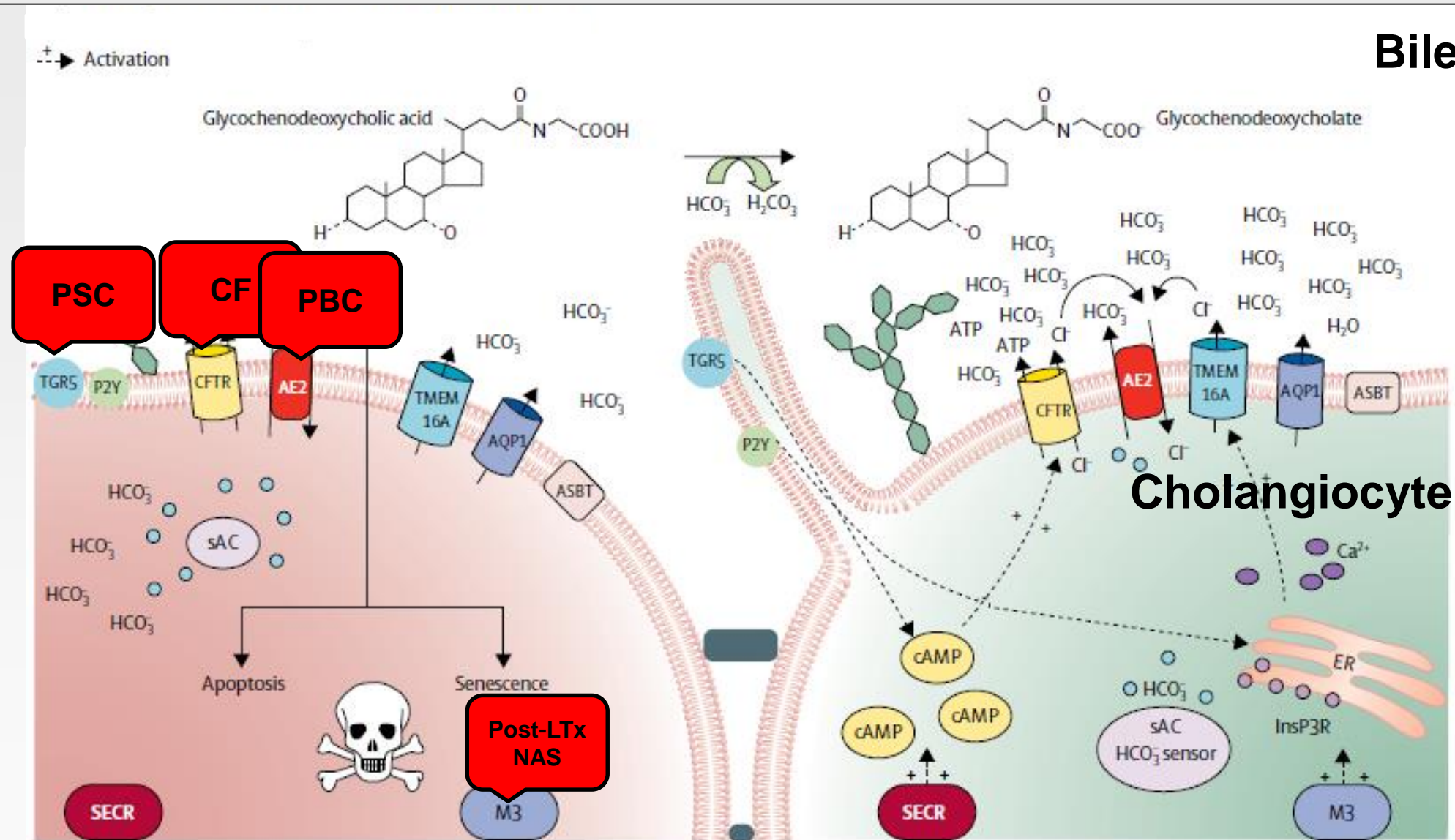
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# Defects of the 'Biliary HCO<sub>3</sub><sup>-</sup> Umbrella' in fibrosing cholangiopathies?



