Dutch Liver Week 2017

Primaire scleroserende cholangitis
IgG4-gerelateerde ziekte

Leiden

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U. Beuers
Department of Gastroenterology & Hepatology
Tytgat Institute for Liver and Intestinal Research
Academic Medical Centre
University of Amsterdam
Amsterdam, The Netherlands

Disclosures

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Intercept, Novartis

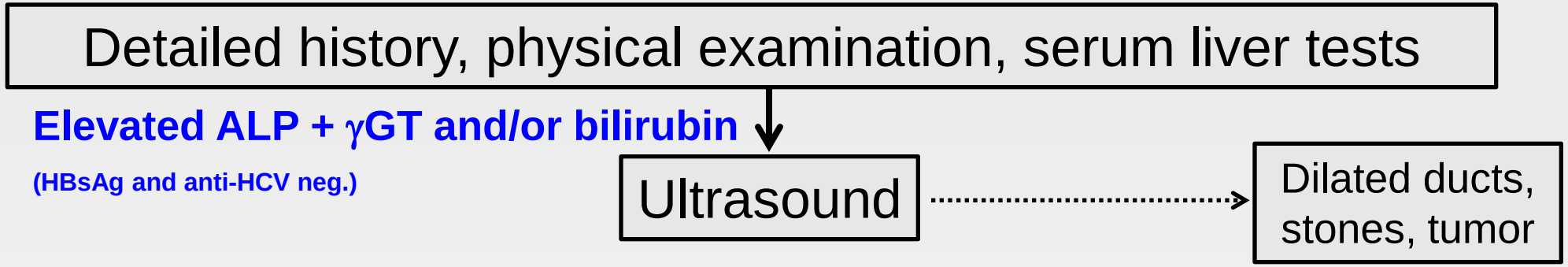
Support for investigator-initiated studies

Falk, Intercept

Primaire sclerosierende cholangitis

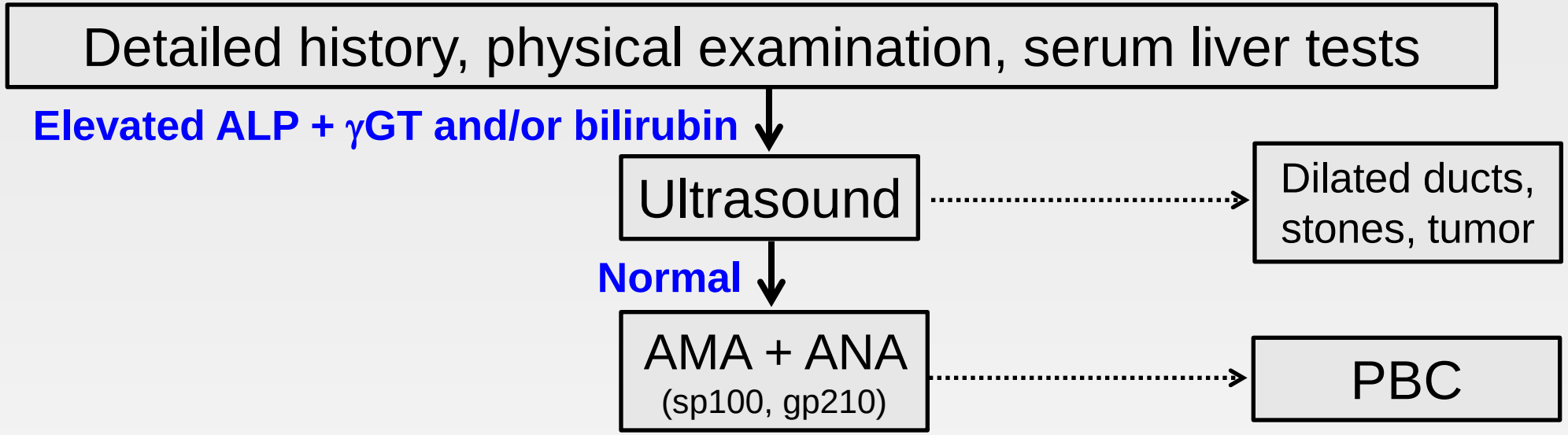
- **Diagnose**
- **Pathogenese**
- **Therapie**

Diagnostic approach to cholestasis



EASL CP Guidelines PBC. J Hepatol 2017; 67:145

Diagnostic approach to cholestasis



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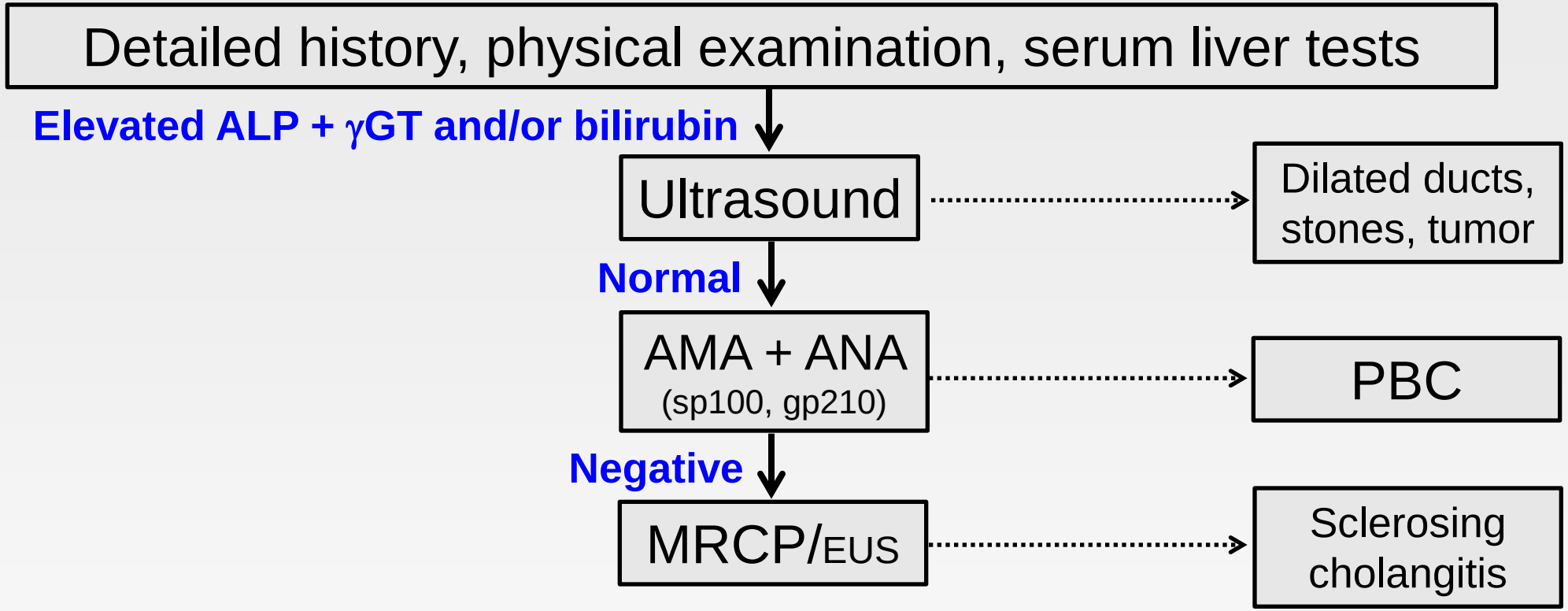
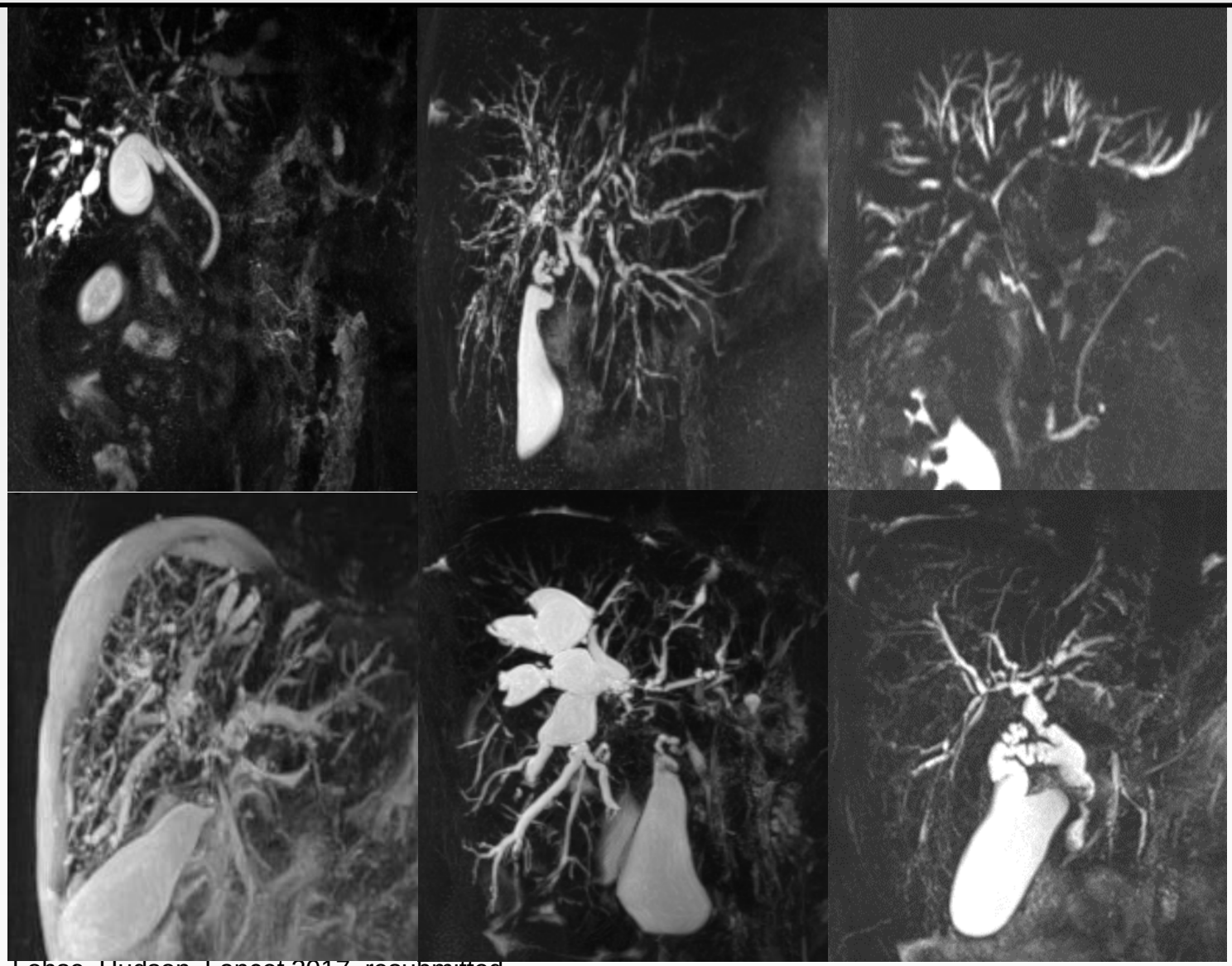


