Dutch Liver Week 2018

Etiologie, pathogenese, diagnostiek en therapie:

Primair biliaire cholangitis, Primair scleroserende cholangitis, IgG4-gerelateerde ziekte

Overeenkomsten en verschillen

Rotterdam

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Disclosures

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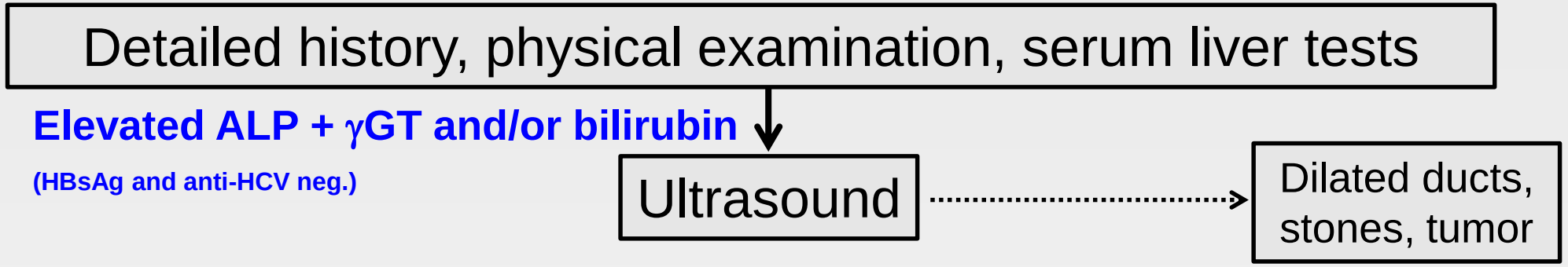
Consulting agreements

Intercept, Novartis

Support for investigator-initiated studies

Falk, Intercept

Diagnostic approach to cholestasis



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

Entry question #1

Which pathological findings fit with the diagnosis of primary biliary cholangitis (PBC)?

A. aP, γGT ↑; AMA+, AMA-M2+; IgM ↑

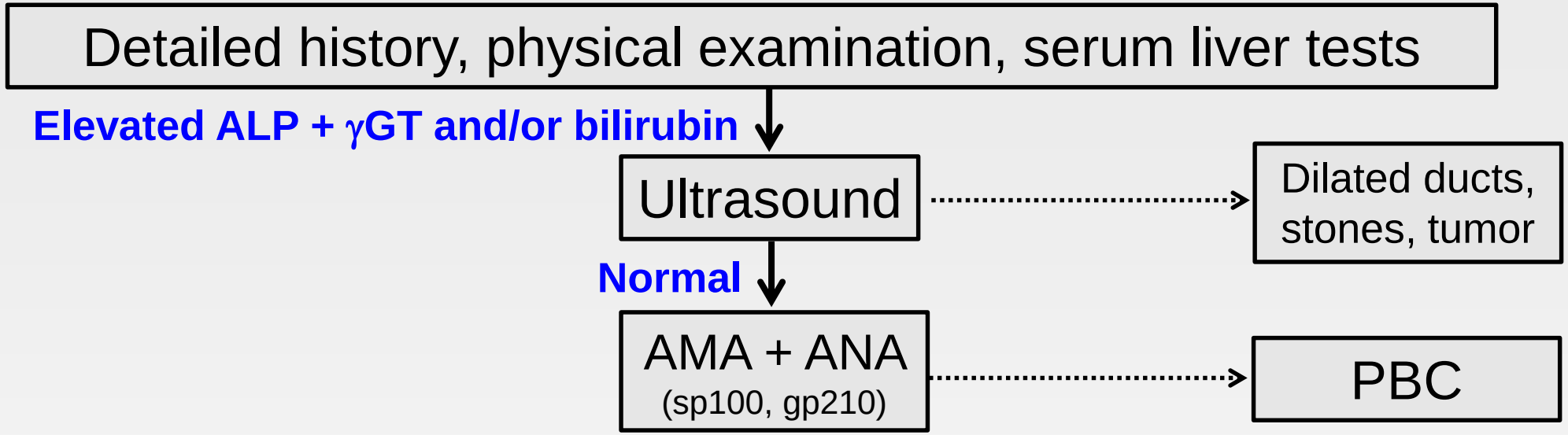
B. ALAT, ASAT ↑; ANA+, SMA+, SLA+; IgG ↑

C. ALAT, ASAT ↑; LKM-1; IgG ↑

D. aP, γGT ↑; p-ANCA

E. ALAT, ASAT ↑; anti-TG-IgA

Diagnostic approach to cholestasis



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D. aP, γGT ↑; p-ANCA

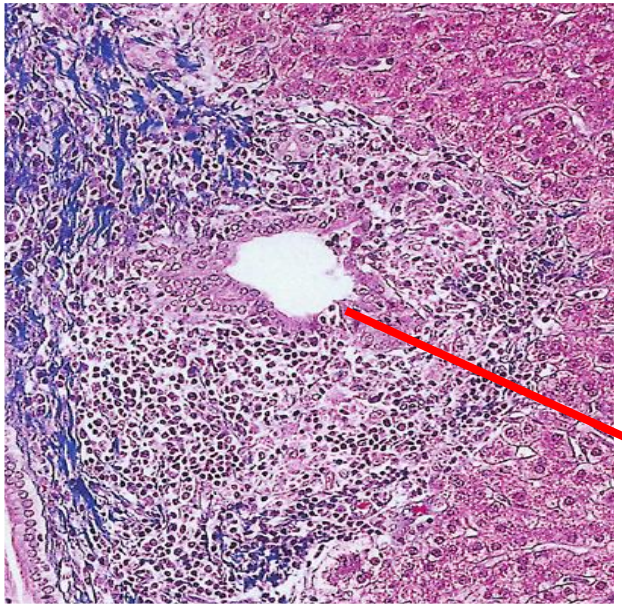
E. ALAT, ASAT ↑; anti-TG-IgA

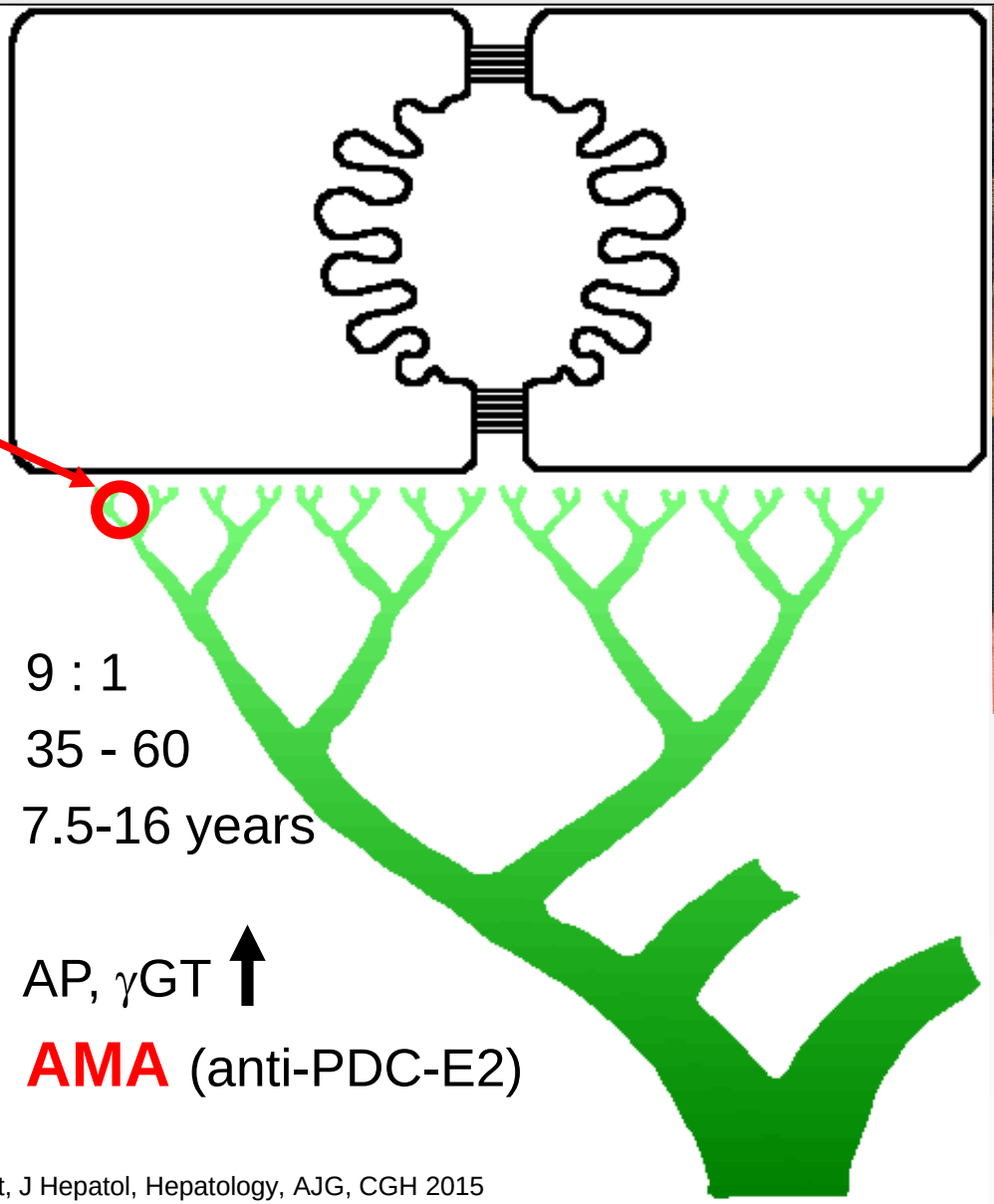
Primair biliaire cholangitis

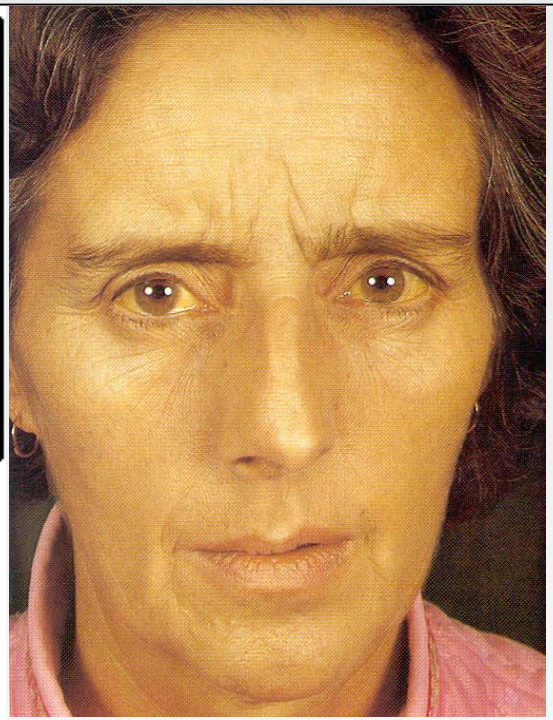
- **Diagnose**
- **Pathogenese**
- **Therapie**

Primary biliary cholangitis [formerly: cirrhosis*]

Characteristics







Sherlock and Summerfield, 1991

Sex (f:m)	9 : 1
Age	35 - 60
Survival without treatm.	7.5-16 years
Cholestatic enzyme pattern	AP, γGT ↑
Autoantibodies	**AMA** (anti-PDC-E2)

Symptoms:

- Fatigue
- Itch
- "Dry eye, dry mouth"
- …

*Beuers, Gershwin, Gish et al. Gastroenterology, Gut, J Hepatol, Hepatology, AJG, CGH 2015

Primair biliaire cholangitis

- Diagnose
- **Pathogenese**
- Therapie

Primary biliary cholangitis:

Pathogenesis

Immune-mediated bile duct injury

↓

Bile duct injury by hydrophobic bile acids

↓

Cholestasis with retention of hydrophobic bile acids in liver

↓

Fibrosis, cirrhosis

↓

Liver failure

Genetic Predisposition

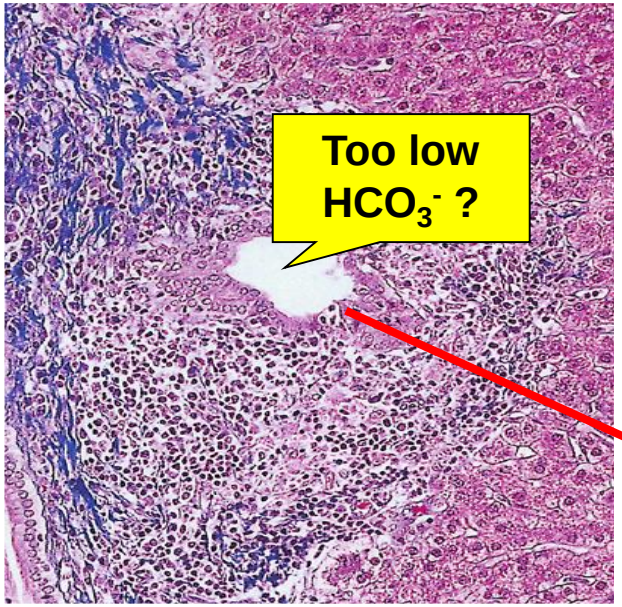
Environmental factors
(molecular mimicry)