Bile

Cholangiocyte

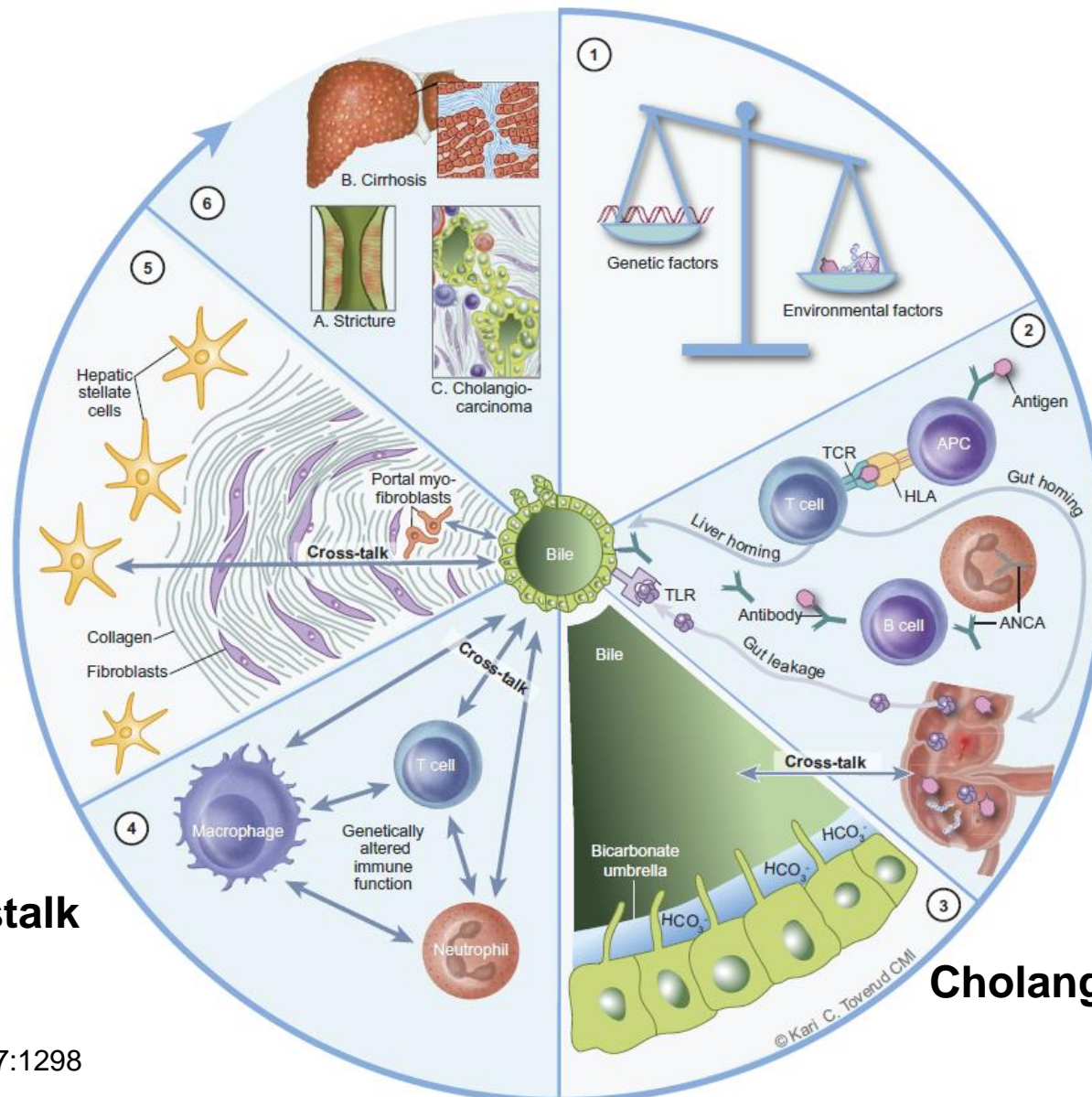
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# Integrated overview of the pathophysiology of PSC