EASL CP Guidelines PBC. J Hepatol 2017; 67:145

Sclerosing cholangitis

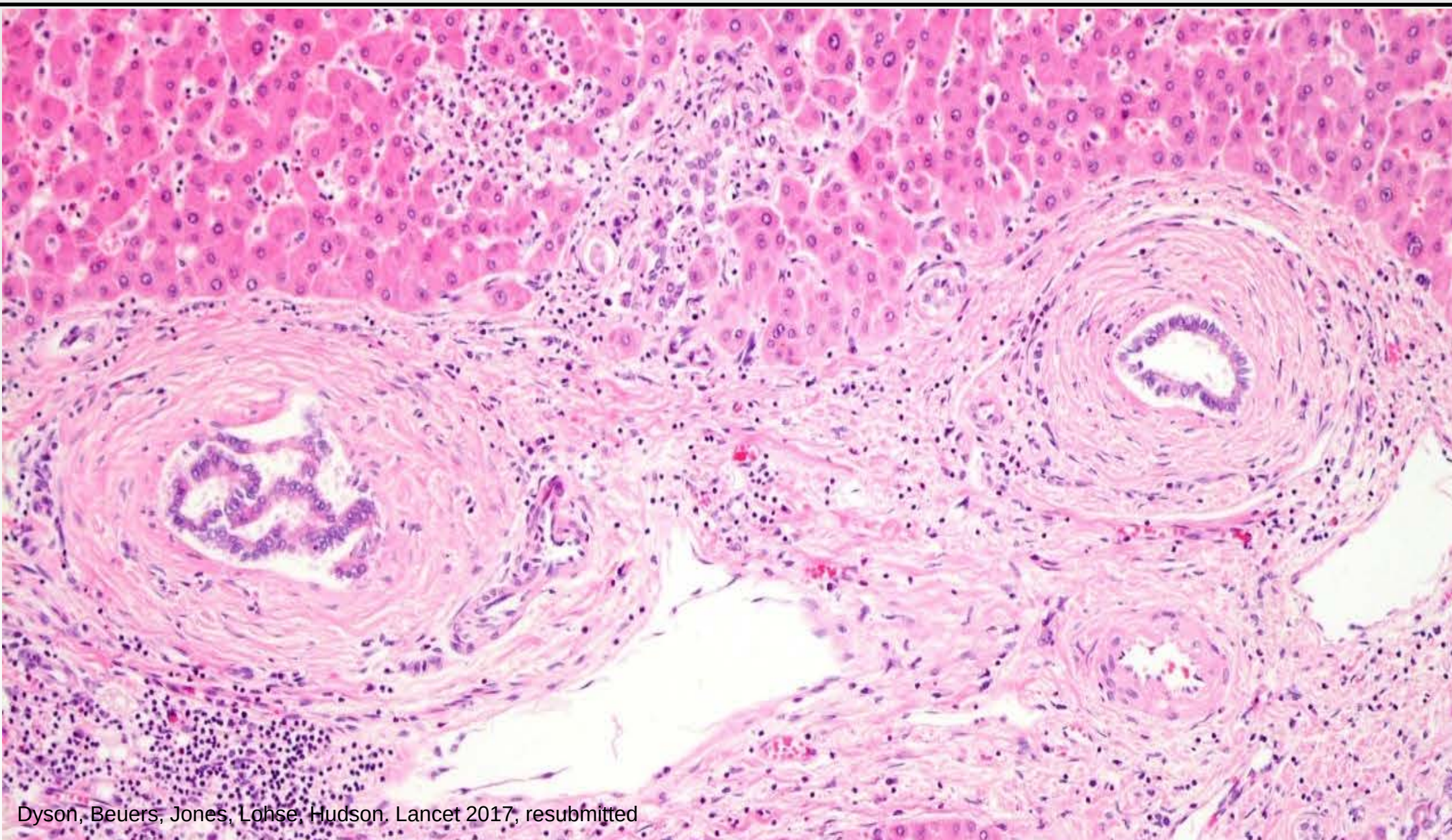
MRCP



Dyson, Beuers, Jones, Lohse, Hudson. Lancet 2017, resubmitted

Sclerosing cholangitis

Histology



Dyson, Beuers, Jones, Lohse, Hudson. Lancet 2017, resubmitted

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-associated cholangitis (IAC)
- Ischaemic cholangitis
- Mast cell cholangiopathy
- Portal hypertensive biliopathy
- Recurrent pyogenic cholangitis
- Sarcoidosis
- Sclerosing cholangitis of the critically ill patient
- Surgical trauma

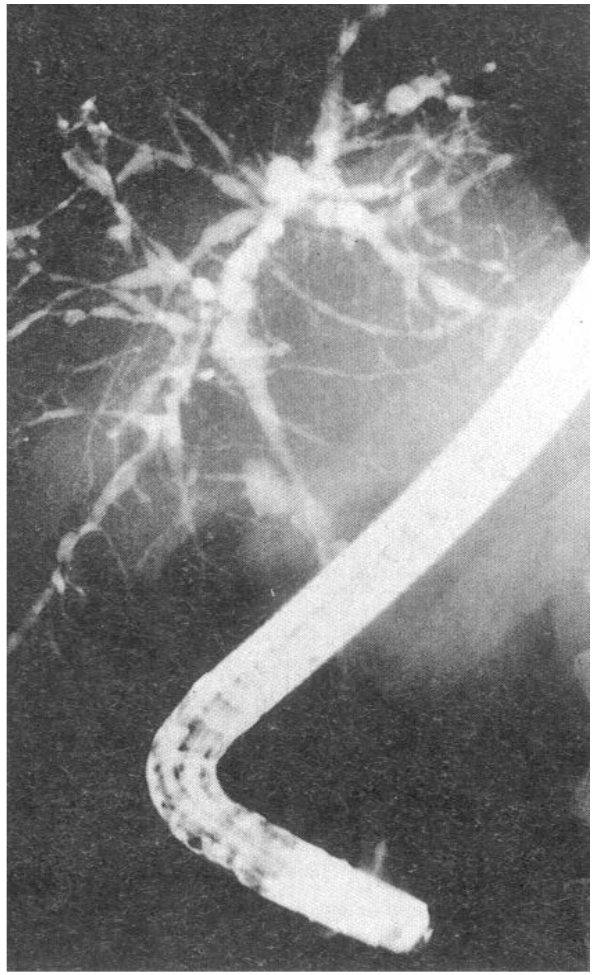
→ **Secondary sclerosing cholangitis**

Dyson, Beuers, Jones, Lohse, Hudson. Lancet 2017, resubmitted

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)	**21.2**
(LTx-free survival of 450 patients at 3 LTx centres	13.2)
Cholangiocarcinoma	7%
Colorectal carcinoma	3%



m, 42 years

Boonstra, Ponsioen et al., Hepatology 2013;58:2045 (population-based cohort [n=590, follow-up 92 months] covering the Northern half of the Netherlands)

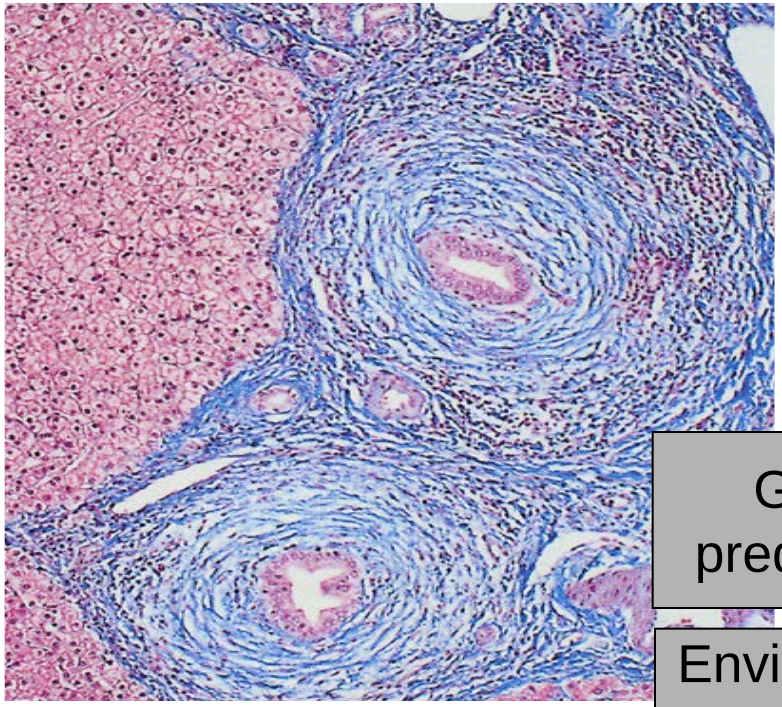
Characteristics of primary biliary cholangitis and primary sclerosing cholangitis

	PBC	PSC
Prevalence (per 100.000)	25 – 40	6 – 14
Gender (w : m)	9 : 1	1 : 2
Age at manifestation	40 - 60	25 - 45
Cholestatic enzyme pattern	+	+
Autoantibodies	AMA (M2)	(p-ANCA)
Bile duct lesion (Histol.)	florid	fibrosing
Cholangiography	–	Stenoses/dilatations of bile ducts

Primaire sclerosierende cholangitis

- Diagnose
- **Pathogenese**
- Therapie

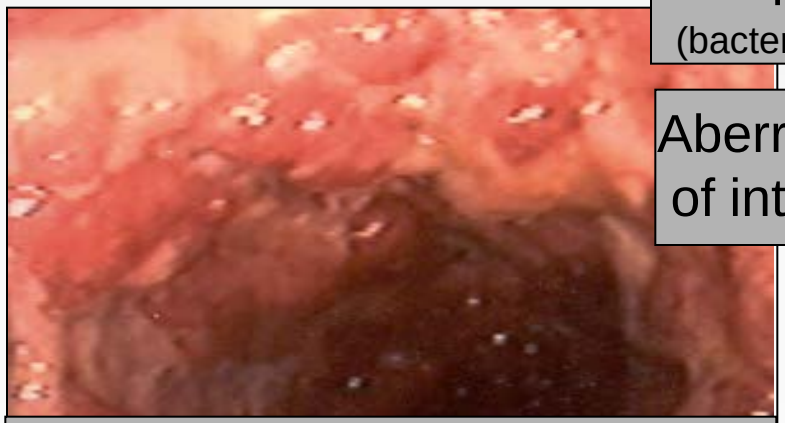
Pathogenesis of primary sclerosing cholangitis