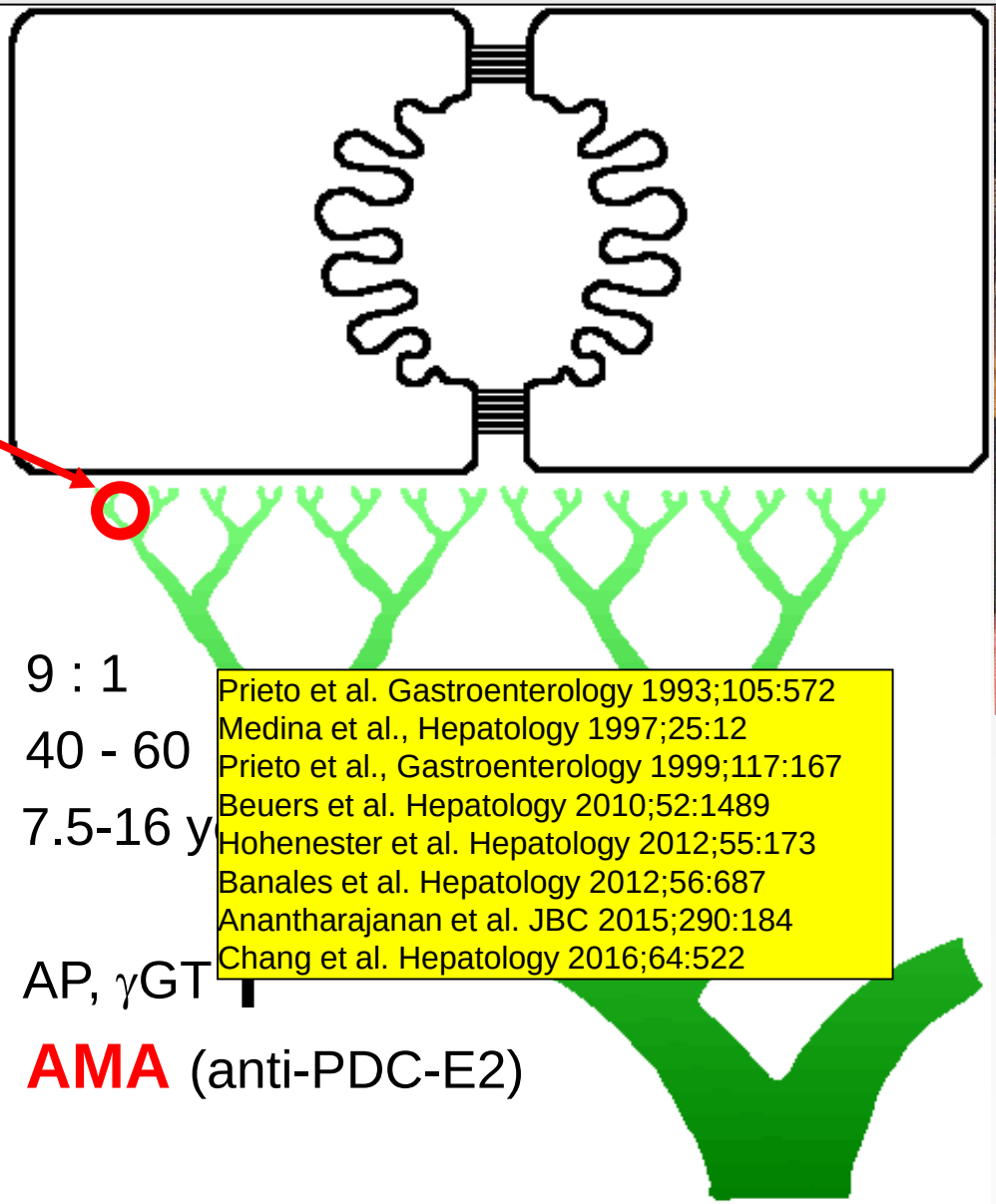
Cellular/humoral immune response

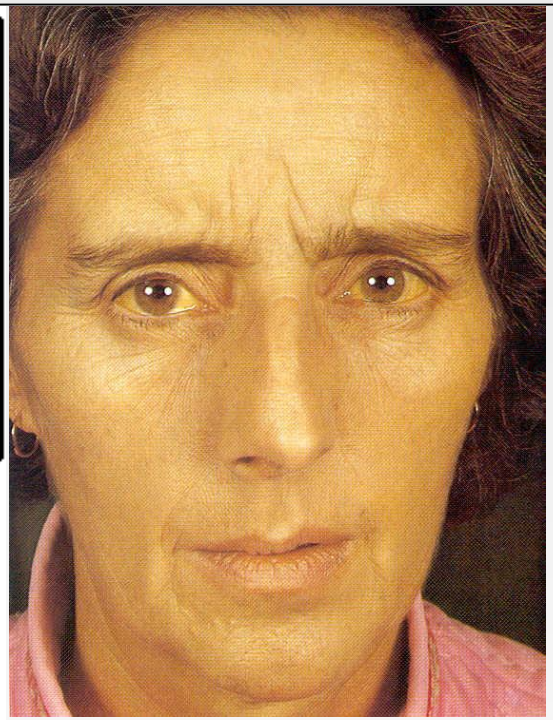
Beuers, Boyer, Paumgartner. Hepatology 1998;28:1449

Primary biliary cholangitis

Pathogenesis







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Sex (f:m)	9 : 1
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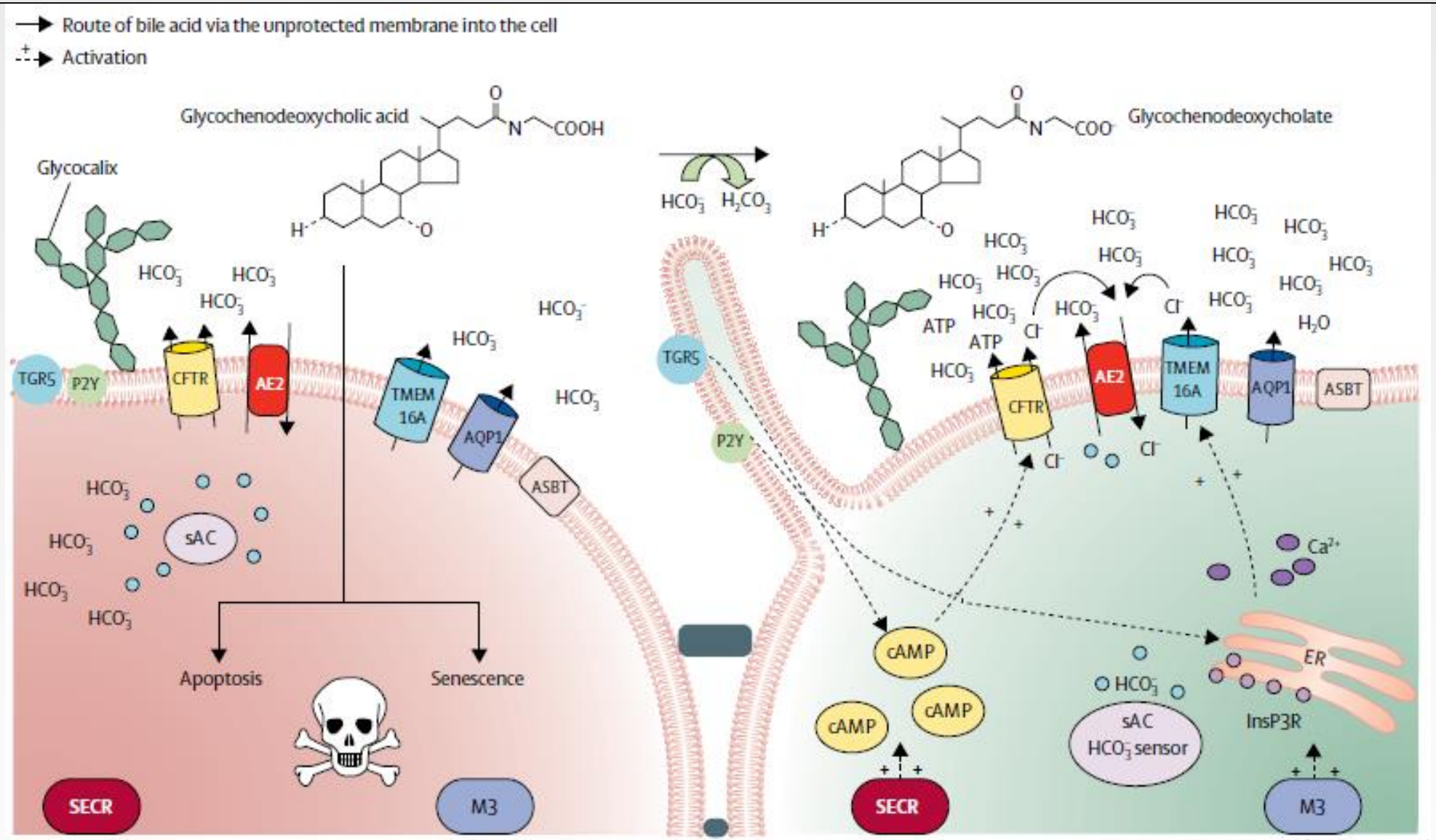
Cholestatic enzyme Pattern	AP, γGT
Autoantibodies	**AMA** (anti-PDC-E2)

Prieto et al. Gastroenterology 1993;105:572
Medina et al., Hepatology 1997;25:12
Prieto et al., Gastroenterology 1999;117:167
Beuers et al. Hepatology 2010;52:1489
Hohenester et al. Hepatology 2012;55:173
Banales et al. Hepatology 2012;56:687
Anantharajanan et al. JBC 2015;290:184
Chang et al. Hepatology 2016;64:522

Symptoms:

- Fatigue
- Itch
- “Dry eye, dry mouth“
- …

Hypothesis: The biliary HCO_3^- umbrella

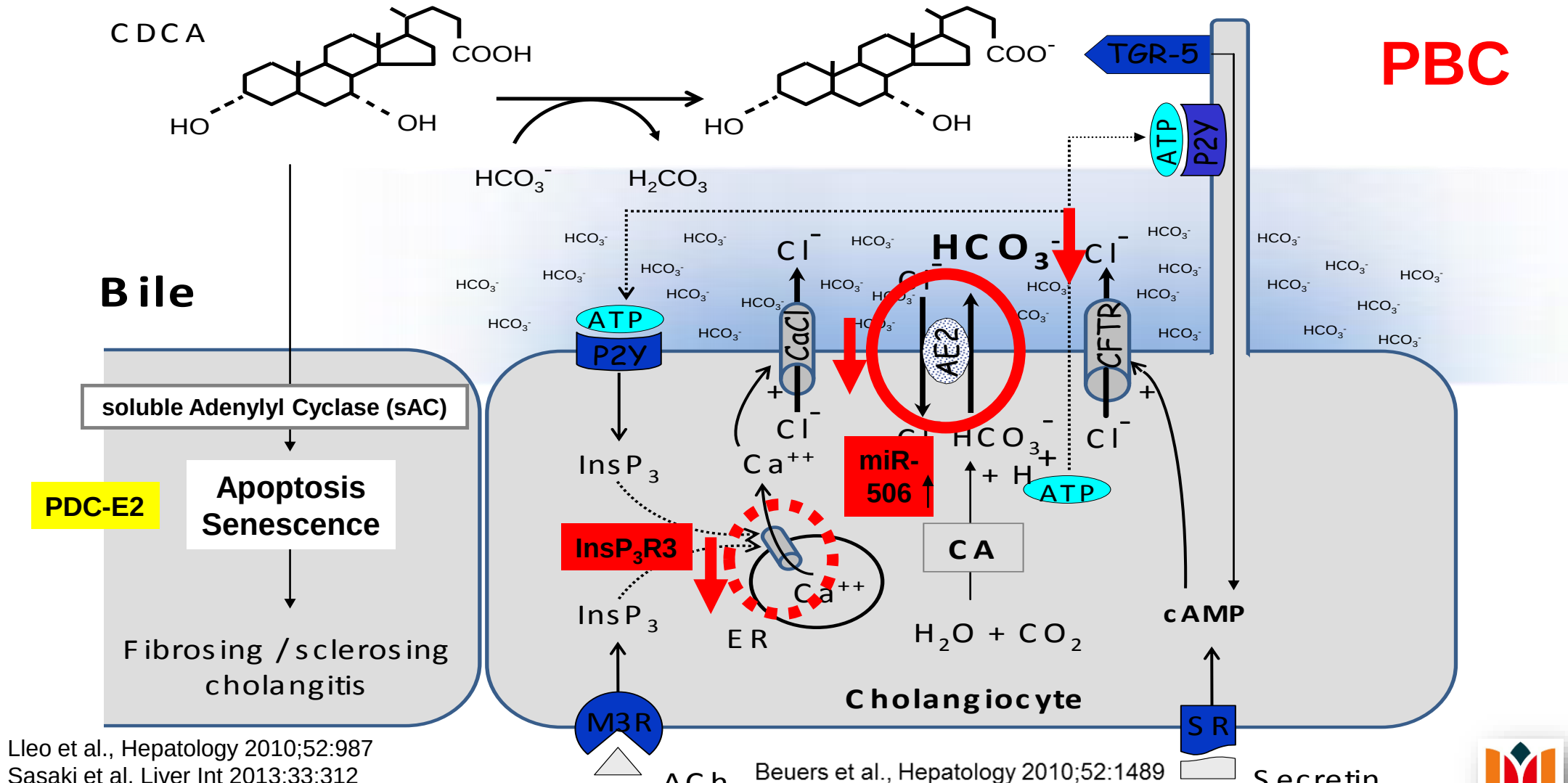


[Lancet 2018, in press]

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

Defect of the biliary HCO_3^- umbrella in PBC ?