## Potential future therapeutic targets



Epigenetic factors

Microbiota

Aberrant homing of intestinal T cells

Cholangiocyte vulnerability

Immune cell crosstalk



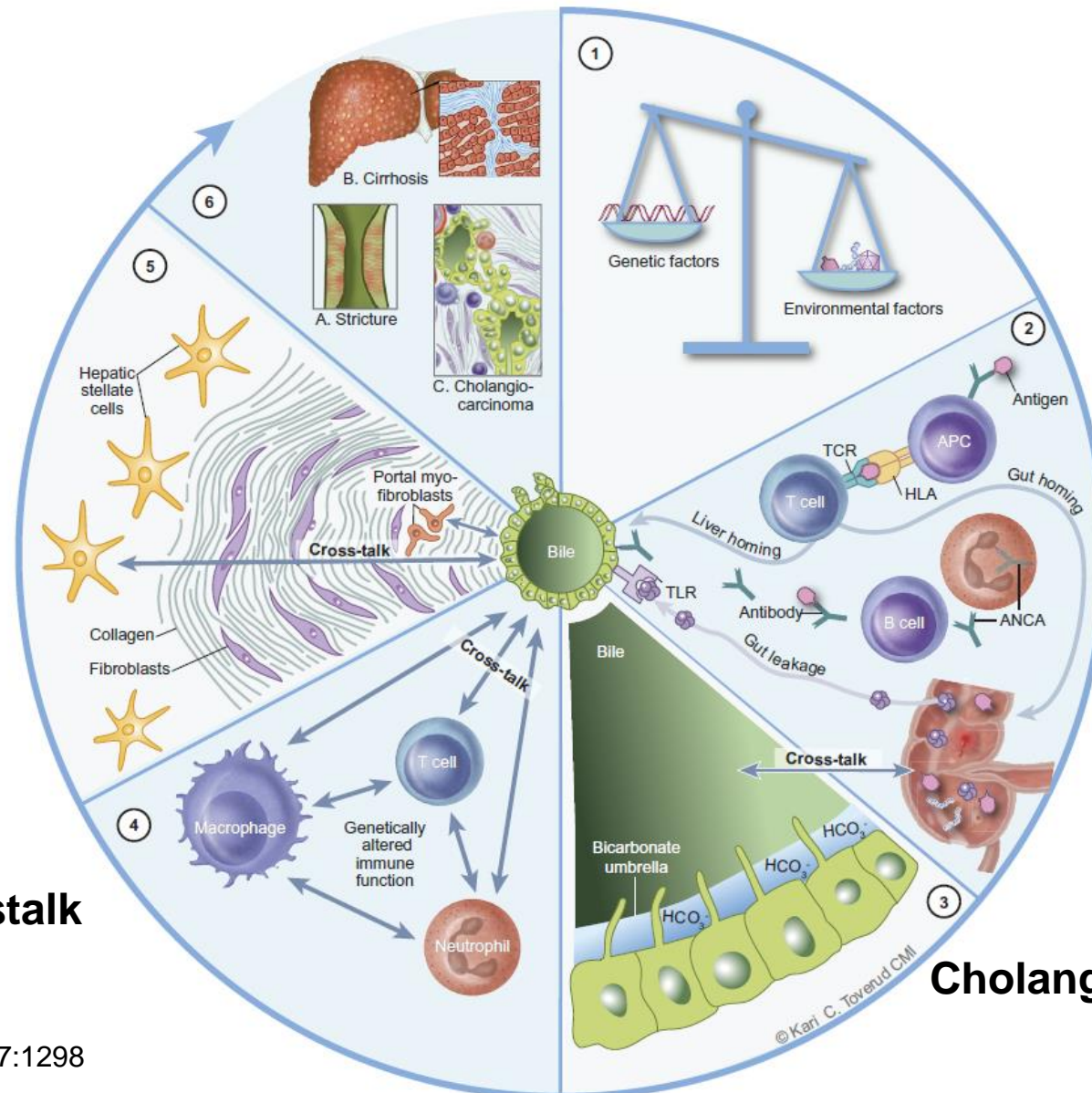
# Integrated overview of the pathophysiology of PSC