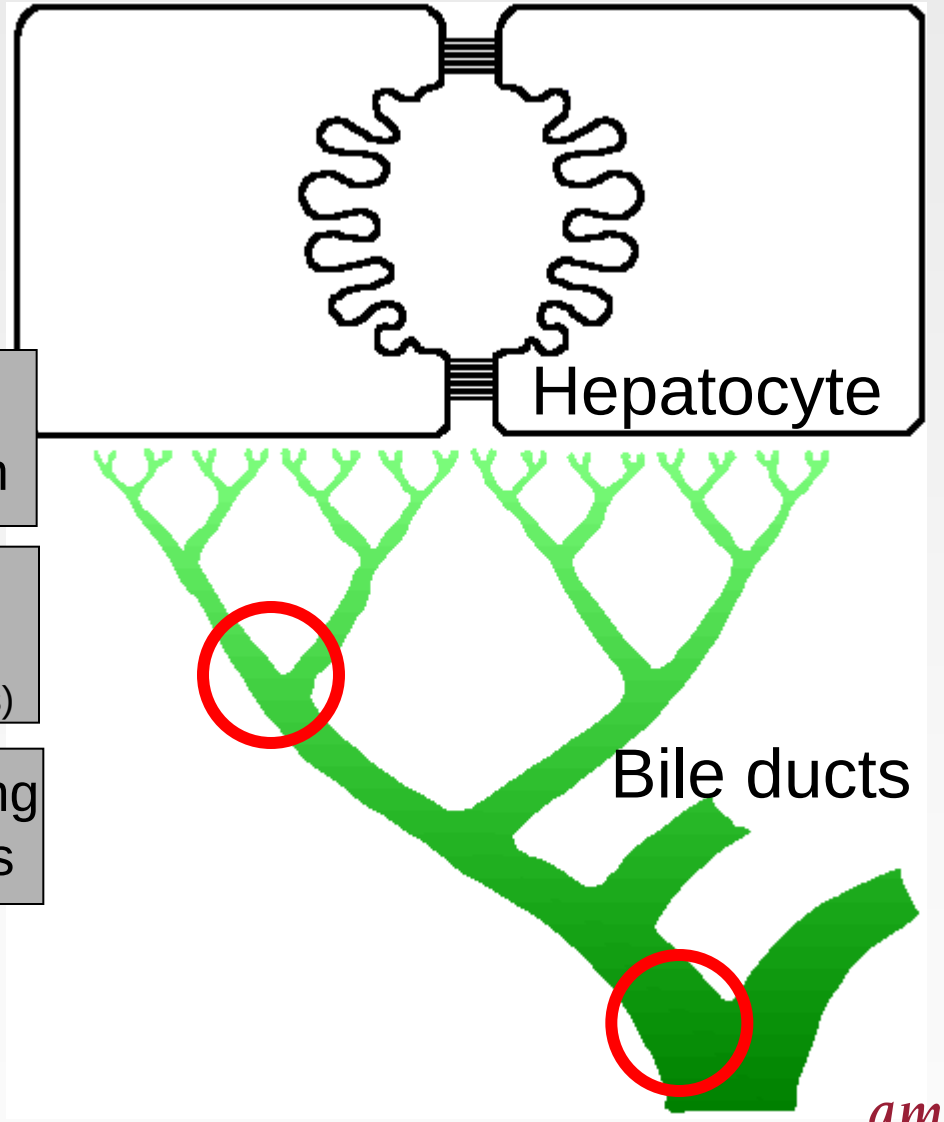
Genetic predisposition

Environmental factors
(bacterial pathogens)

Aberrant homing of intest.T-cells



Association with IBD ≥70%

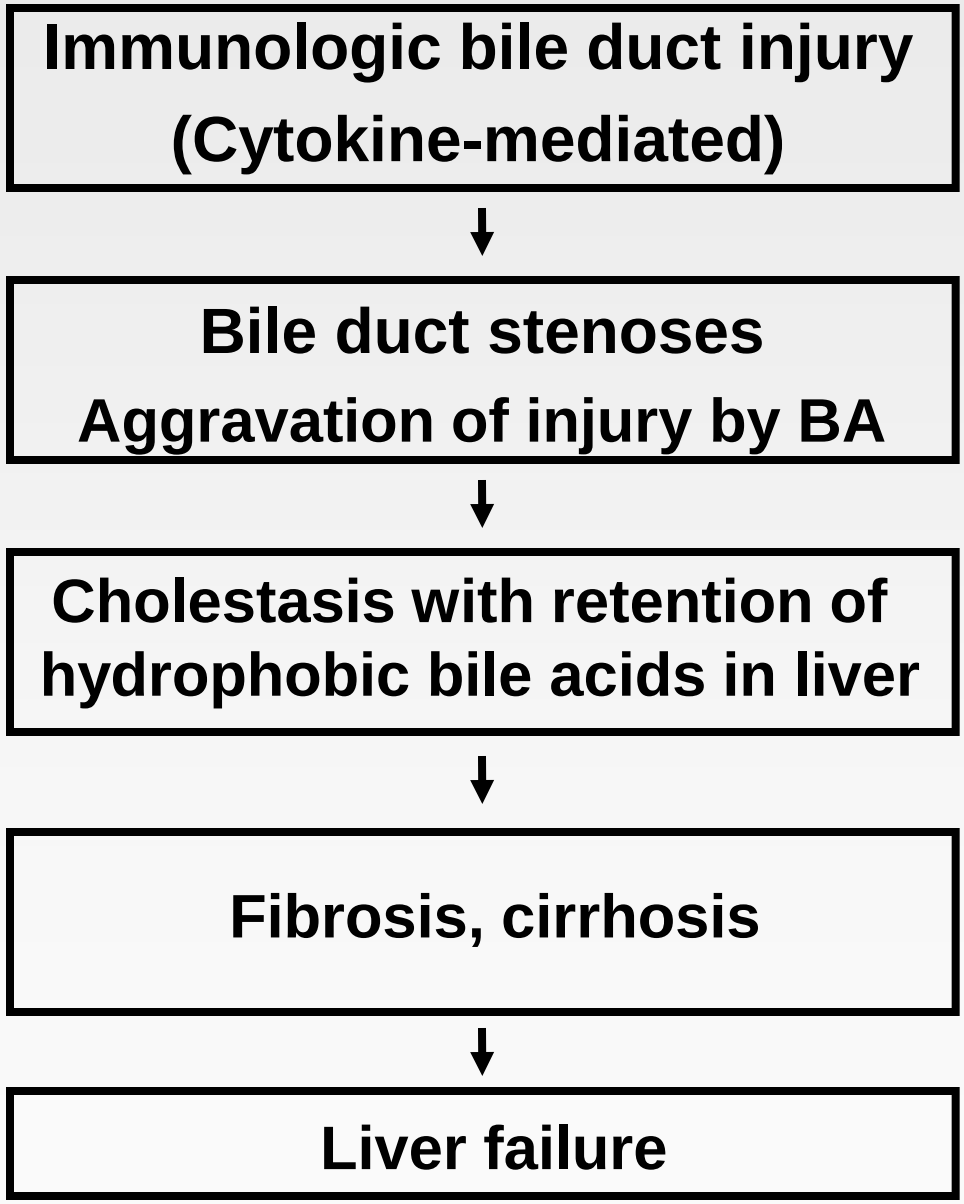


Primaire sclerosierende cholangitis

- Diagnose
- Pathogenese
- **Therapie**

PSC : Therapy

Pathogenetic model



Ursodeoxycholic acid

(15-20 mg/kg/d)

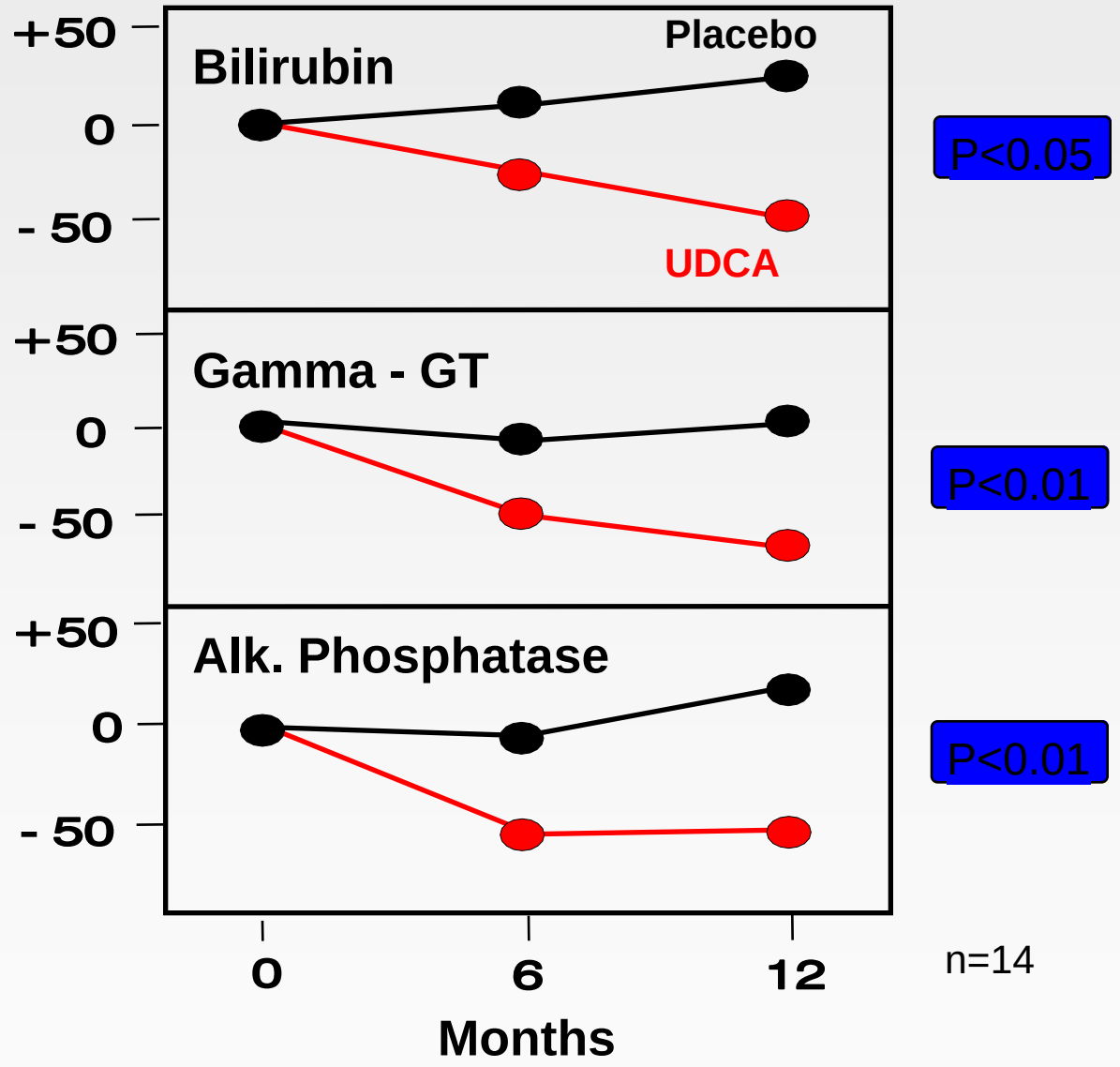
?