Elevated miR-506 downregulates AE2 and $InsP_3R3$, critical for HCO_3^- secretion



Lleo et al., Hepatology 2010;52:987
Sasaki et al. Liver Int 2013;33:312
Banales et al. Hepatology 2012;56:687
Ananthananarayanan et al. JBC 2015;290:184

Beuers et al., Hepatology 2010;52:1489
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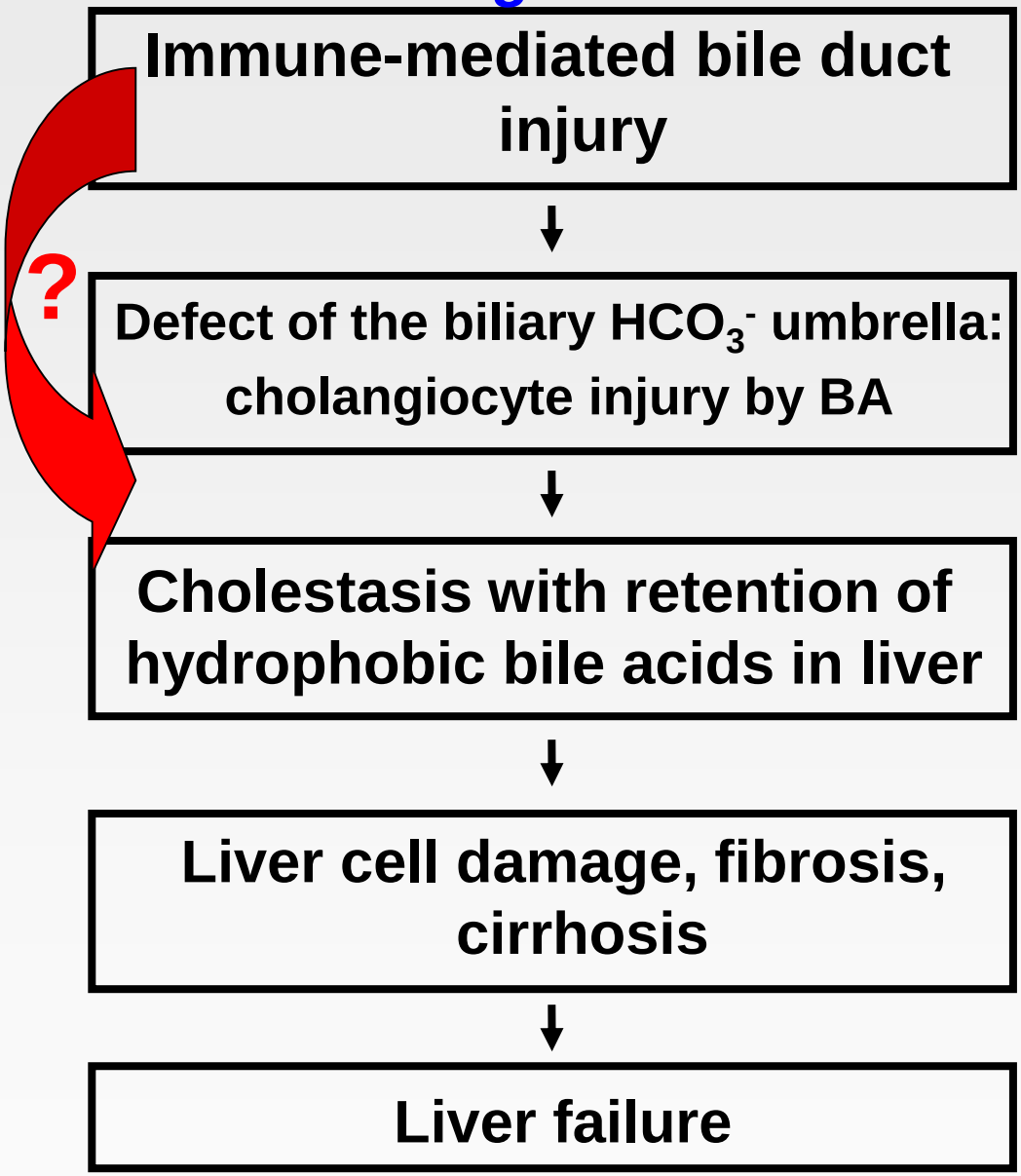
Primary biliary cholangitis

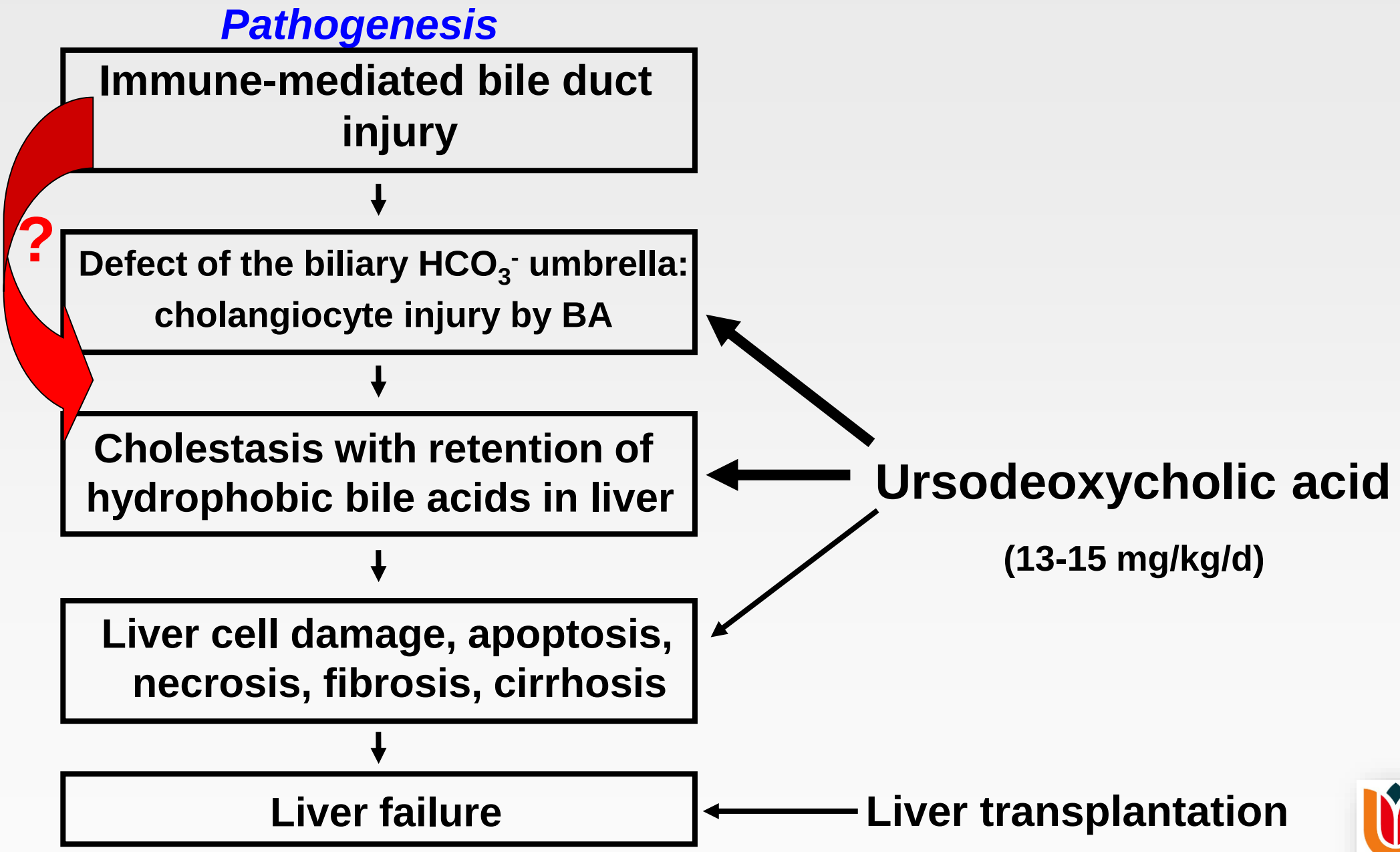
Pathogenesis



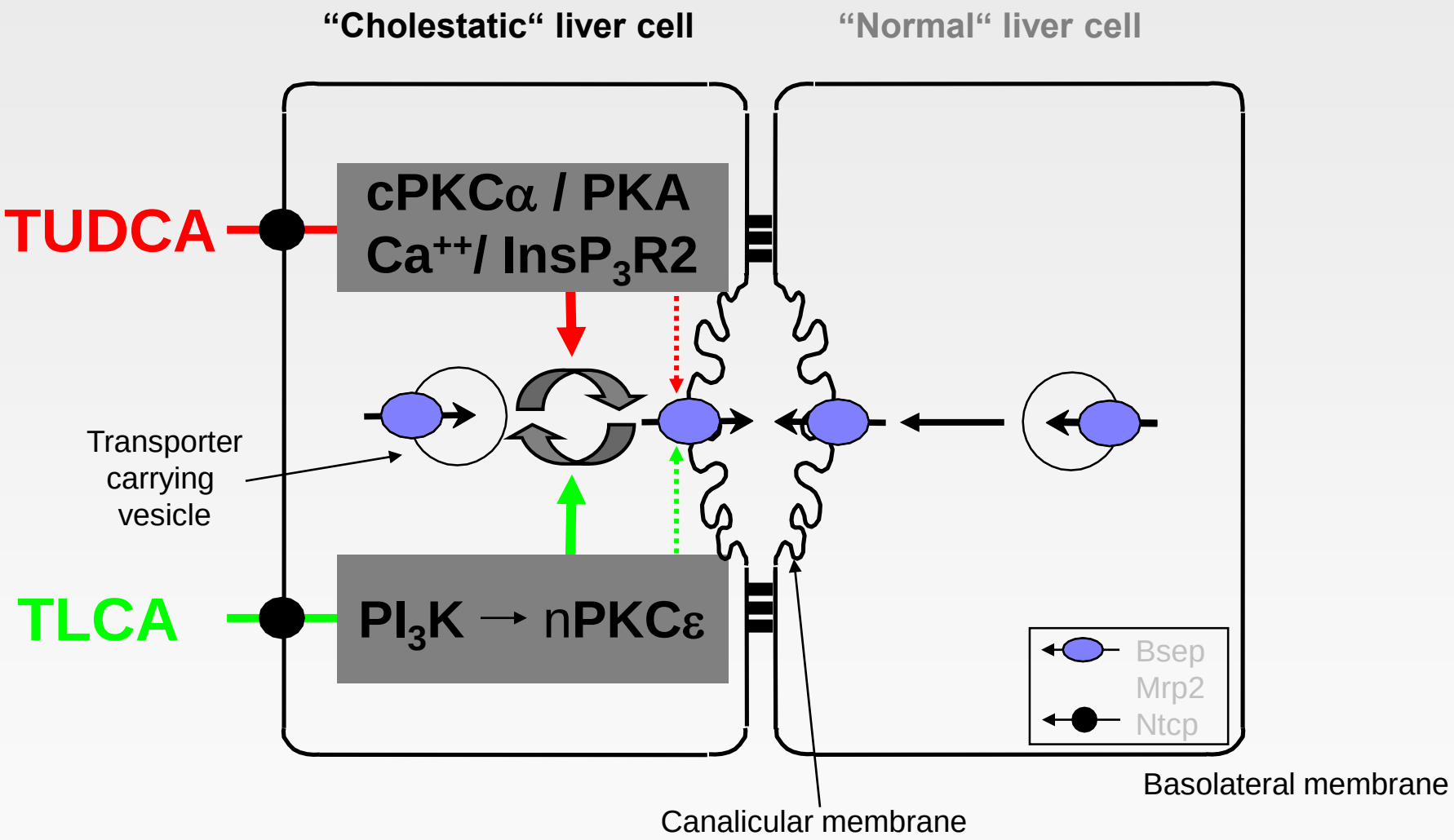
Primair biliaire cholangitis

- Diagnose
- Pathogenese
- **Therapie**

Primary biliary cholangitis: Standard therapy



UDCA conjugates act as posttranscriptional secretagogues in experimental cholestasis