## Potential future therapeutic targets

**Stellate cells**

**Portal myofibroblasts**

**Immune cell crosstalk**



**Epigenetic factors**

**Microbiota**

**Aberrant homing of intestinal T cells**

**Cholangiocyte vulnerability**

# Integrated overview of the pathophysiology of PSC

## Potential future therapeutic targets

**Cholangiocarcinogenesis**

**Stellate cells**

**Portal myofibroblasts**

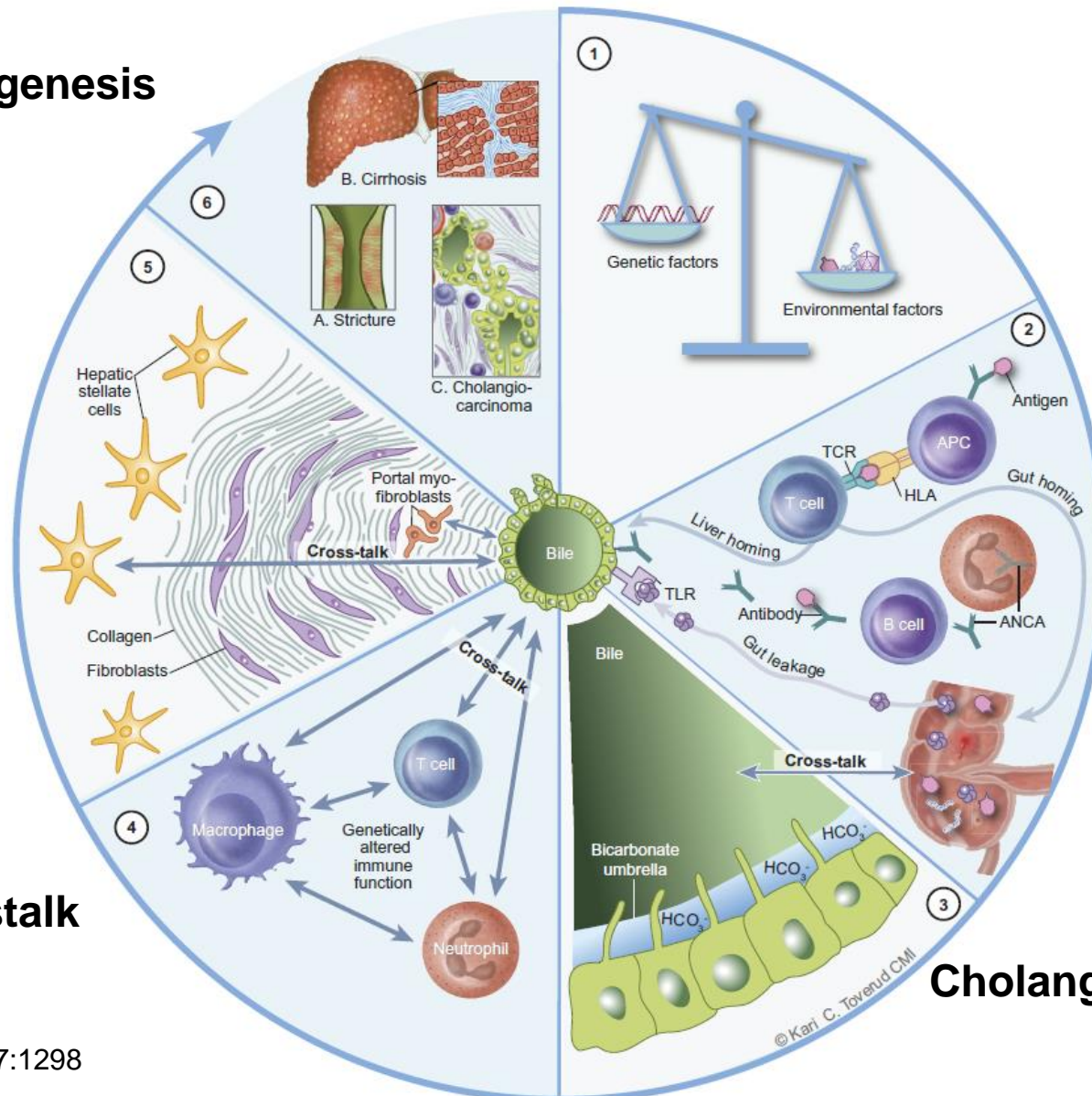
**Immune cell crosstalk**

**Epigenetic factors**

**Microbiota**

**Aberrant homing of intestinal T cells**

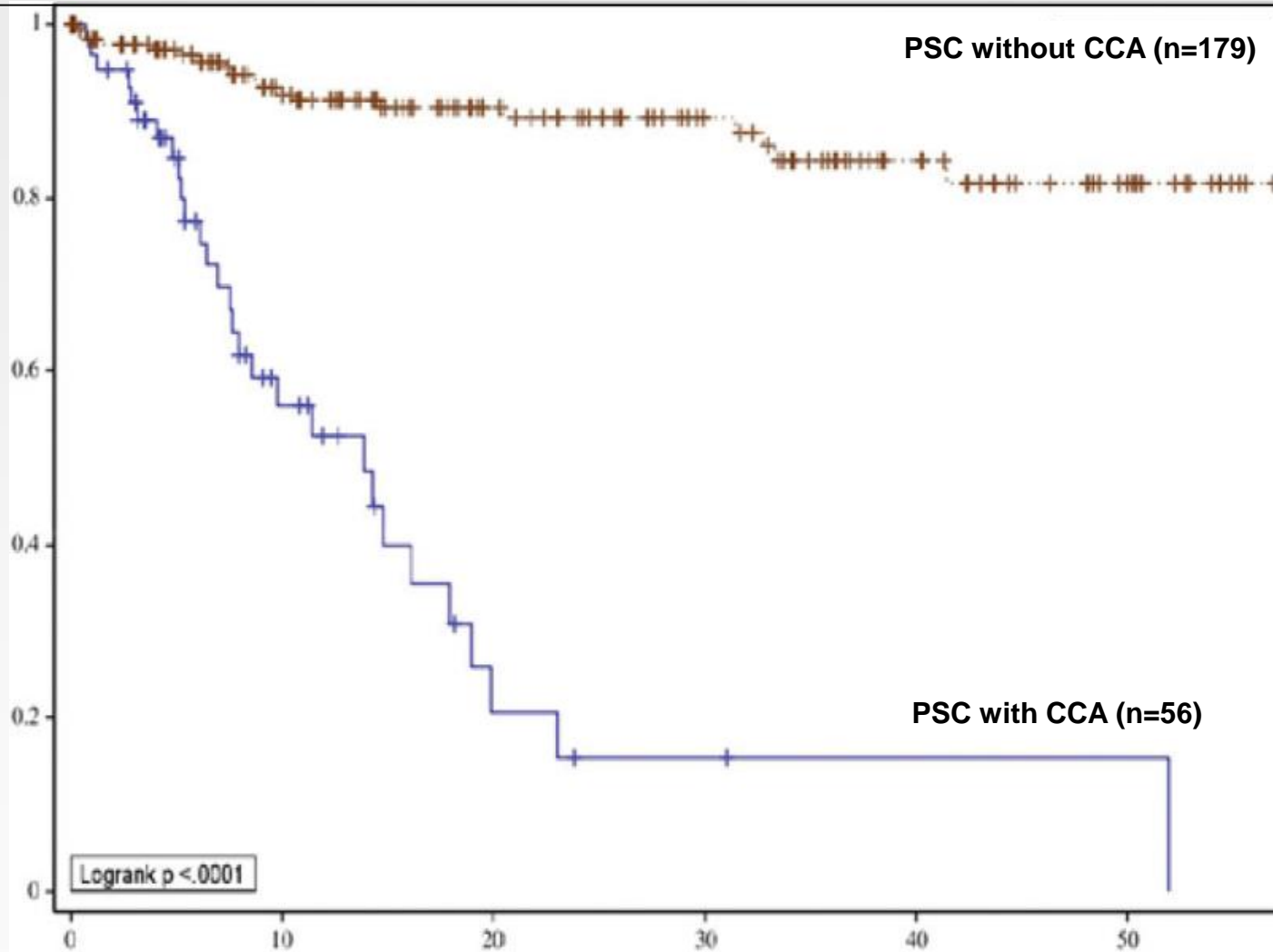