Liver transplantation

EASL CP Guidelines, J Hepatol 2009;51:237

Treatment of primary sclerosing cholangitis with UDCA

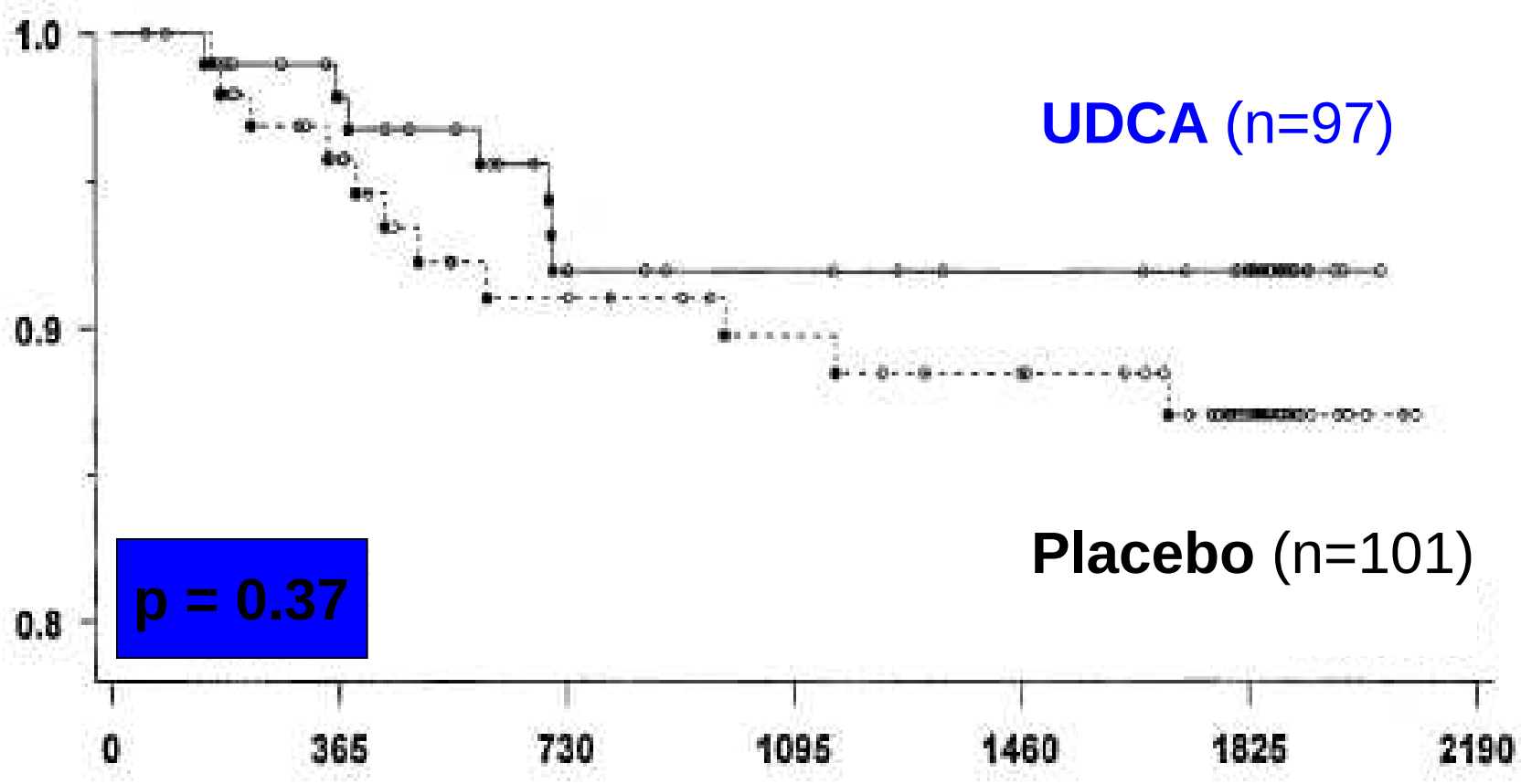
Serum liver tests



Beuers et al., Hepatology 1992;16:707

Treatment of primary sclerosing cholangitis with UDCA

- Transplant-free survival -

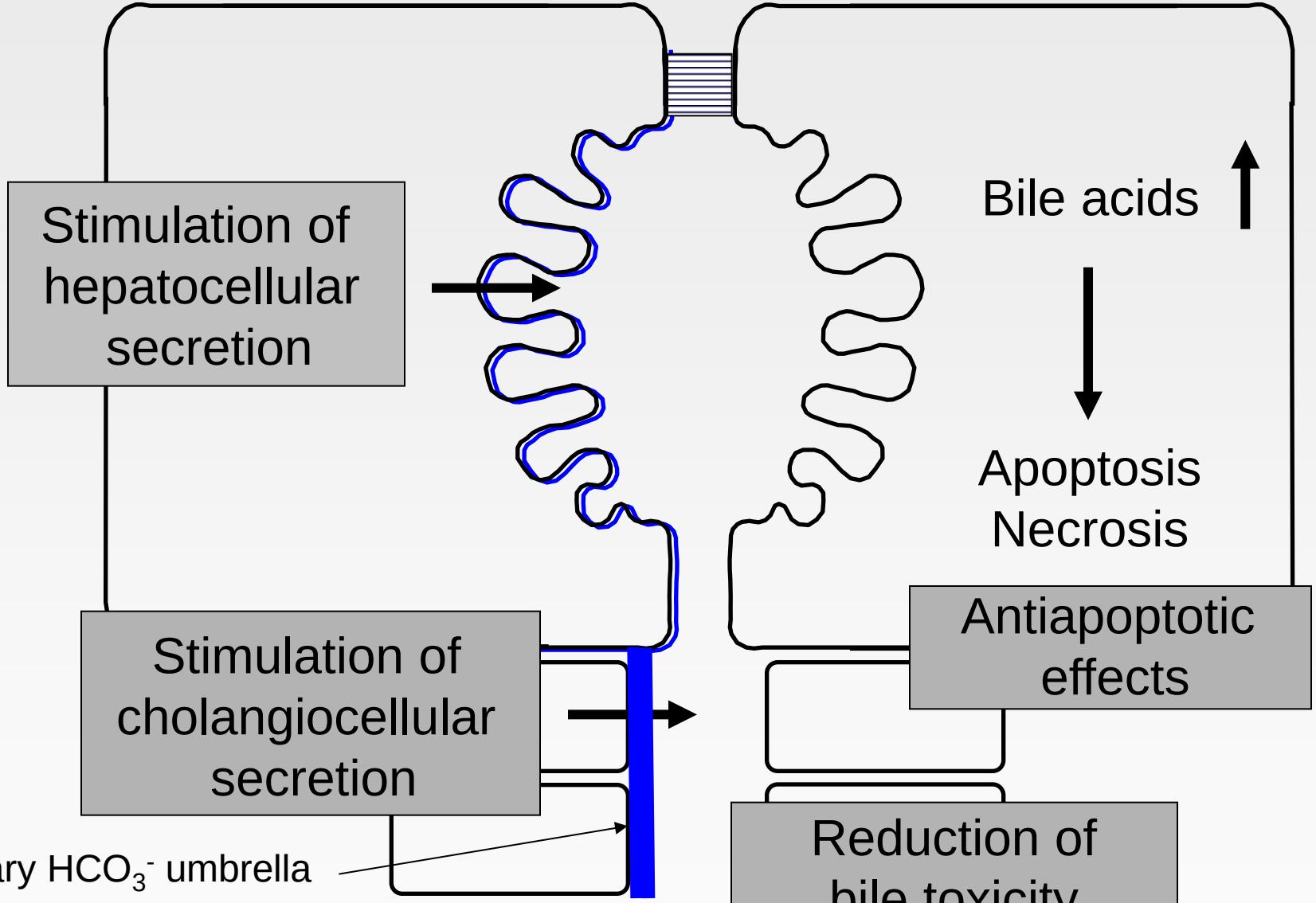


Survival without liver trans-plantation

Power analysis *a priori*: n = 346

Olsson et al., Gastroenterology 2005;129:1464

Potential mechanisms and sites of action of UDCA in cholestatic liver diseases



Beuers et al. Hepatology 2010;52:1489
Hohenester et al.Hepatology 2012;55:173

Beuers, Trauner, Jansen, Poupon. J Hepatol 2015;62:S35

Treatment of primary sclerosing cholangitis with UDCA

Summary

- The available data base shows that **UDCA** ***at therapeutic doses*** **(15-20 mg/kg/d)** improves serum liver tests and surrogate markers of prognosis (I/B1), but does not reveal a proven benefit on survival (III/C2).

  EASL Clinical Practice Guidelines, J Hepatol 2009;51:237

- In adult patients with PSC, we recommend against the use of UDCA as medical therapy (IA).

  AASLD Practice Guidelines PSC. Hepatology 2010;51:660

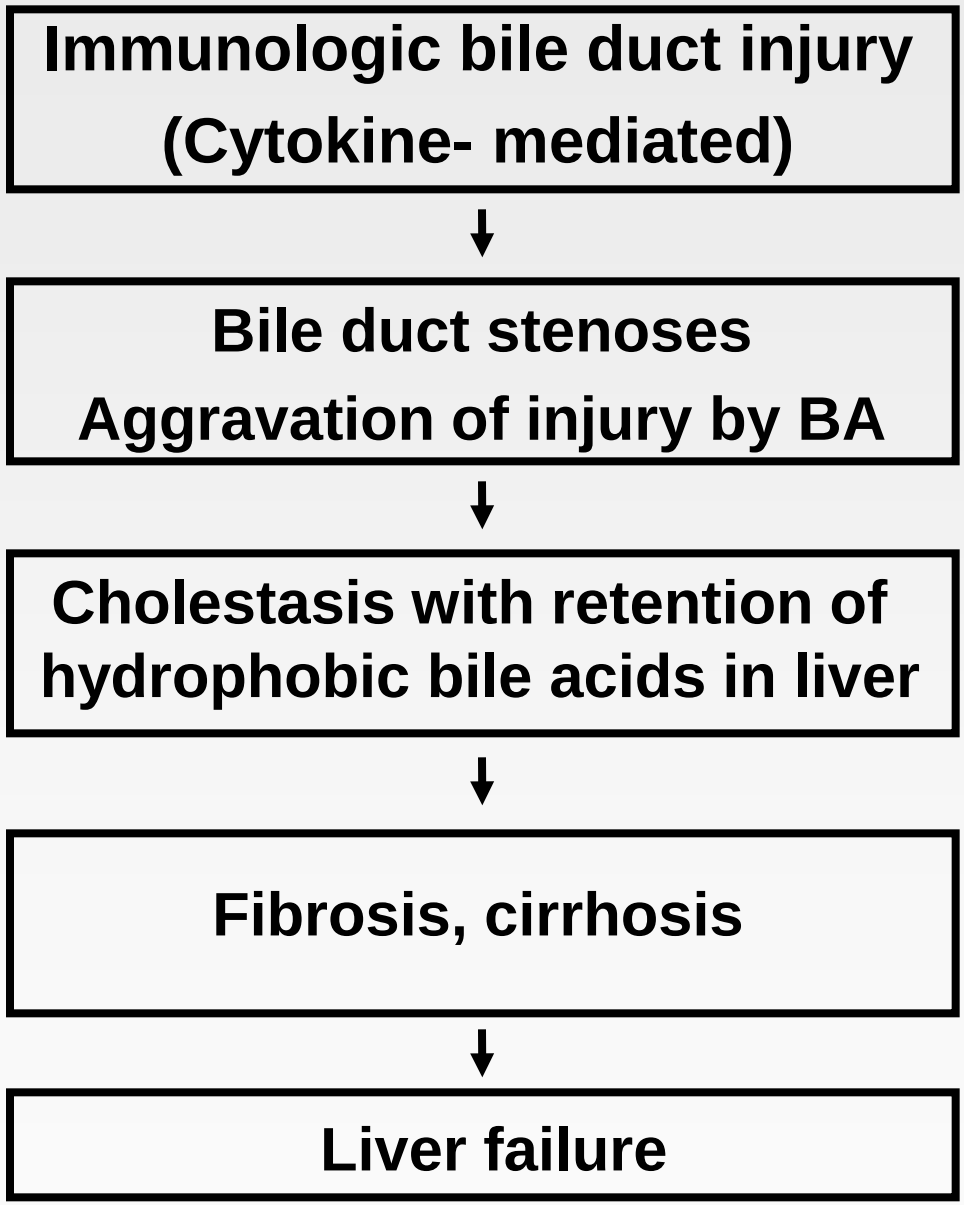
- UDCA in doses > 28 mg/kg/d should not be used for the management of patients with PSC (IA).