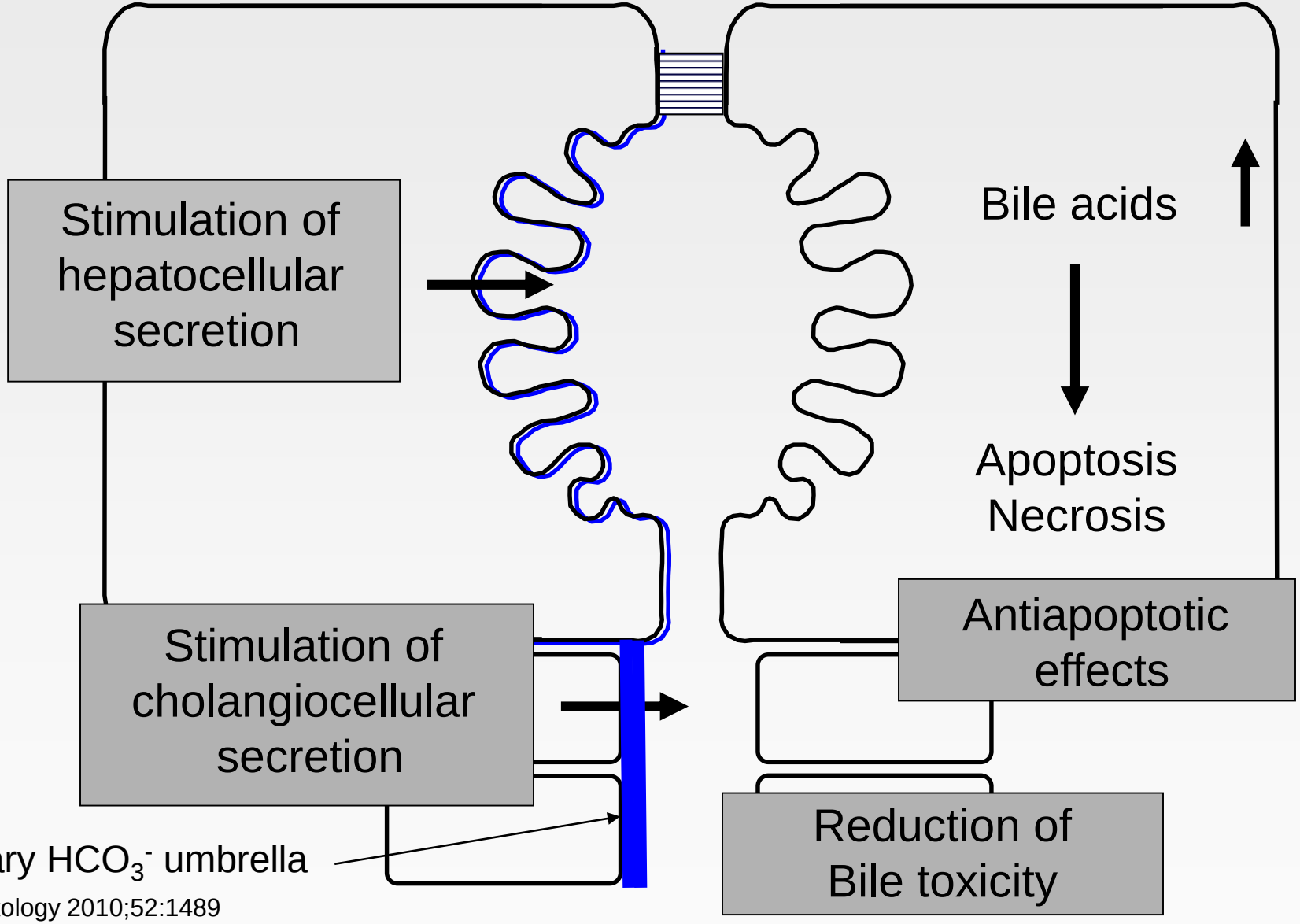


Beuers. Nature CP Gastroenterol Hepatol 2006;3:318 (references 1992-2006)

Wimmer, Hohenester et al., Gut 2008; 57: 1448

Cruz et al., Hepatology 2010; 52: 327

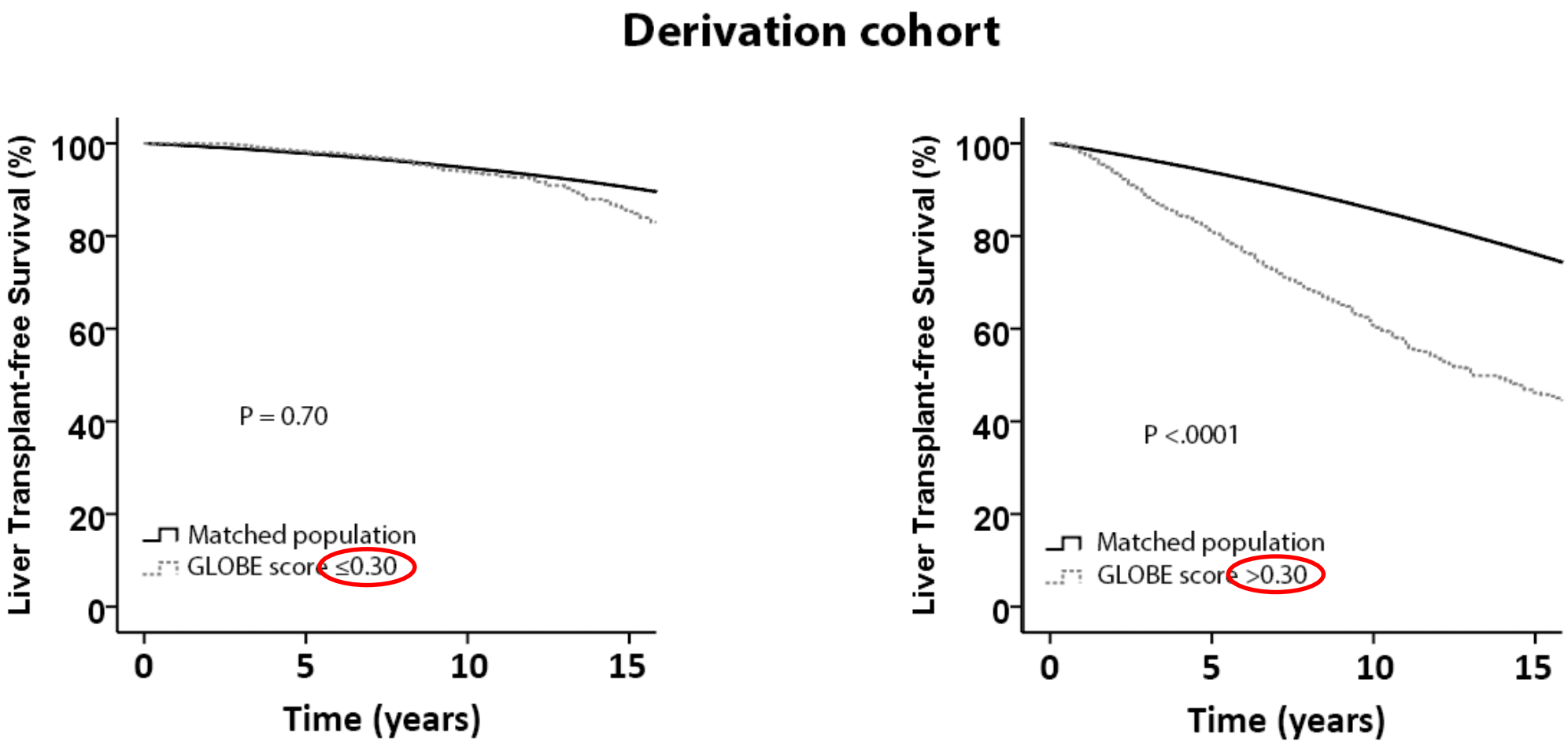
Putative mechanisms and sites of action of UDCA in cholestatic liver diseases



Hepatology 2010;52:1489
Hepatology 2012;55:173

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

The PBC GLOBE score predicts outcome after 1 year of UDCA



GLOBE score: Age, bilrubin, alkaline phosphatase, albumin, platelets

n=4111 PBC patients

Lammers et al., Gastroenterology 2015;149:1804

Primary biliary cholangitis: Standard *and potential 2nd line* therapy

Pathogenesis

Immune-mediated bile duct injury

↓

?

Defect of the biliary HCO_3^- umbrella: cholangiocyte injury by BA

↓

Cholestasis with retention of hydrophobic bile acids in liver

↓

Liver cell damage, fibrosis, cirrhosis

↓

Liver failure

RCT (Phase 3)

FXR agonists: e.g., **obeticholic acid**

*PPARa agonists: e.g.**bezafibrate***

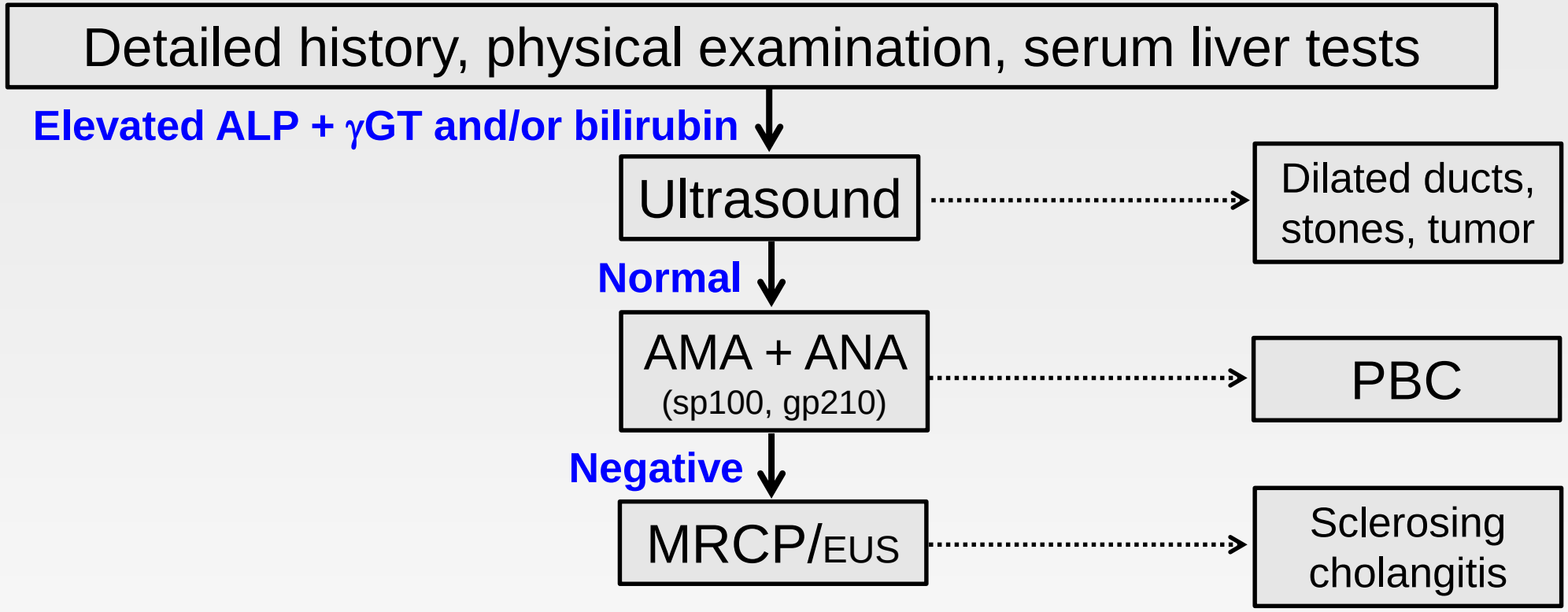
GR/PXR agonists: e.g., budesonide?

Ursodeoxycholic acid

(13-15 mg/kg/d)