**Cholangiocyte vulnerability**



# Primary sclerosing cholangitis

- Cholangiocarcinoma dramatically worsens prognosis -

Survival



Months

# Primary sclerosing cholangitis

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- Diagnosis
- Pathogenesis
- **Therapy**

# PSC :

# Therapy

## *Pathogenetic model*

Immunologic bile duct injury  
(Cytokine-mediated)



Bile duct stenoses  
Aggravation of injury by BA



Cholestasis with retention of  
hydrophobic bile acids in liver



Fibrosis, cirrhosis



Liver failure

**Ursodeoxycholic acid**

(15-20 mg/kg/d)

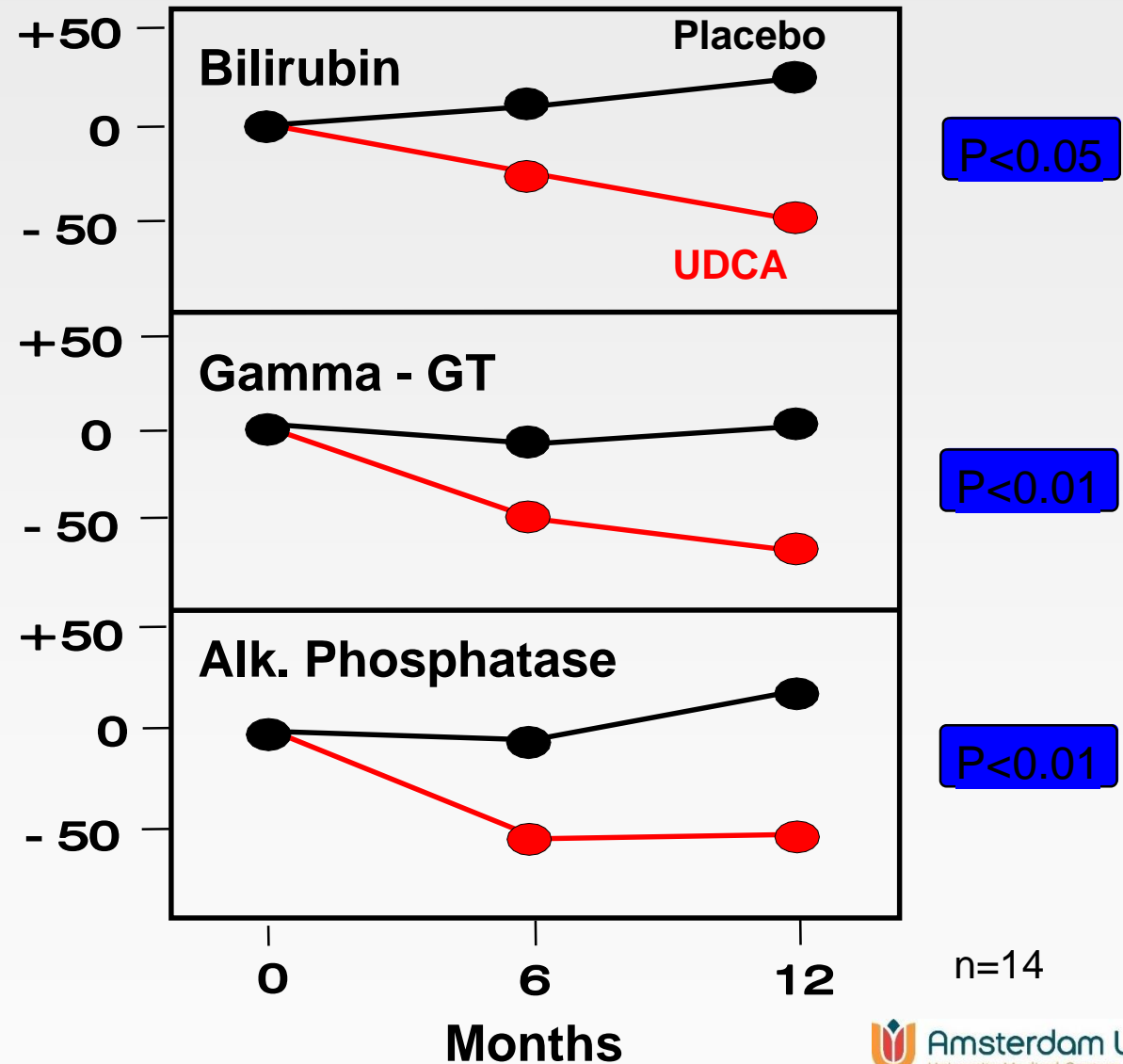
?