  ACG Clinical Guideline PSC. AJG 2015;110:646

- I : Randomized, placebo-controlled trials, meta-analyses
- III : Opinion of respected authorities
- A : Strong recommendation – strong evidence
- B1 : Moderate evidence – strong recommendation (GRADE)
- C2 : Weak evidence - weak recommendation (GRADE)

PSC : Therapy *under evaluation*

Pathogenetic model



Vedolizumab ?
norUDCA ?
RCT (Phase 2)

Endoscopic dilatation
RCT (Phase 3)

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

Nuclear receptor agonists ?
- PPARα
RCT (Phase 2)
FGF19 homologues ?

Liver transplantation

Vraag 1

Uw 27-jarige patiënt met PSC en Colitis ulcerosa vraagt u: Voor welke kwaadaardige tumor heb ik de relatief sterkste verhoging van risico door mijn ziekte ?

- Cholangiocellulair carcinoom
- Colorectaal carcinoom
- Hepatocellulair carcinoom
- Melanoom
- Pancreas carcinoom

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	Advies
• **Cholangiocellulair carcinoom**	**Echo jaarlijks**
• Colorectaal carcinoom	**Coloscopie jaarlijks**
• Hepatocellulair carcinoom	
• Melanoom	
• Pancreas carcinoom	

Primary sclerosing cholangitis

Conclusions

- The typical PSC patient is a young(er) man with IBD.
- The pathogenesis remains unclear and may involve genetic, environmental and immunological factors.
- PSC is associated with an enhanced risk for malignancies.
- UDCA at moderate doses and balloon dilatation for dominant strictures are widely used in PSC. Liver transplantation is the only proven treatment which improves long-term survival.

The patient with sclerosing cholangitis

History, additional diagnostic procedures:
Causes of secondary sclerosing cholangitis ?

no → **Primary sclerosing cholangitis**

yes →

- AIDS-related cholangiopathy
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→ **Secondary sclerosing cholangitis**

Dyson, Beuers, Jones, Lohse, Hudson. Lancet 2017, resubmitted

Vraag 2

U begeleid een 65-jarige schilder met een IgG4-geassociëerde cholangitis (IAC). Hij vraagt u voor meer informaties over het ziektebeeld.

Wat is correct?

- Het ziektebeeld betreft vooral vrouwen.
- Inductie therapie met prednisolon wordt gevolgd door cyclische onderhoudsbehandeling met rituximab.
- Patiënten hebben een hoge genetische predispositie.
- IAC stelt vaak een van meerdere orgaan manifesties van de systemische IgG4-gerelateerde ziekte voor.
- Serum IgG4 is zeer sensitief en specifiek voor de diagnose van IgG4-RD.

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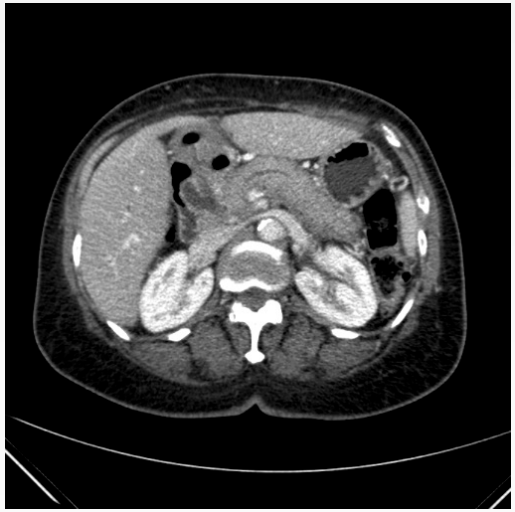
IgG4-geassocieerde cholangitis

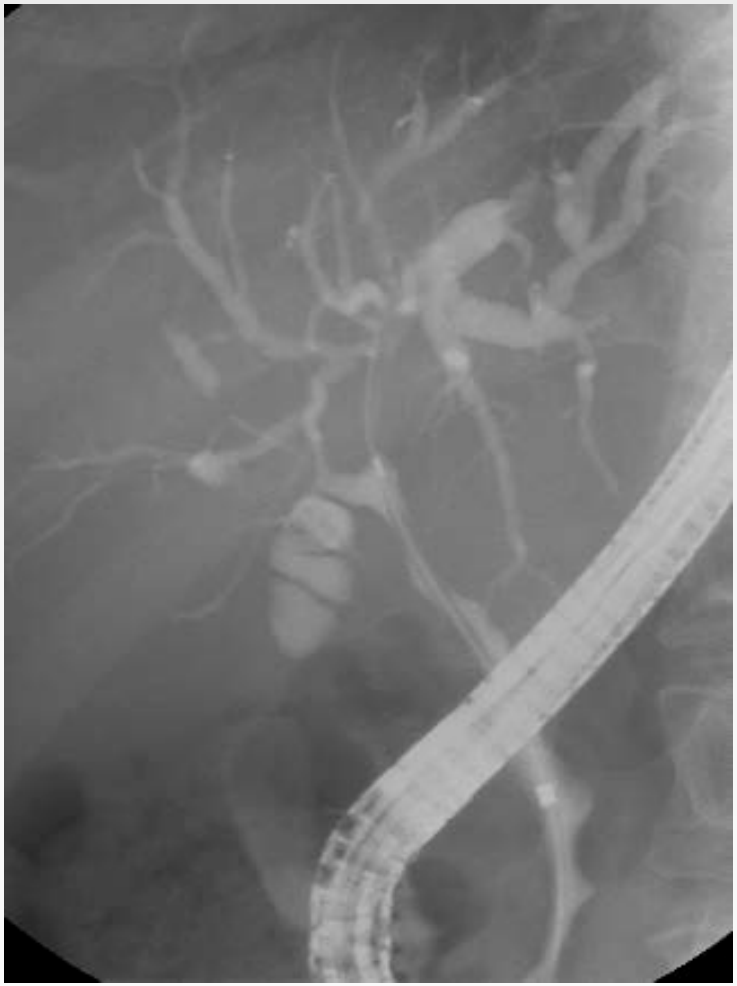
- **Diagnose**
- **Pathogenese**
- **Therapie**

IgG4-associated cholangitis (IAC)

The typical patient

- Male (80-85%)
- Middle aged / elderly (> 60 yrs)
- Jaundice, weight loss, abdominal compl.
- Localized organ swelling / tumor
- Elevated serum / tissue IgG4
- Other organ manifestations of IgG4-RD





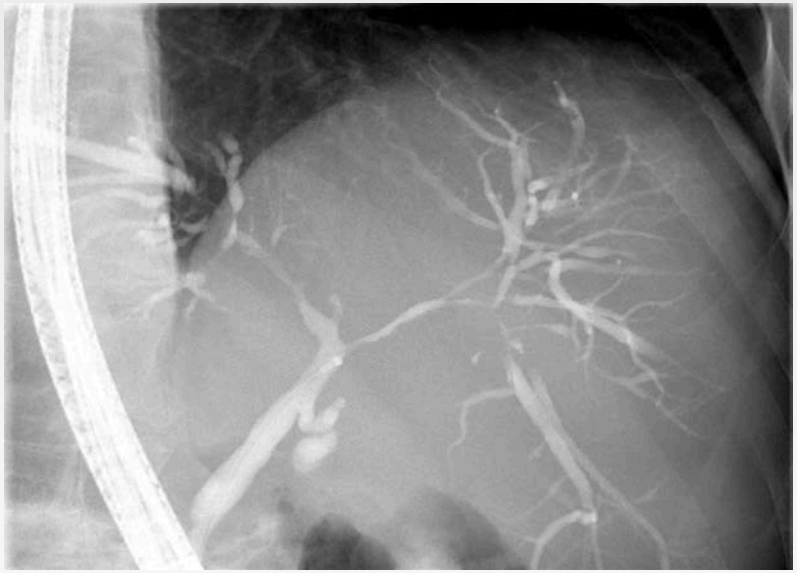
71 yrs, m; IgG4 11.9 g/L (n < 1.4)

Alderlieste et al., Digestion 2009;79:220

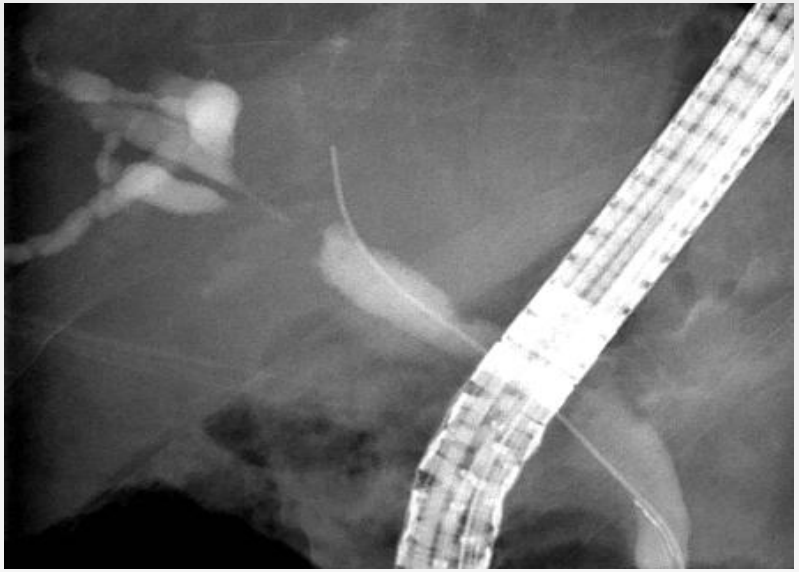
Stone et al N Engl J Med 2012;366:539

Hubers et al. Clin Rev Allerg Immunol 2015;48:198

IgG4-associated cholangitis mimics PSC and CCA



Cholangiographic appearance mimicking primary sclerosing cholangitis (**PSC**)



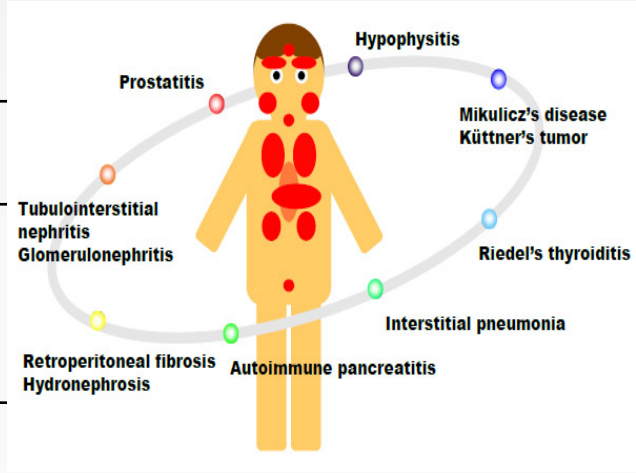
Cholangiographic appearance mimicking cholangiocarcinoma (**CCA**)

Misdiagnosis is common!