Liver transplantation

Diagnostic approach to cholestasis



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

Primair scleroserende cholangitis

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

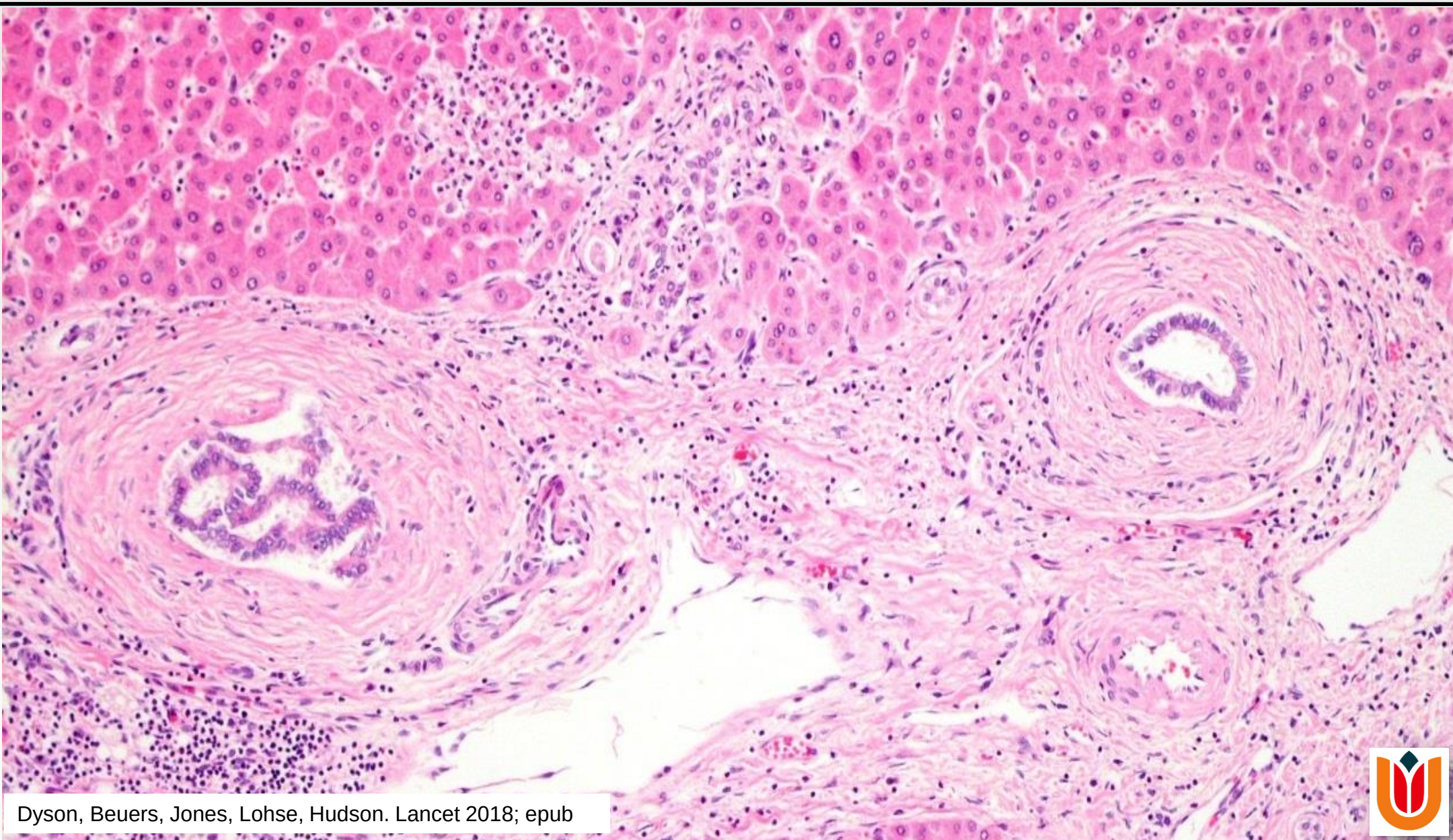
Sclerosing cholangitis

MRCP

Dyson, Beuers, Jones, Lohse, Hudson. Lancet 2018, epub

Sclerosing cholangitis

Histology



Dyson, Beuers, Jones, Lohse, Hudson. Lancet 2018; epub

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

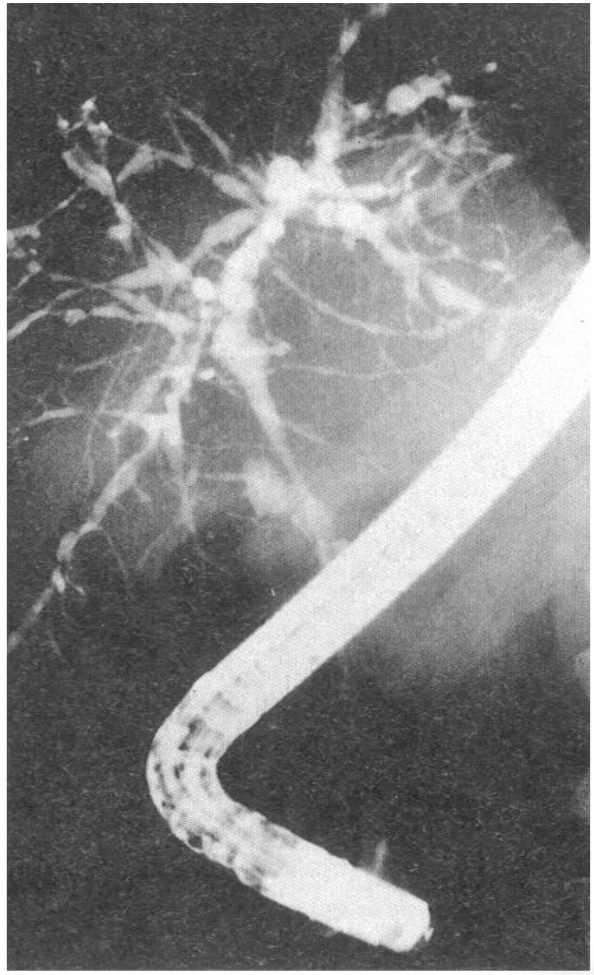
→ **Secondary sclerosing cholangitis**

Dyson, Beuers, Jones, Lohse, Hudson. Lancet 2018; epub

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%



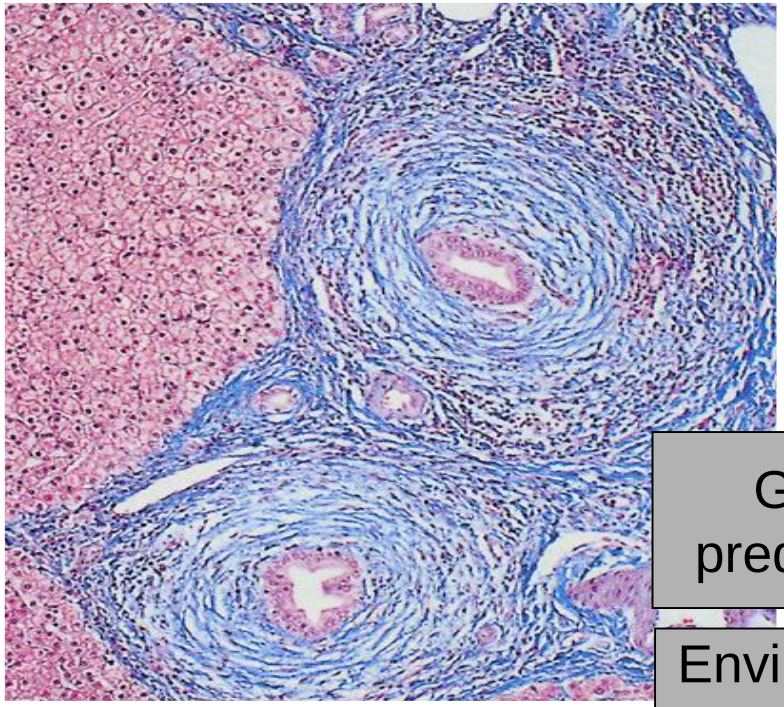
m, 42 years

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

Primair scleroserende cholangitis

- Diagnose
- **Pathogenese**
- Therapie

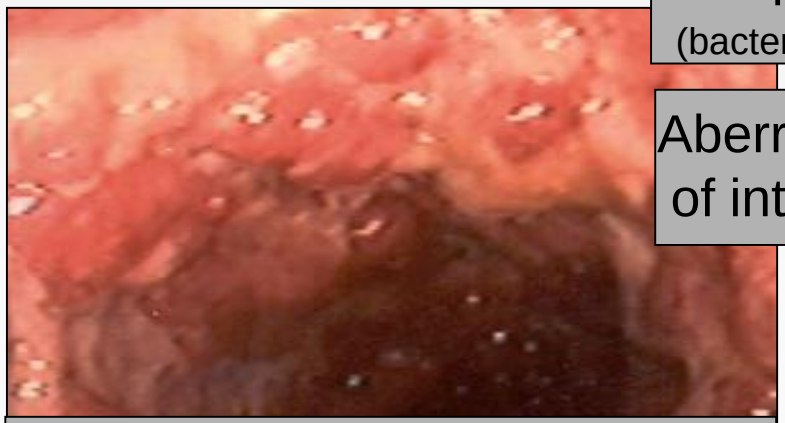
Pathogenesis of primary sclerosing cholangitis



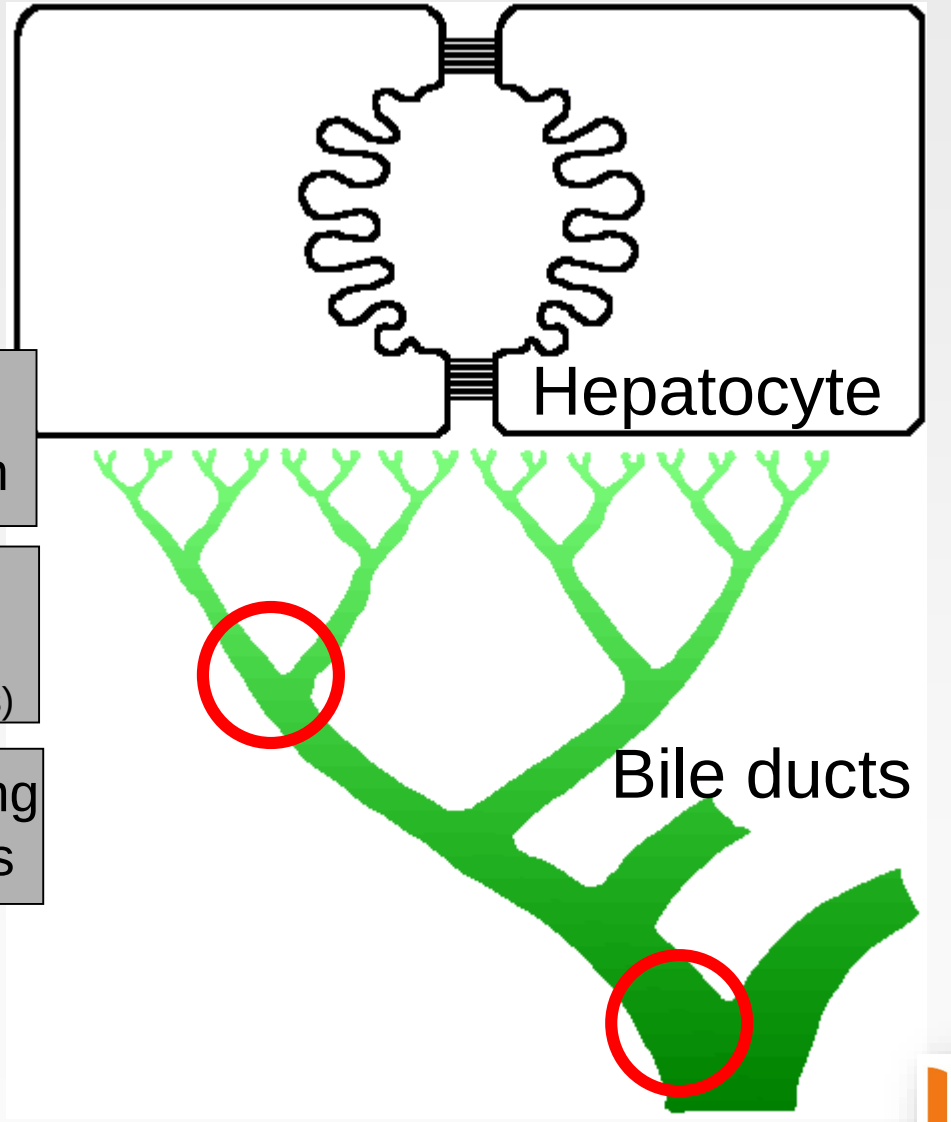
Genetic predisposition

Environmental factors
(bacterial pathogens)

Aberrant homing of intest.T-cells



Association with IBD ≥70%

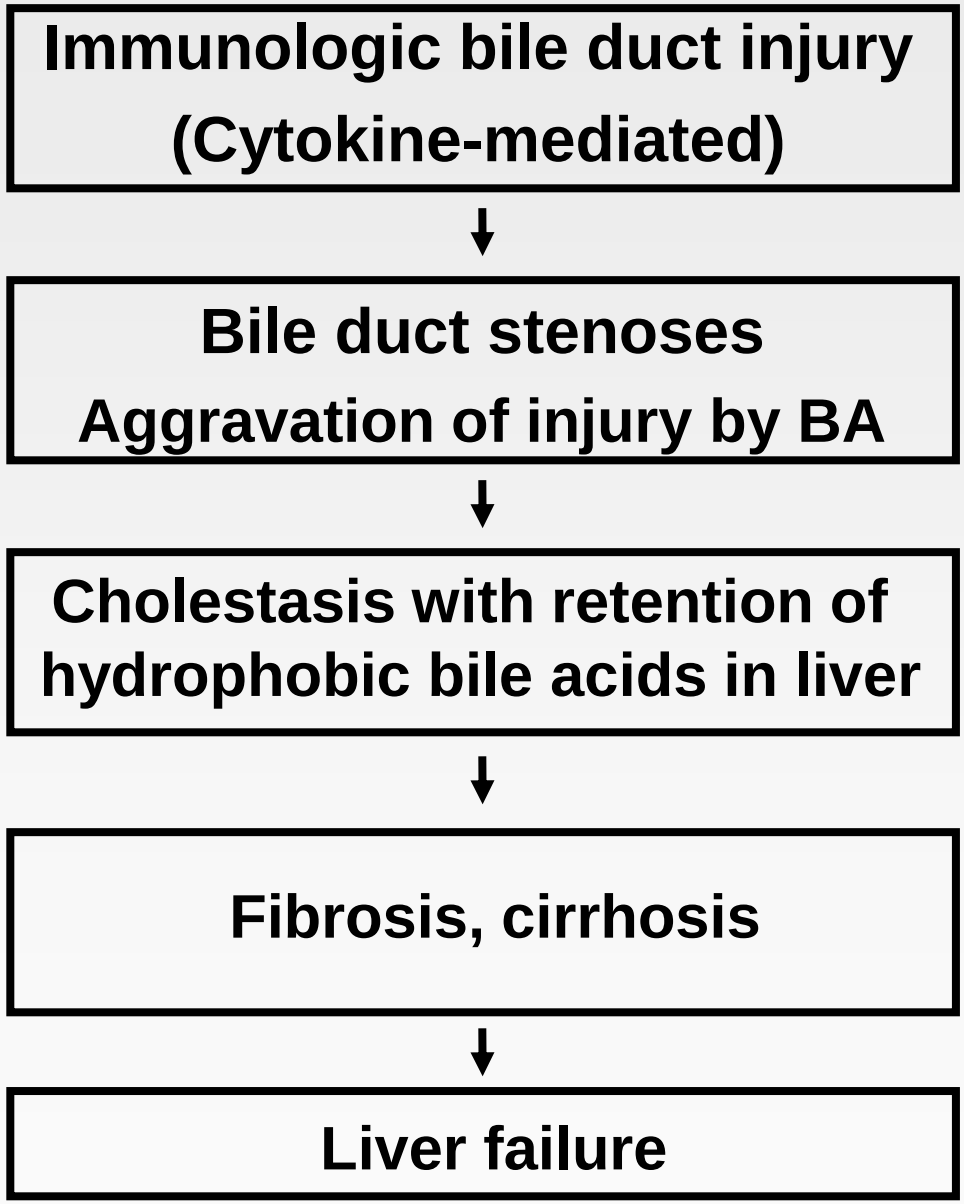


Primair scleroserende cholangitis

- Diagnose
- Pathogenese
- **Therapie**

PSC : Therapy

Pathogenetic model



Ursodeoxycholic acid

(15-20 mg/kg/d)