**Liver transplantation**

# Treatment of primary sclerosing cholangitis with UDCA

## Serum liver tests

Change  
[%]

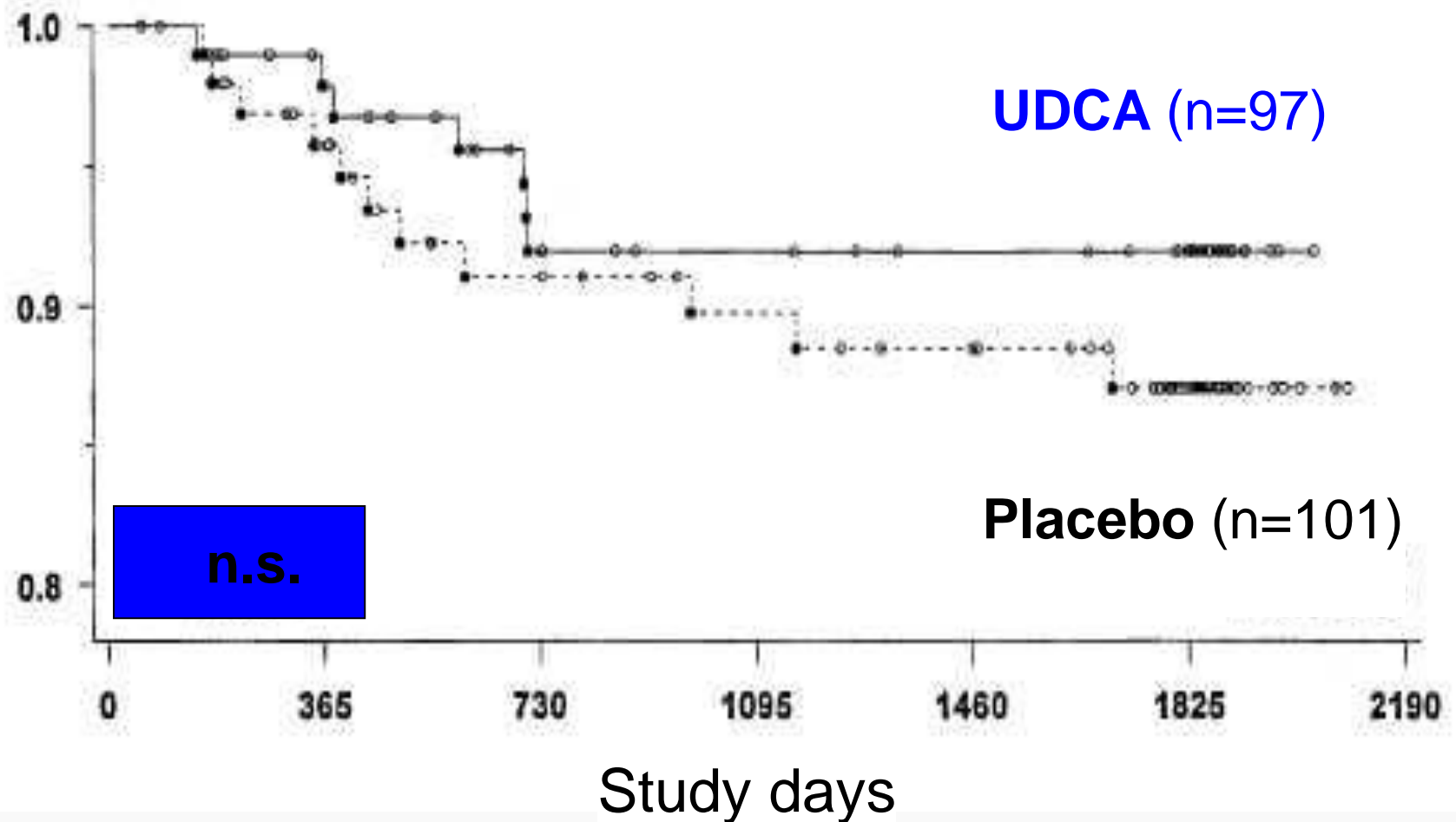




# Treatment of primary sclerosing cholangitis with UDCA

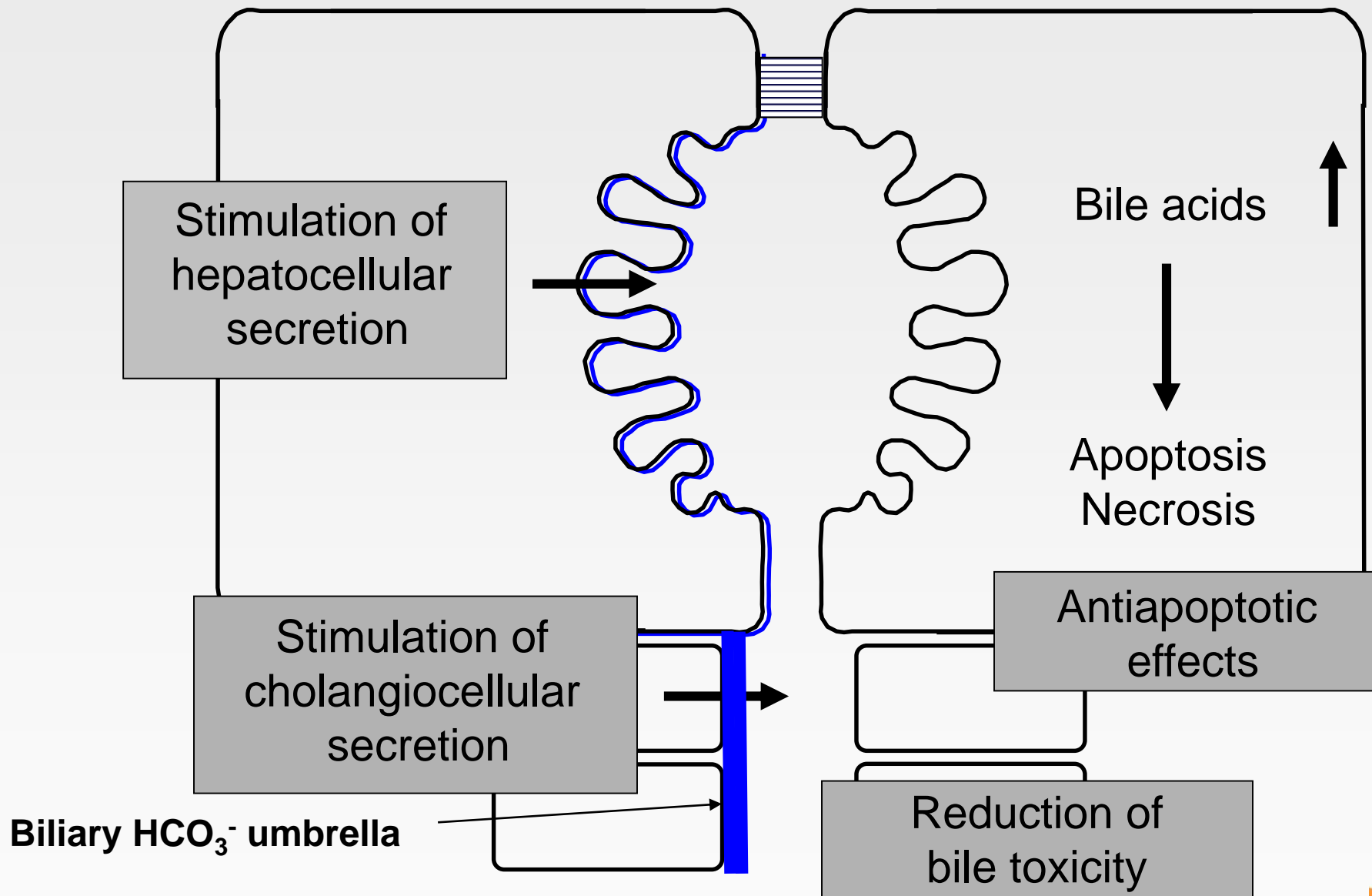
## - Transplant-free survival -

Survival  
without  
liver  
trans-  
plantation



Power analysis *a priori*: n = 346

# Putative mechanisms and sites of action of UDCA in cholestatic liver diseases





## *Pathogenetic model*

**Immunologic bile duct injury  
(Cytokine- mediated)**



**Bile duct stenoses  
Aggravation of injury by BA**



**Cholestasis with retention of  
hydrophobic bile acids in liver**



**Fibrosis, cirrhosis**



**Liver failure**

**Endoscopic balloon dilatation**

Ponsioen et al., Gastroenterology 2018;155:752

**Ursodeoxycholic acid**

**(15-20 mg/kg/d)**

?

**Liver transplantation**

# PSC :

# Therapy *under evaluation*

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**Fibrosis, cirrhosis**



**Liver failure**

*Vedolizumab ??  
norUDCA ?*

*RCT  
(Phase 2)*

Fickert,...Trauner. J Hepatol 2017;67:549

**Endoscopic balloon dilatation**

**Ursodeoxycholic acid  
(15-20 mg/kg/d)**

?

**Liver transplantation**

# PSC :

# Therapy *under evaluation*

## *Pathogenetic model*

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**Endoscopic balloon dilatation**

**Ursodeoxycholic acid  
(15-20 mg/kg/d)**

*Nuclear receptor agonists ?*

- PPAR ?
- FXR ?