Hubers & Beuers, Viszeralmedizin 2015;31:185

IgG4-Related Disease (IRD)

Abdominal and pelvic IRD localisation	Extra-abdominal IRD localisation
Bile ducts (IAC), gallbladder and liver	Hypophysis
Pancreas (AIP)	Eye, retro-orbital tumor
Stomach, intestine, ileal pouch	Salivary and lacrimal glands
Retroperitoneum	Thyroid gland
Kidney	Lungs
Pseudotumor	Lymphatic system (lung hilus !)
Prostate	Vascular system (aortitis)
Testis	



Stone et al N Engl J Med 2012;366:539 Hubers et al. Clin Rev Allerg Immunol 2015;48:198

Diagnosis of IgG4-associated Cholangitis

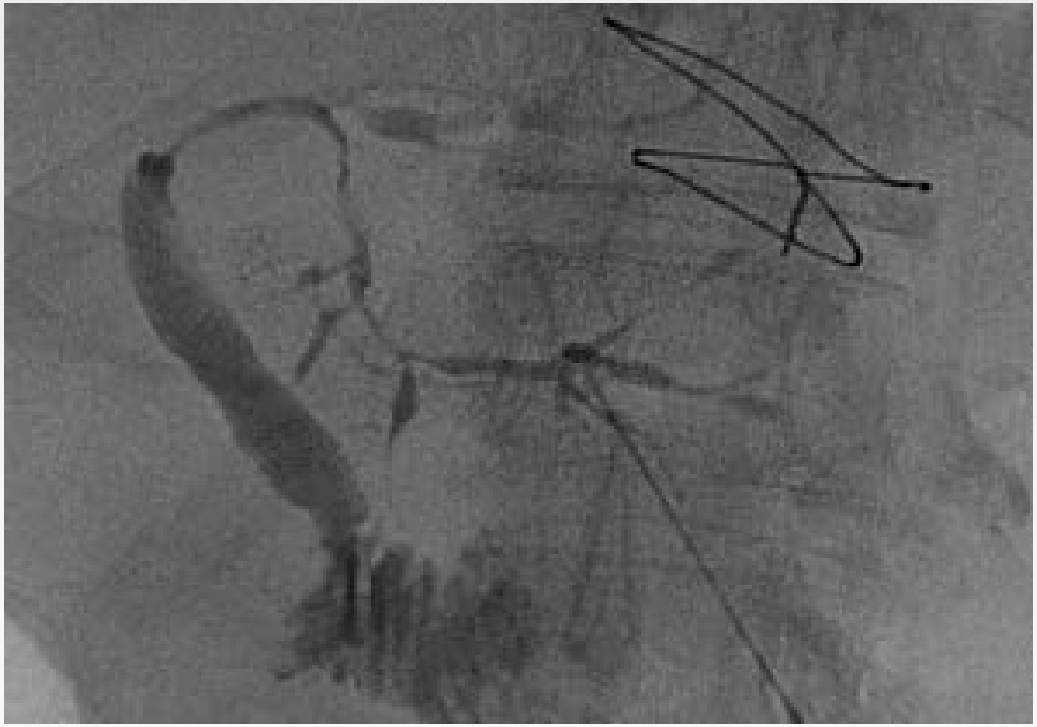
- HISORt Criteria -

Biliary strictures: intrahepatic, proximal and/or distal extrahepatic

A

Previous pancreatic / biliary resection or core biopsy of pancreas showing diagnostic features of AIP / IAC

Definite IAC



76 yrs, m; IgG4 12.5 g/L (n < 1.4)

Alderlieste et al., Digestion 2009;79:220

Ghazale et al., Gastroenterology 2008;134:706
EASL Clinical Practice Guidelines, J Hepatol 2009;51:237

Diagnosis of IgG4-associated Cholangitis

- HISORt Criteria -

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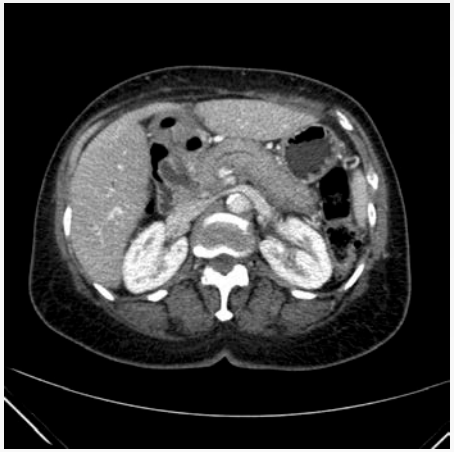
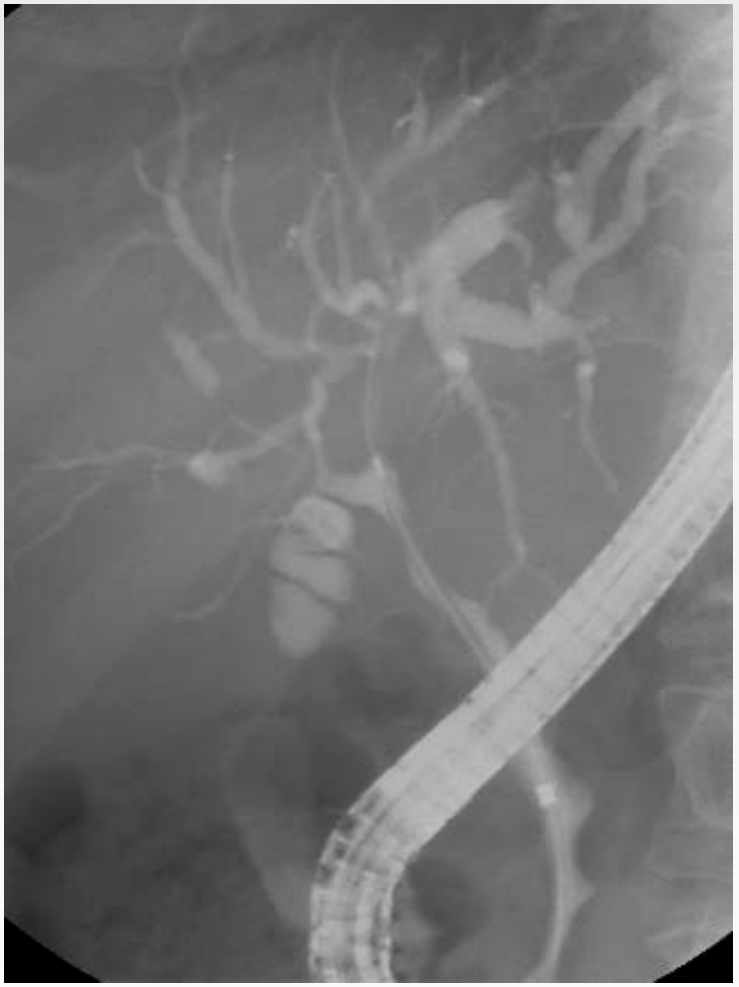
Previous pancreatic / biliary resection or core biopsy of pancreas showing diagnostic features of AIP / IAC

B

Classical imaging findings of AIP
+
Elevated serum IgG4



Definite IAC



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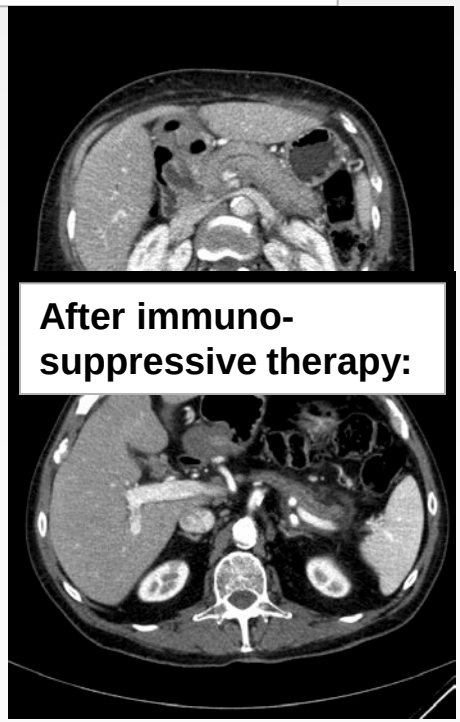
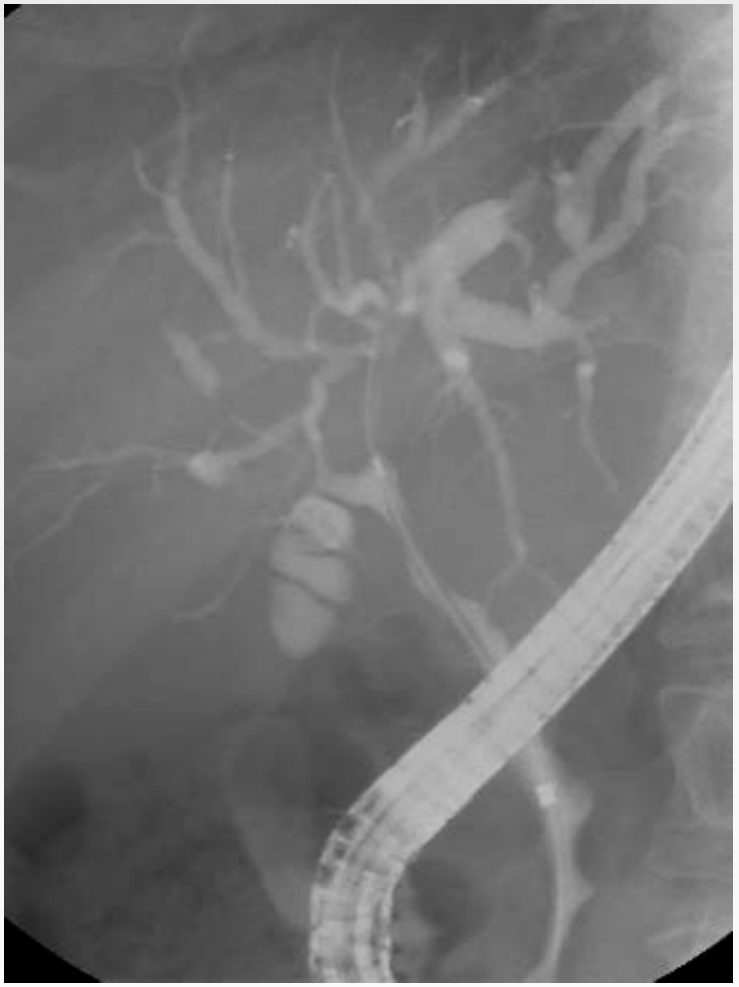


After immuno-suppressive therapy:

Definite IAC



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Diagnosis of IgG4-associated Cholangitis

Biliary strictures: intrahepatic, proximal and/or distal extrahepatic

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Previous pancreatic / biliary resection or core biopsy of pancreas showing diagnostic features of AIP / IAC

B

Classical imaging findings of AIP
+
Elevated serum IgG4

C

Two or more of the following:

- Elevated serum IgG4
- Suggestive pancreatic imaging
- Other organ involvement
- Bile duct biopsy with > 10 IgG4-positive cells/HPF

Probable IAC

After 4 weeks of corticosteroids:

- Markedly improved biliary strictures
- Serum liver tests < 2 x ULN
- Decreasing IgG4 and CA19.9

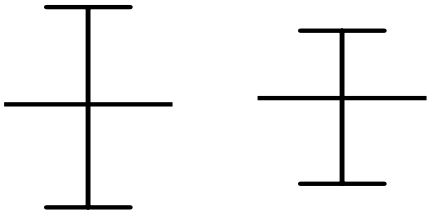
Definite IAC

Ghazale et al., Gastroenterology 2008;134:706

Diagnostic value of serum IgG4 is limited

Sensitivity = 86%
Specificity = 75%

1.4



Doorenspleet, Hubers et al. Hepatology. 2016; 64: 501

n=125

CA: Biliary and pancreatic malignancies

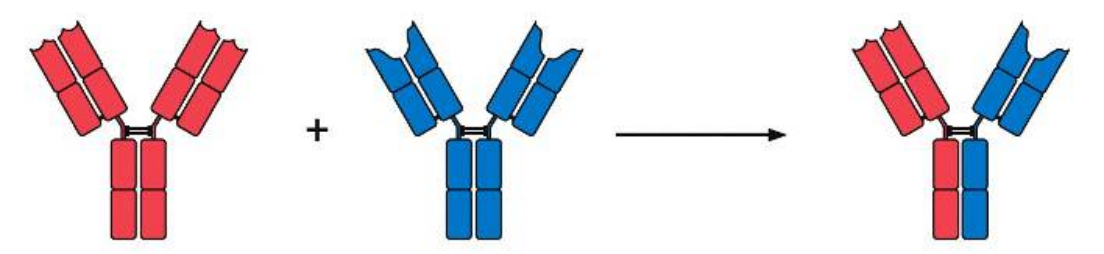
IgG4-geassocieerde cholangitis

- Diagnose
- **Pathogenese**
- Therapie

Pathogenesis of IgG4-Related Disease

Role of IgG4 ?