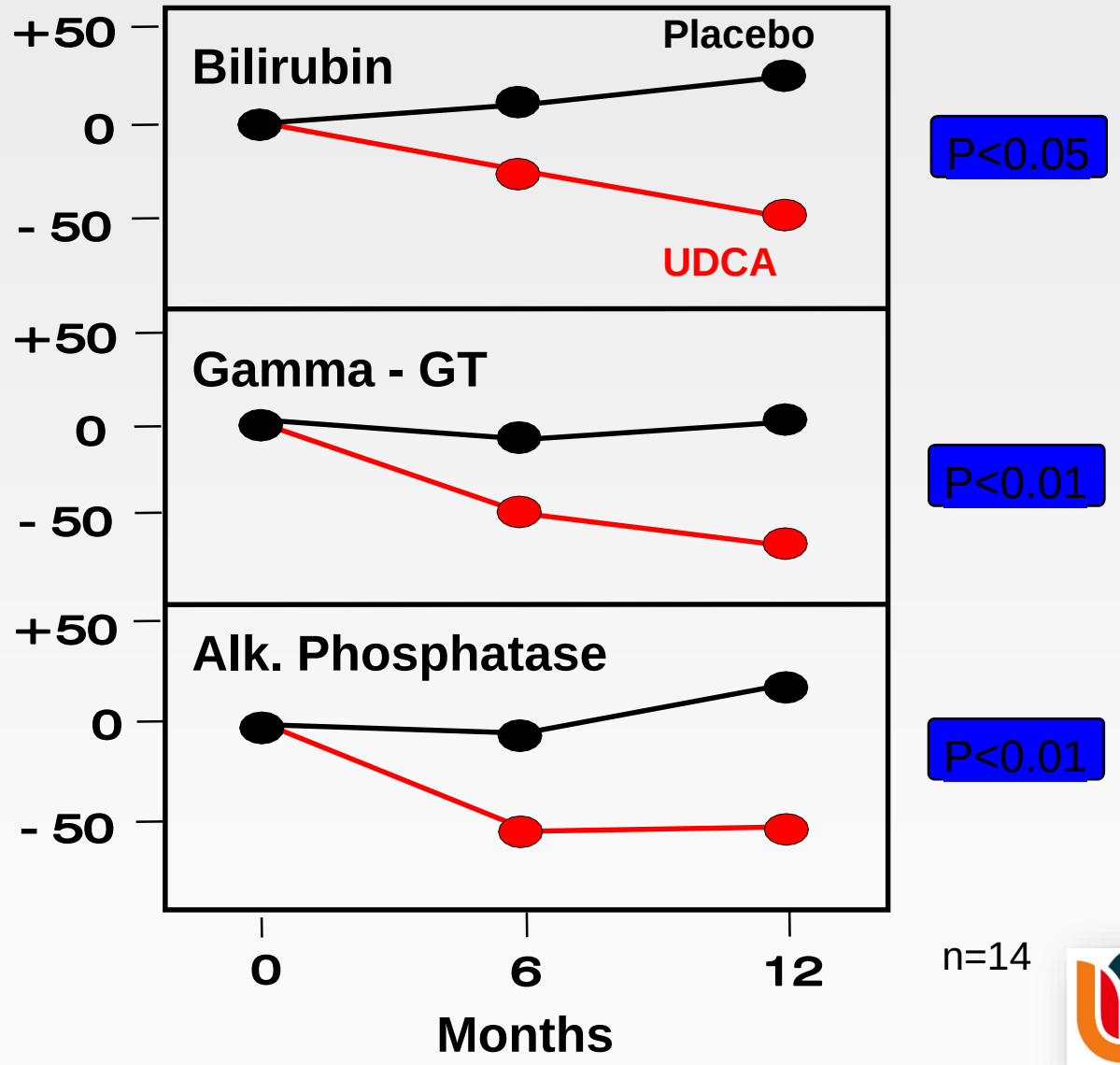
?

Liver transplantation

EASL CP Guidelines, J Hepatol 2009;51:237

Treatment of primary sclerosing cholangitis with UDCA

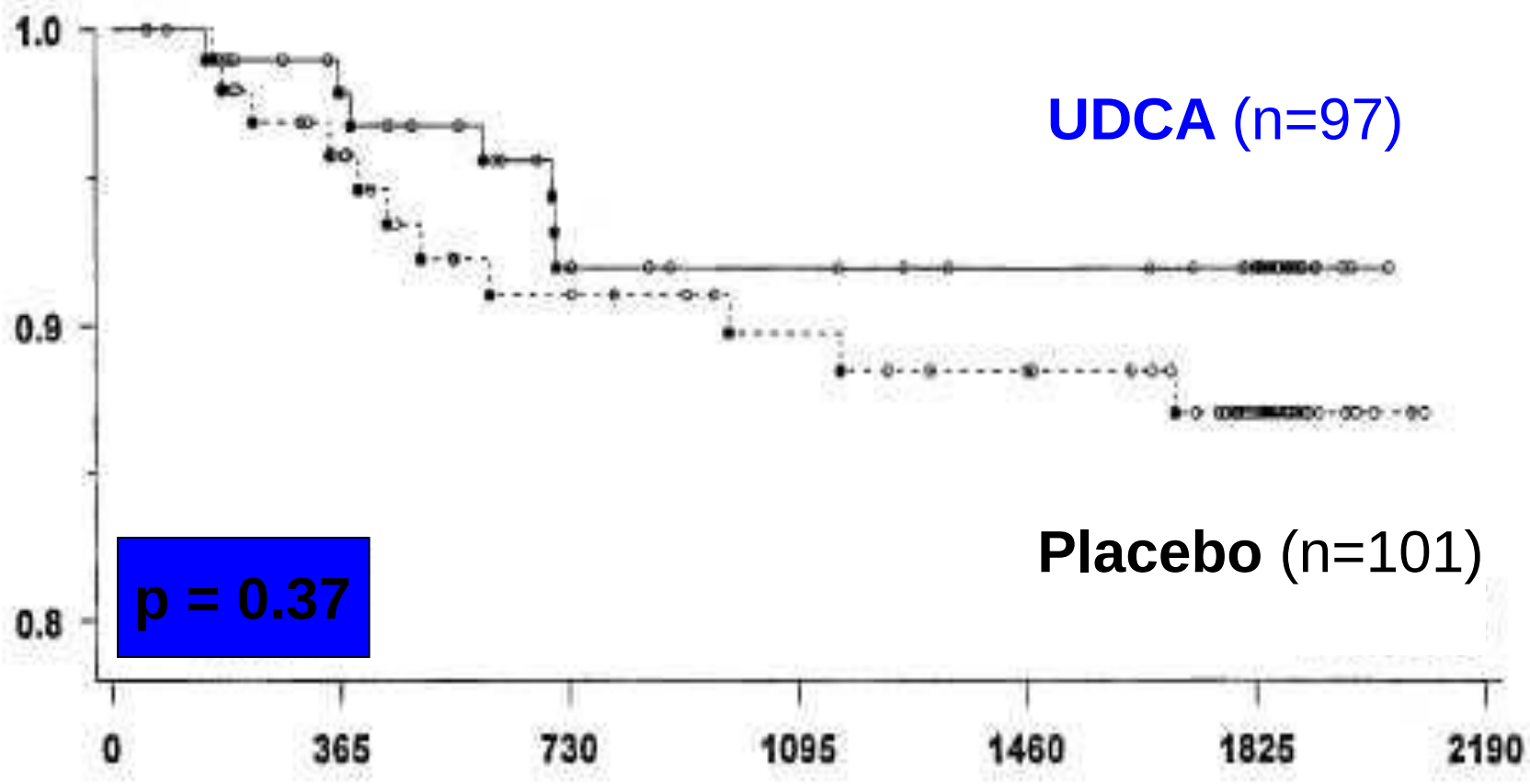
Serum liver tests



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

PSC : Therapy *under evaluation*

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

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

Entry question #2

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

Entry question #2

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Entry question #2

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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
- Cholangiocarcinoma*
- Choledocholithiasis*
- Chronic biliary infestation (liver fluke, ascaris)
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- **IgG4-associated cholangitis (IAC)**
- Ischaemic cholangitis
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- 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

IgG4-geassocieerde cholangitis

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

Entry question #3

What is the most frequent initial clinical sign / symptom of the hepatobiliary manifestation of IgG4-RD?

A. Abdominal complaints

B. Jaundice

C. New onset diabetes

D. Steatorrhea

E. Weight loss

Entry question #3

What is the most frequent initial clinical sign / symptom of the hepatobiliary manifestation of IgG4-RD?

A. Abdominal complaints

B. Jaundice

C. New onset diabetes

D. Steatorrhea

E. Weight loss

Entry question #4

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

Wat is correct?

A. Het ziektebeeld betreft vooral vrouwen.

B. Inductie therapie met prednisolon wordt gevolgd door cyclische onderhoudsbehandeling met rituximab.

C. Patiënten hebben een hoge genetische predispositie.

D. IAC stelt vaak een van meerdere orgaan manifesties van de systemische IgG4-gerelateerde ziekte voor.

E. Serum IgG4 is zeer sensitief en specifiek voor de diagnose van IgG4-RD.

Entry question #4

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

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C. Patiënten hebben een hoge genetische predispositie.

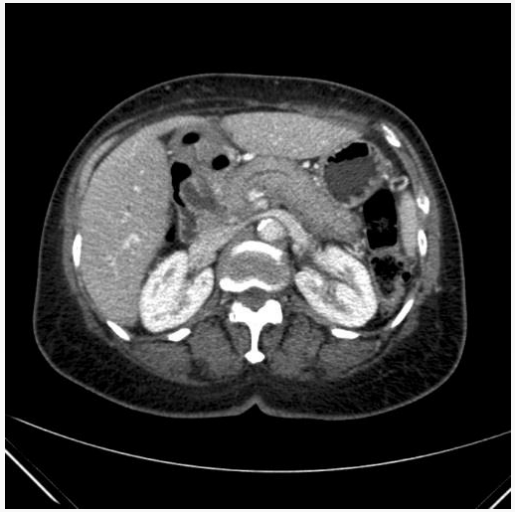
D. IAC stelt vaak een van meerdere orgaan manifesties van de systemische IgG4-gerelateerde ziekte voor.

E. Serum IgG4 is zeer sensitief en specifiek voor de diagnose van IgG4-RD.

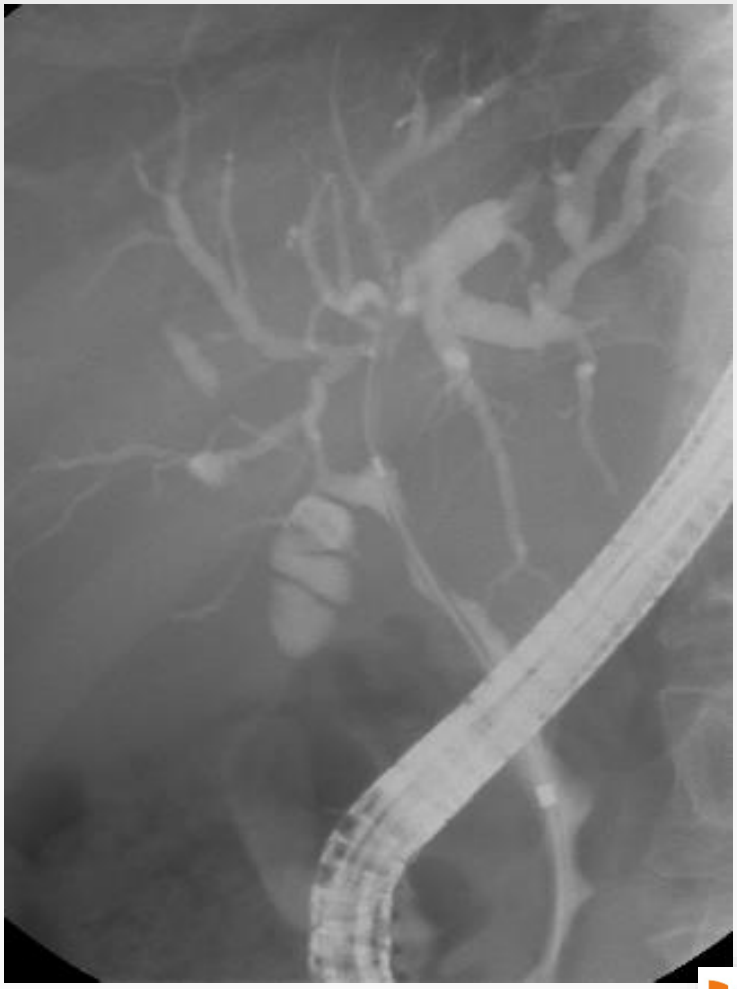
IgG4-associated cholangitis (IAC)