*RCT  
(Phase 2)*

*FGF19 analogues ? (NGM282)*

Hirschfield,...Beuers. J Hepatol 2019;70:483

**Liver transplantation**

# Fibrates for ITCH (FITCH Trial)

Prospective, randomized, placebo-controlled, investigator-initiated, non-sponsored multicentre trial (Bezafibrate 400 mg/d versus Placebo)

Inclusion: Patients with fibrosing cholangiopathies (PSC, PBC, SSC) suffering from moderate to severe itch (VAS  $\geq$  5/10)

Primary endpoint: ●  $\geq$  50% decrease of itch intensity (after 21 days)

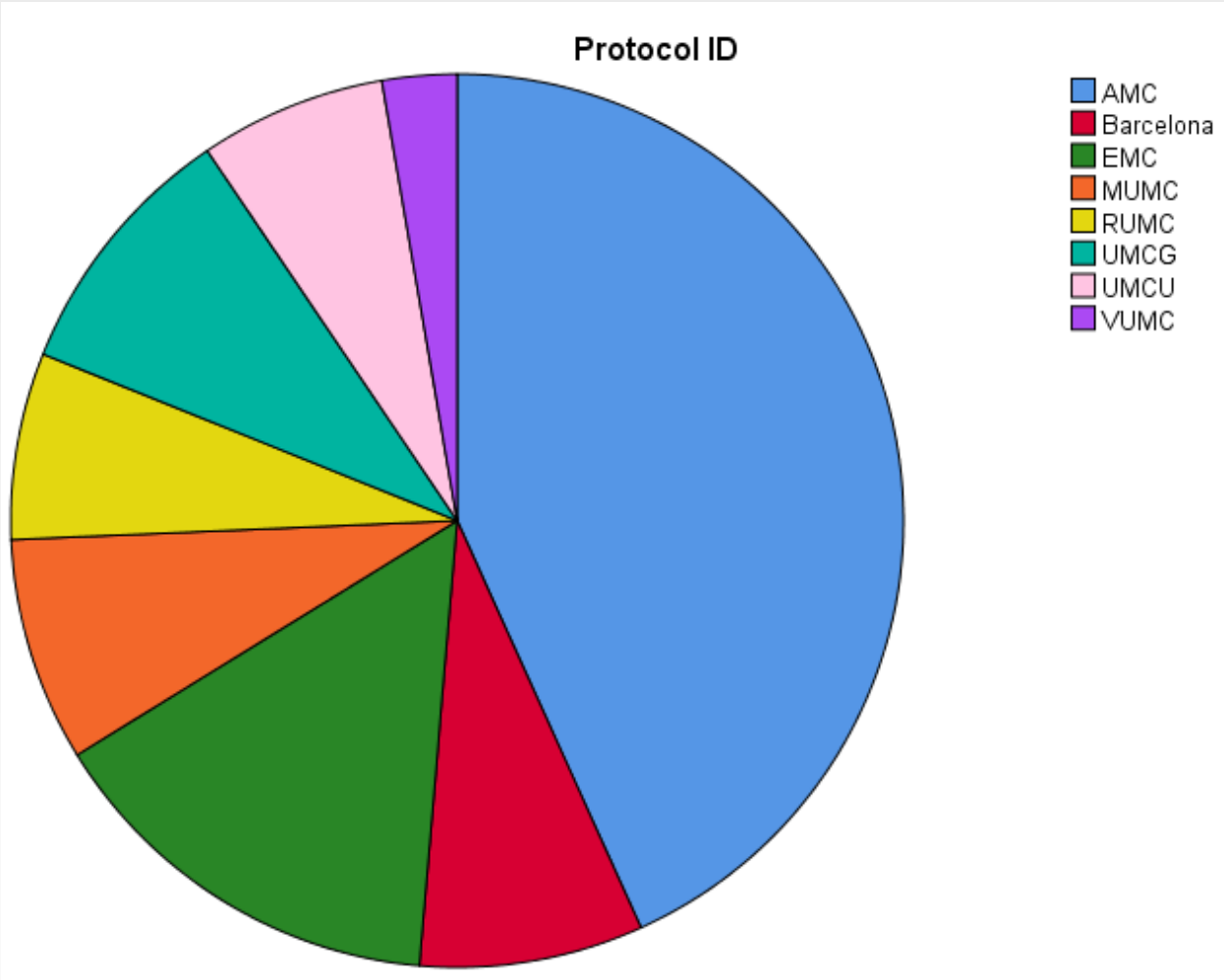
Secondary endpoints: ● 5D Itch score

● Liver disease symptom index 2.0

● Morning and evening itch diary

● Serum biomarkers

# Fibrates for ITCH (FITCH Trial)



	Frequency	Percent
AMC	32	43.2
Barcelona	6	8.1
EMC	11	14.9
MUMC	6	8.1
RUMC	5	6.8
UMCG	7	9.5
UMCU	5	6.8
VUMC	2	2.7
Total	74	100.0

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● Liver disease symptom index 2.0 [itch]

● Morning and evening itch diary

● Serum biomarkers

# From Pathophysiology to Treatment in PSC

Promising future therapeutics

**Cholangiocarcinogenesis**

**Stellate cells**

**FGF19 analogs?**  
(NGM282)

**Portal  
myofibroblasts**

**PPAR agonists?**

**Immune cell crosstalk**

**Epigenetic factors**

**Microbiota**

**Aberrant homing of  
intestinal T cells**

**Vedolizumab ??**

**Cholangiocyte vulnerability**

**UDCA**  
**norUDCA?**