- Smallest fraction of total IgG in serum
- ‘Regulatory’ antibody
- Unable to bind C1q, low Fc affinity
- Upregulated in chronic immune stimulation (e.g., helminthic infections, allergies)
- Can exchange Fab arm



van der Neut Kolfschoten et al., Science 2007;317:1554

Role of IgG4 in health and disease

→ IgG4 is upregulated in chronic immune stimulation

Beekeepers [1]

- Bee poison-specific IgG4

Patients with melanoma [2]

- Melanoma-specific IgG4

Animal workers [3]

- Rodent-specific IgG4

1 Garcia-Robaina et al., Clin Exp Allergy 1997;27:418

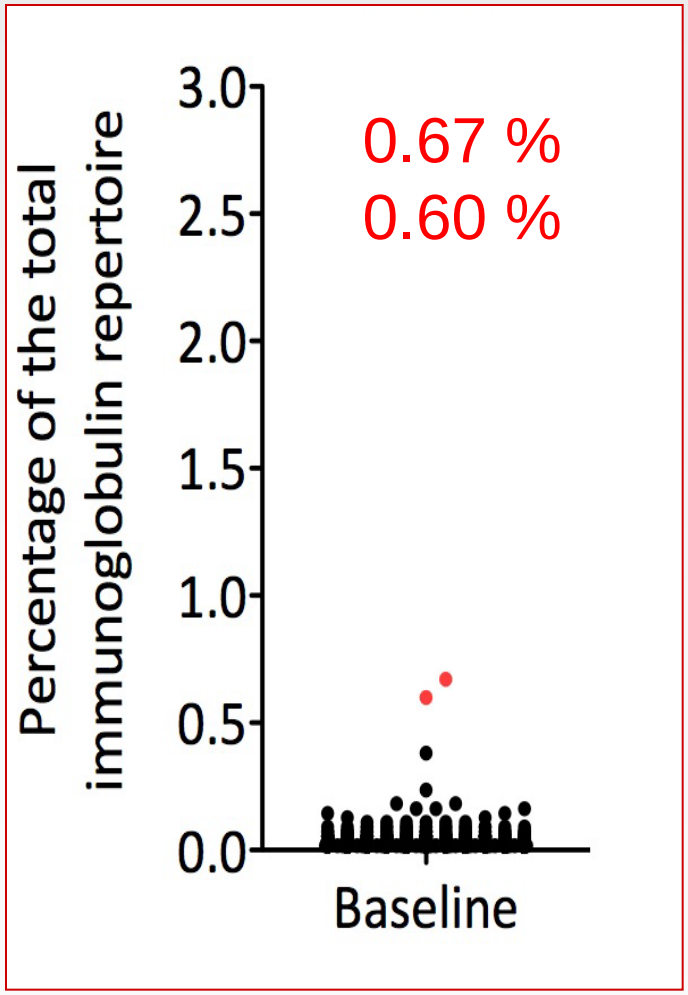
2 Karagiannis et al., J Clin Invest, 2013;123:1457

3 Jones et al., Occup Environm Medicine 2014; 71: 619

IgG4-associated cholangitis

B-cell receptor sequencing

Patient #1



- **Two highly expanded IgG4^{+} B cell clones**

➡ **Specific B-cell responses may be relevant in the pathogenesis of IgG4-related disease**

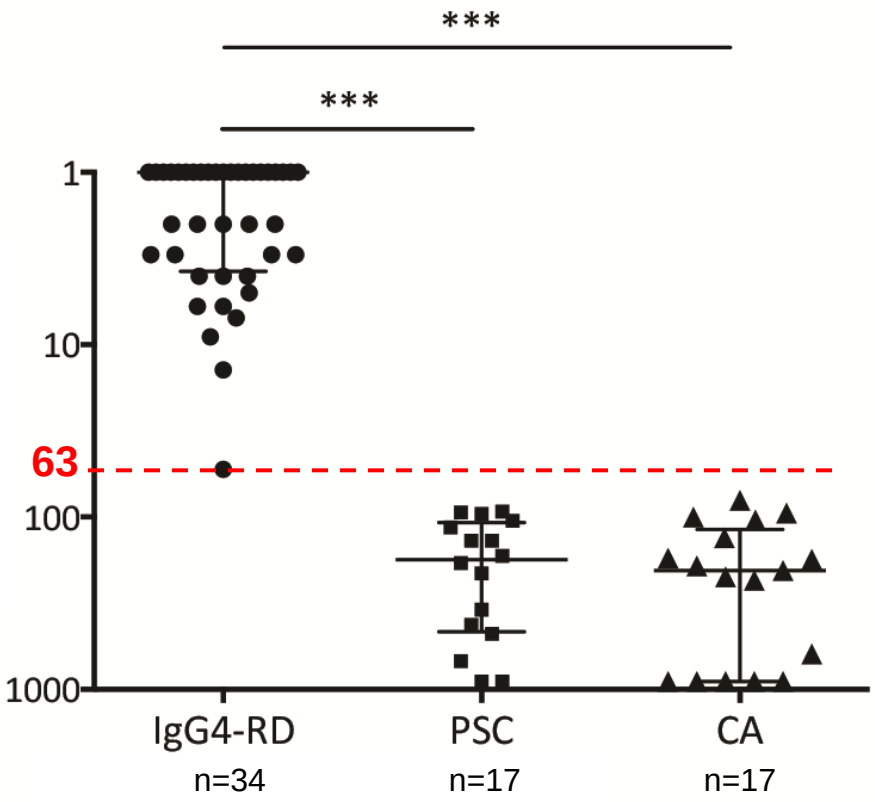
Maillette de Buy Wenniger, Doorenspleet et al. Hepatology 2013; 57: 2340 (epub 2012)

Distinguishing PSC and IgG4-associated cholangitis

The most prominent IgG4+ BCR clone ranks higher in IgG4-RD than PSC

Rank of the most prominent IgG4+ BCR clone

among all IgG clones



Sensitivity = 100%
Specificity = 100%

Doorenspleet, Hubers et al. Hepatology 2016; 64: 501

Maillette de Buy Wenniger, Doorenspleet et al. Hepatology 2013; 57: 2340

BCR: B-cell receptor

CA: Biliary and pancreatic malignancies

Distinguishing PSC and IgG4-associated cholangitis

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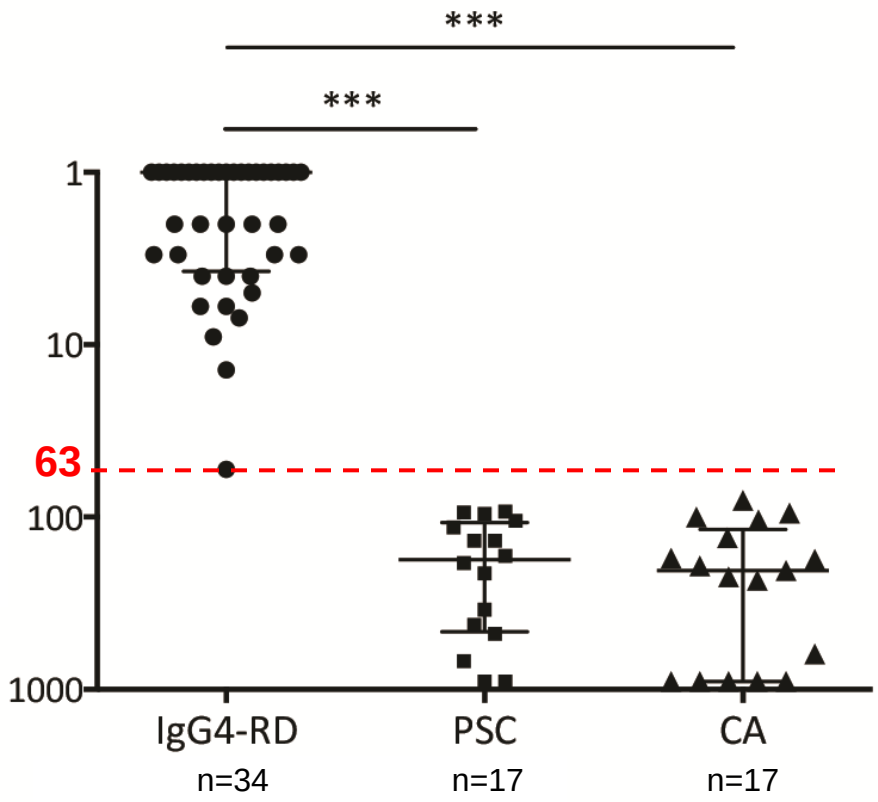
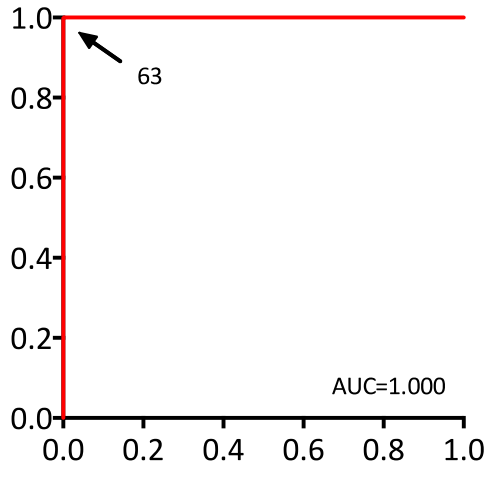
Rank of the most prominent IgG4+ BCR clone