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

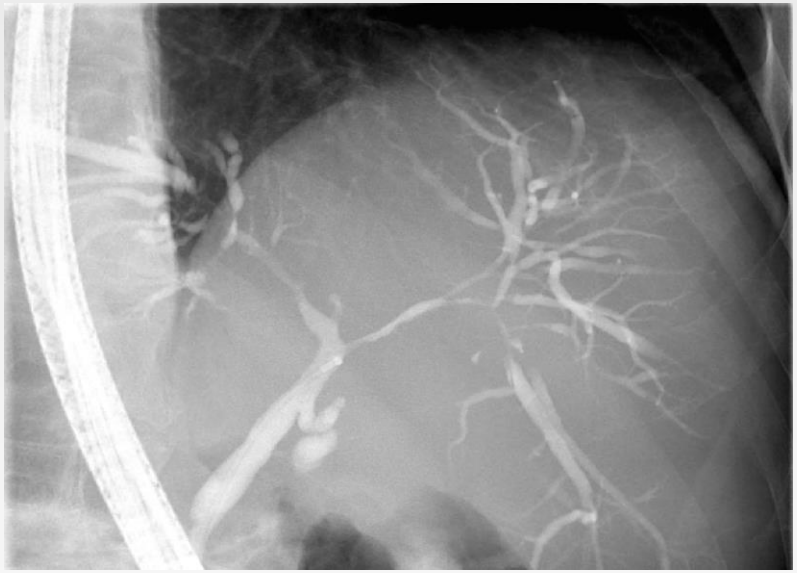


Stone et al N Engl J Med 2012;366:539
Hubers et al. Clin Rev Allerg Immunol 2015;48:198

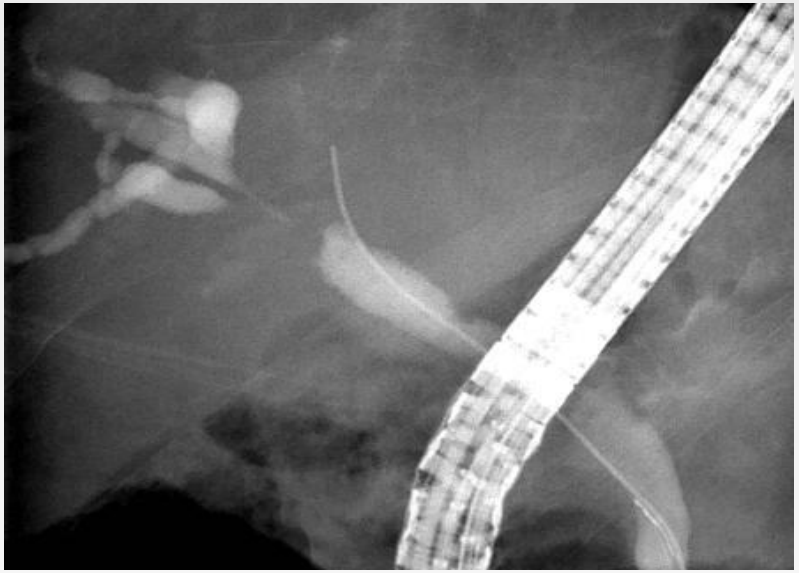


71 yrs, m; IgG4 11.9 g/L (n < 1.4)
Alderlieste et al., Digestion 2009;79:220

IgG4-associated cholangitis mimics PSC and CCA



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



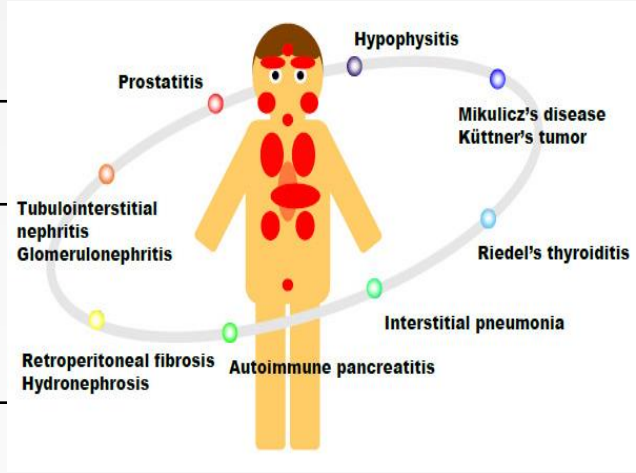
Cholangiographic appearance mimicking cholangiocarcinoma (**CCA**)

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

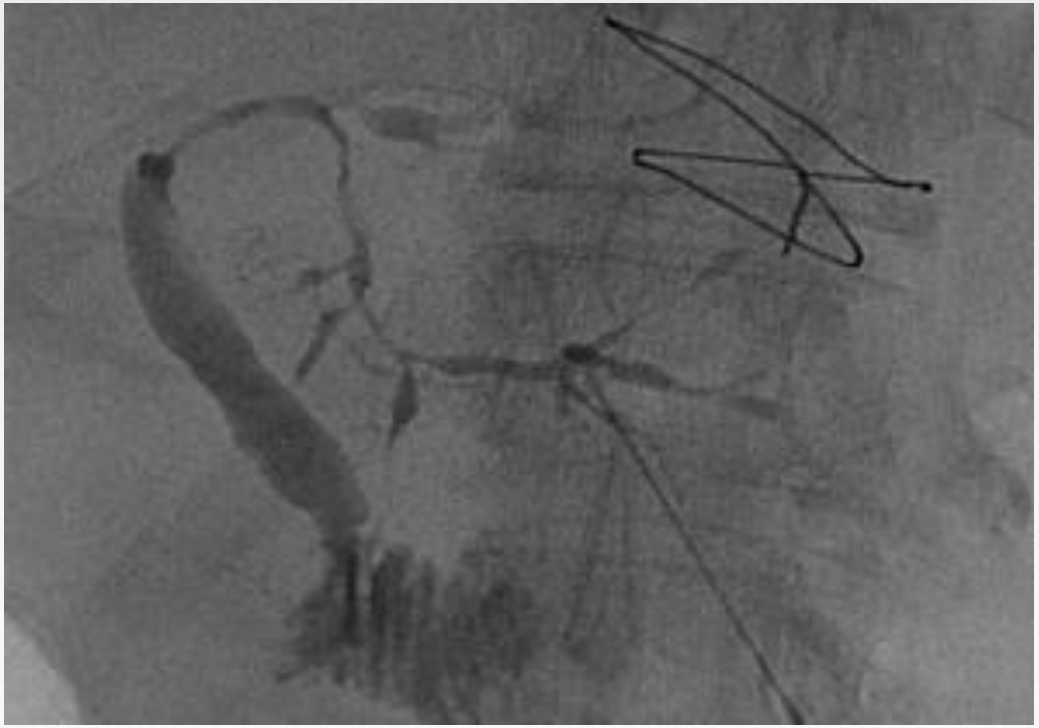
- HISORt Criteria -

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 -

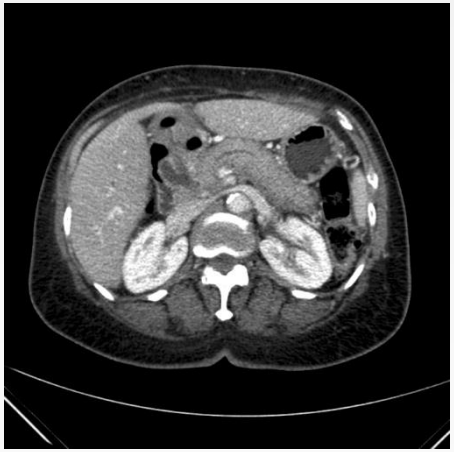
Biliary strictures: intrahepatic, proximal and/or distal extrahepatic

A

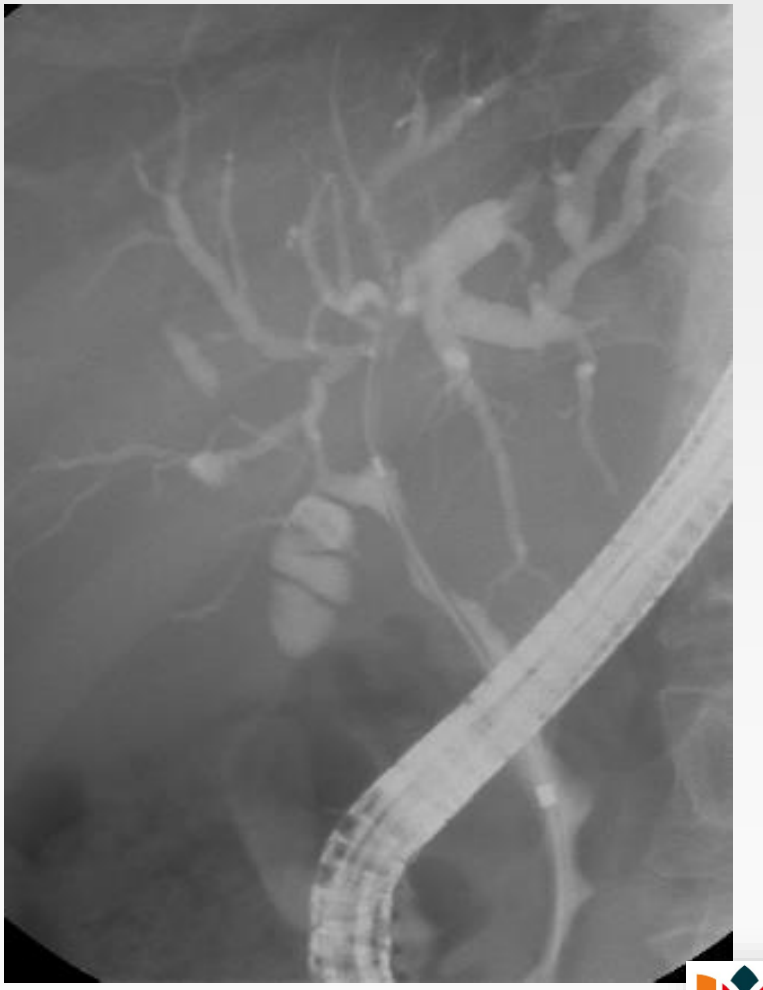
Previous pancreatic / biliary resection or core biopsy of pancreas showing diagnostic features of AIP / IAC

B

Classical imaging findings of AIP
+
Elevated serum IgG4



Definite IAC



71 yrs, m; IgG4 11.9 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

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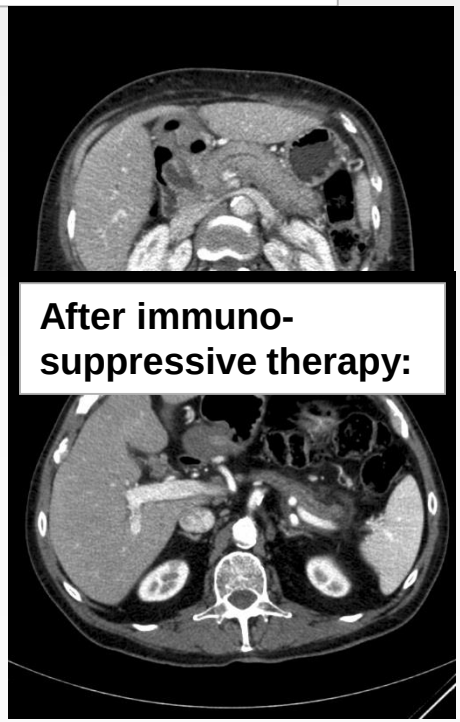
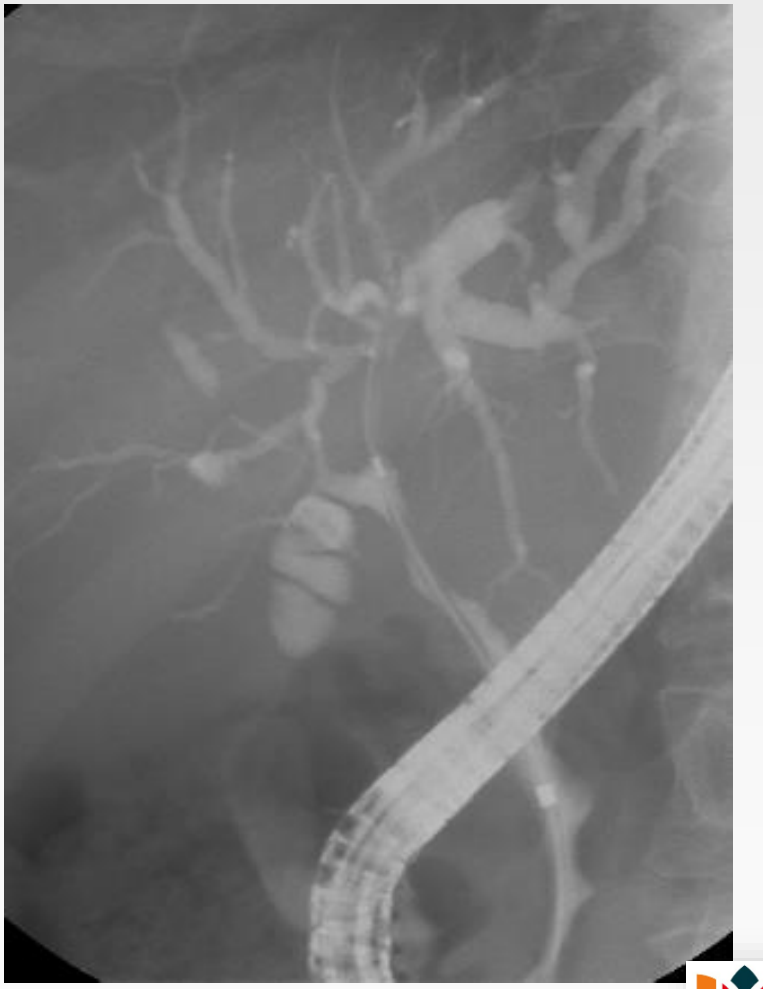