among all IgG clones



Sensitivity = 100%
Specificity = 100%



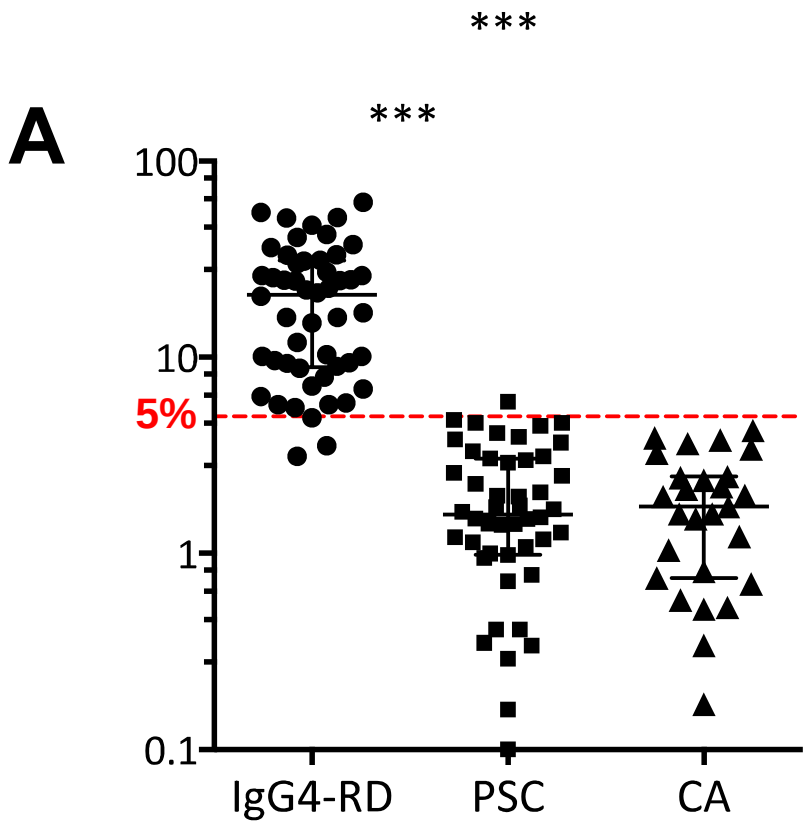
Doorenspleet, Hubers et al. Hepatology 2016; 64: 501

Maillette de Buy Wenniger, Doorenspleet et al. Hepatology 2013; 57: 2340

CA: Biliary and pancreatic malignancies

Distinguishing PSC and IgG4-Related Disease

An affordable IgG4/IgG RNA qPCR is almost as accurate as NGS technology



Sensitivity = 94%
Specificity = 99%

Doorenspleet, Hubers et al. Hepatology 2016; 64: 501

n=125

CA: Biliary and pancreatic malignancies

Chronic Exposure to Occupational Antigens May Play a Key Role in the Initiation and/or Maintenance of IgG4-Related Disease

“Blue collar” work (> 1 year, mostly lifelong)	Amsterdam	Oxford
IAC/AIP (n=25 and 44, resp.)	88 %	61 %
PSC (n=21 and 22, resp.)	16 %	22 %

Maillette de Buy Wenniger, Curver, Beuers. Hepatology 2014: 60:1453

IgG4-geassocieerde cholangitis

- Diagnose
- Pathogenese
- **Therapie**

Treatment of IgG4-associated cholangitis

1. Initial treatment:

- 40 mg* predniso(lo)ne / day for 4 weeks
- Tapering of daily predniso(lo)ne: 5 mg/week
- Total treatment duration: 11 weeks

* (10-)**20 mg predniso(lo)n / day may be sufficient**

Buijs et al. Pancreas 2014;43:261

2. Long-term maintenance treatment (incomplete responders):

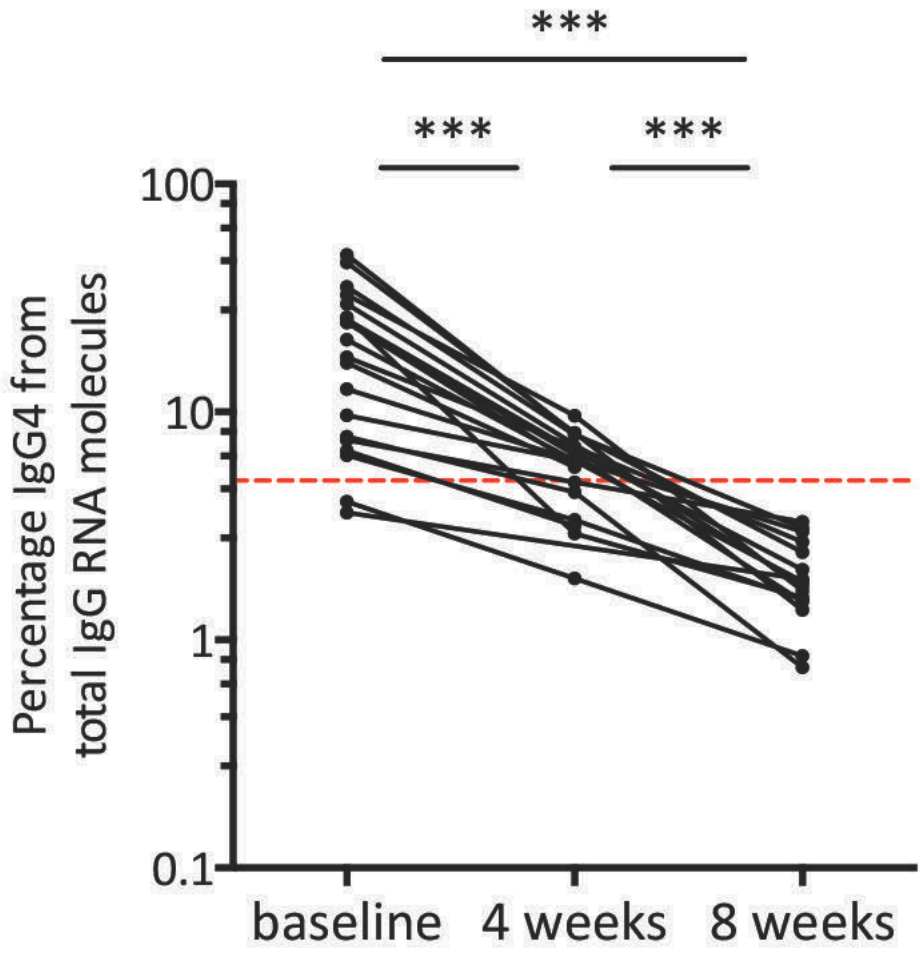
- 5(-10) mg/d Predniso(lo)ne
- ≤ 2 mg/kg/d Azathioprine

3. Experimental (corticosteroid-refractory patients): Rituximab

Ghazale et al., Gastroenterology 2008;134:706
EASL Clinical Practice Guidelines, J Hepatol 2009;51:237

How to monitor treatment response in IgG4-RD?

IgG4/IgG RNA ratio: promising marker for monitoring of disease activity

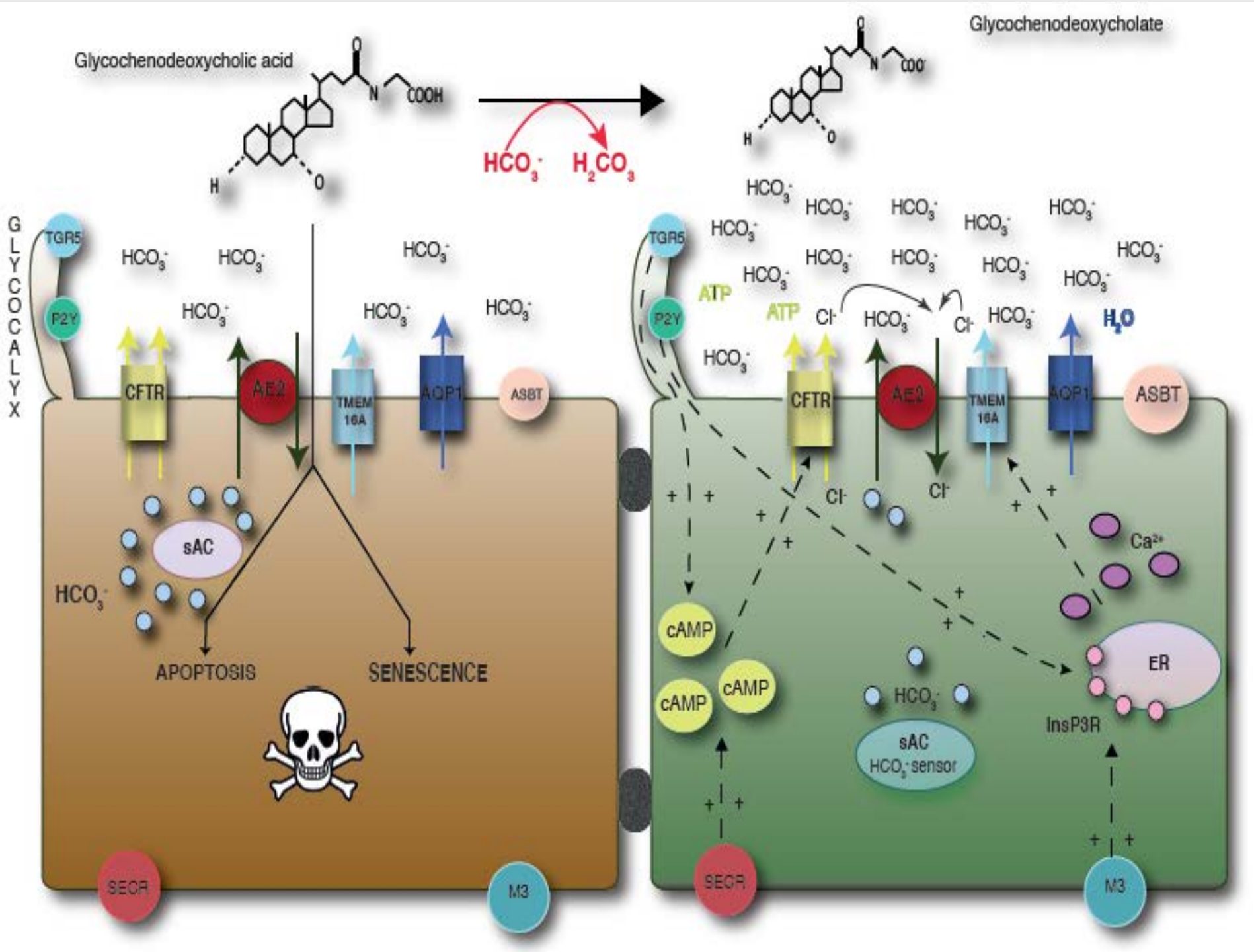


Doorenspleet, Hubers et al. Hepatology 2016; 64: 501

IgG4-associated cholangitis

Conclusions

- Bile ducts and pancreas are major targets of IgG4-RD, a multiorgan disease characterized by highly specific B-cell responses.
- Environmental risk factors (“blue collar worker“) might explain the typical gender and age distribution.
- A highly accurate and affordable IgG4/IgG RNA qPCR distinguishes IgG4-RD from PSC and pancreatobiliary malignancies and may help to monitor treatment response.
- Immunosuppressive treatment is effective in IgG4-RD.


Glycochenodeoxycholic acid
COOH
Glycochenodeoxycholate
COO⁻
HCO3⁻
H2CO3
GLYCOCALYX
TGR5
P2Y
CFTR
AE2
TMEM 16A
AQP1
ASBT
sAC
APOPTOSIS
SENESCENCE
SECR
M3
ATP
Cl⁻
H2O
cAMP
Ca2+
ER
InsP3R
sAC
HCO3⁻ sensor