After immuno-suppressive therapy:

Definite IAC



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Diagnosis of IgG4-associated Cholangitis

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A

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

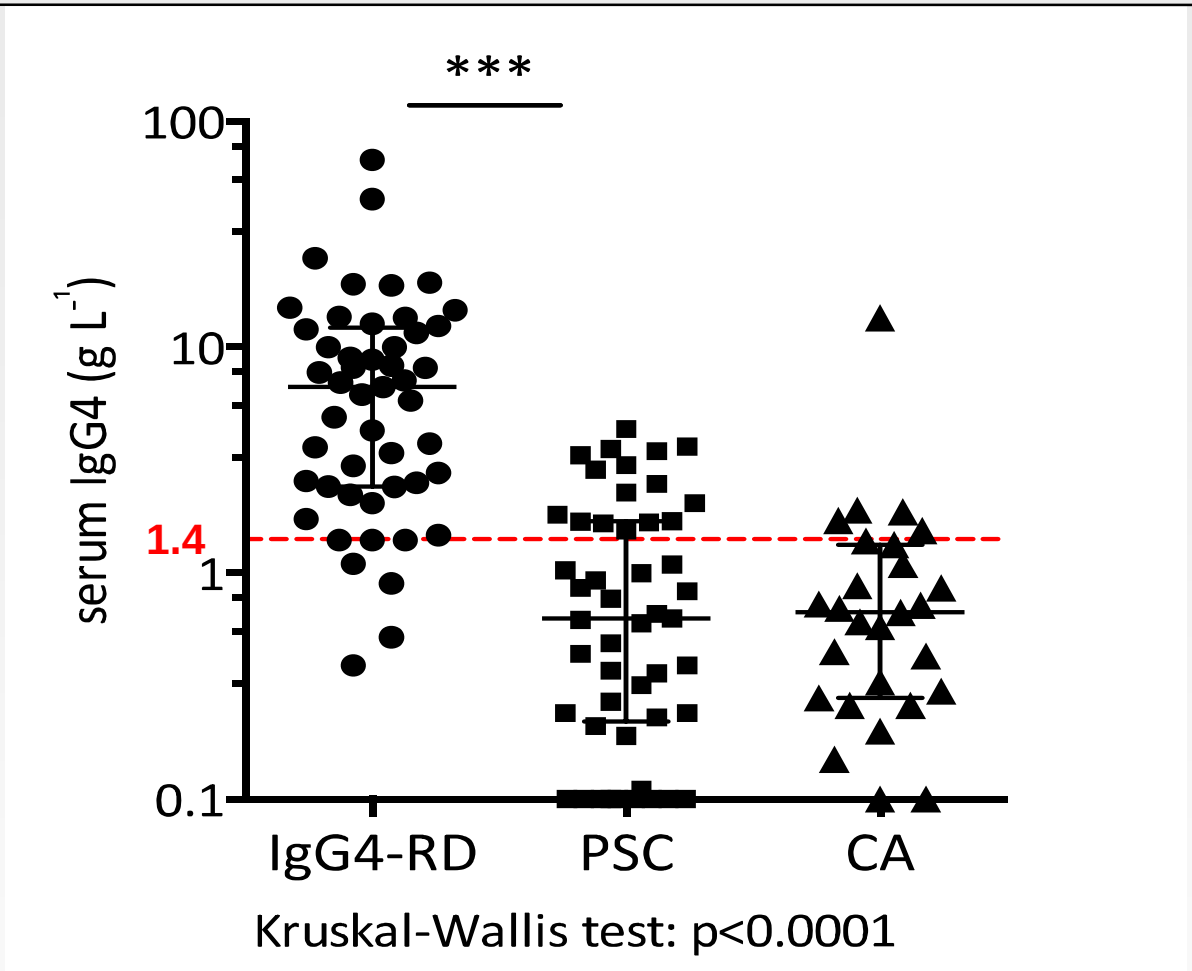
After 4 weeks of corticosteroids:

- 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%

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

n=125

CA: Biliary and pancreatic malignancies

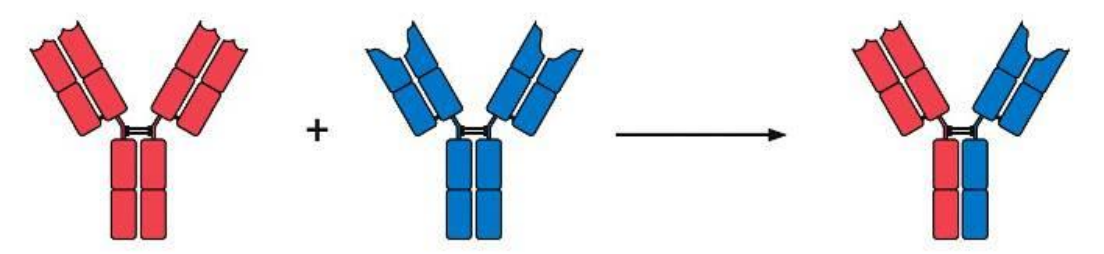
IgG4-geassocieerde cholangitis

- 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

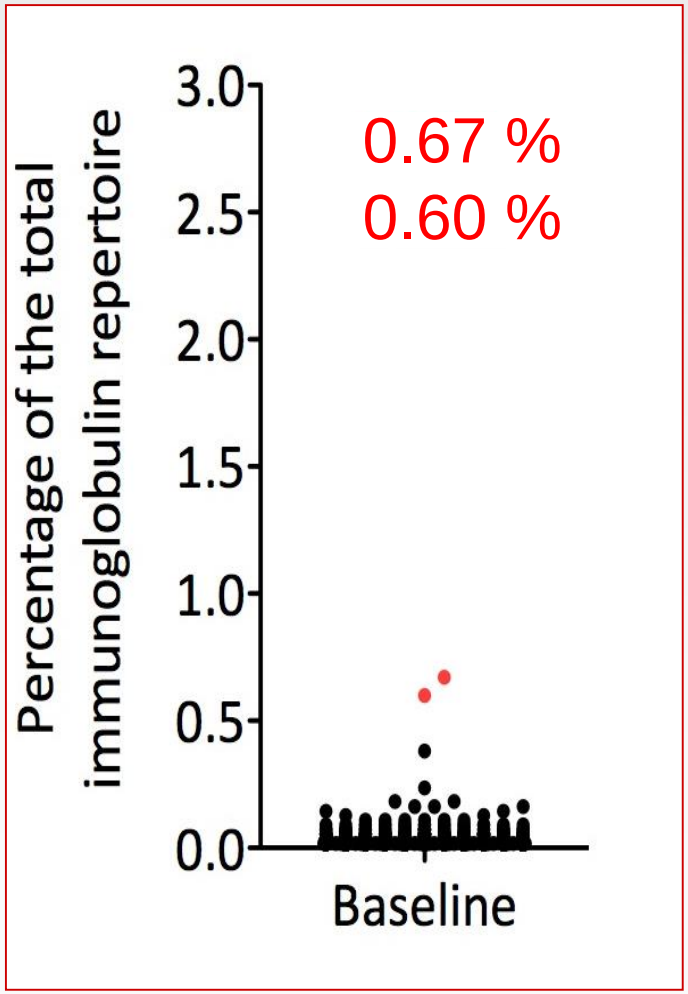
2 Karagiannis et al., J Clin Invest, 2013;123:1457

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**

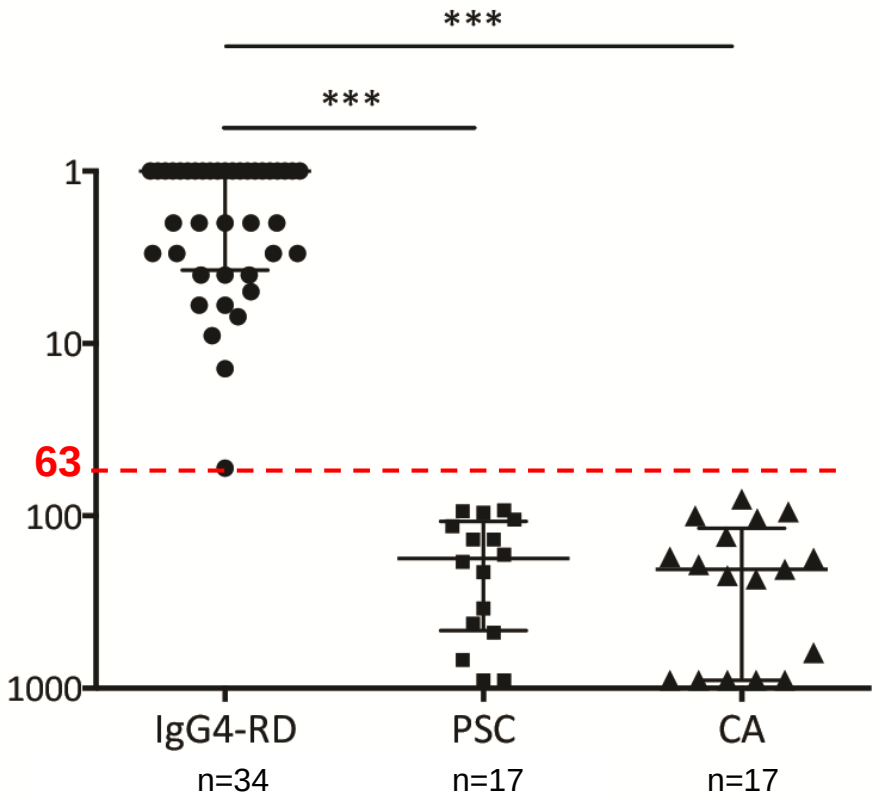
Maillette de Buy Wenniger, Doorenspleet et al. Hepatology 2013; 57: 2340 (epub 2012)

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

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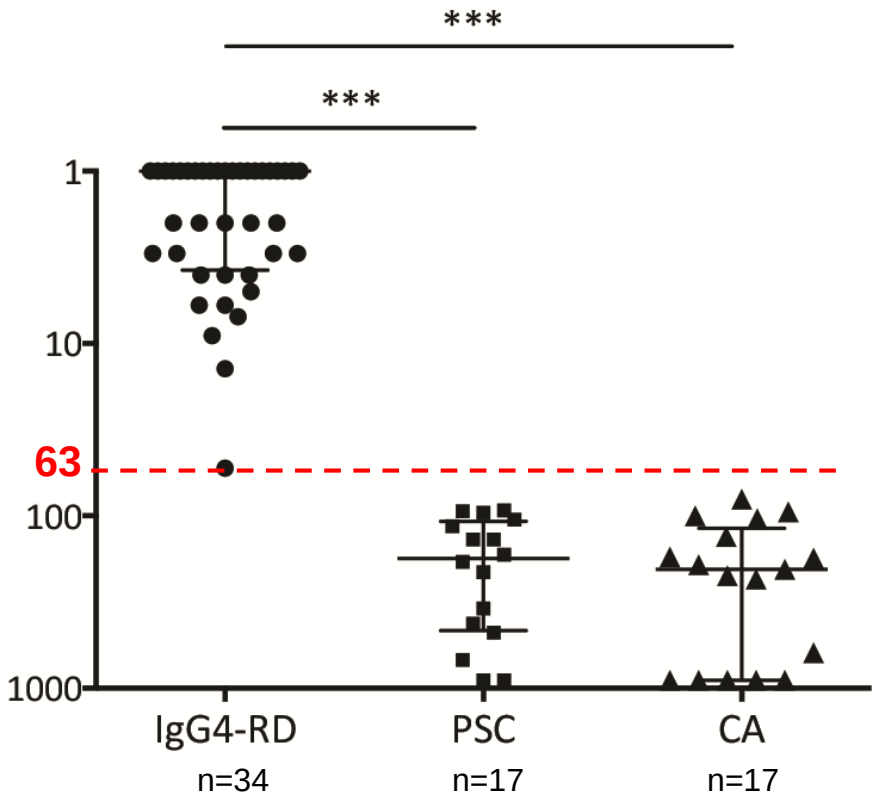

Sensitivity = 100%
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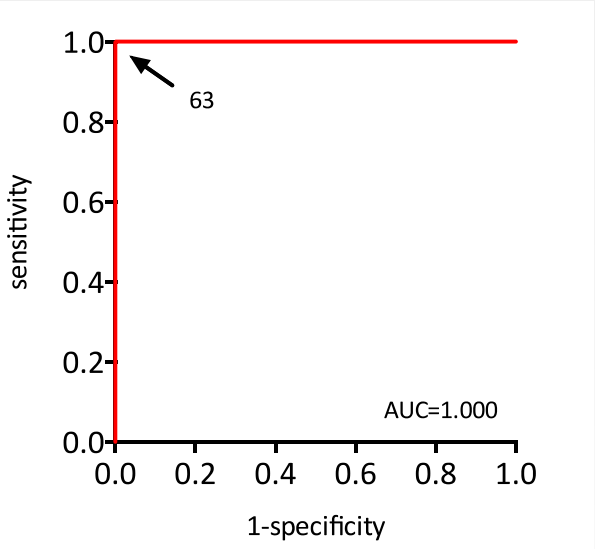


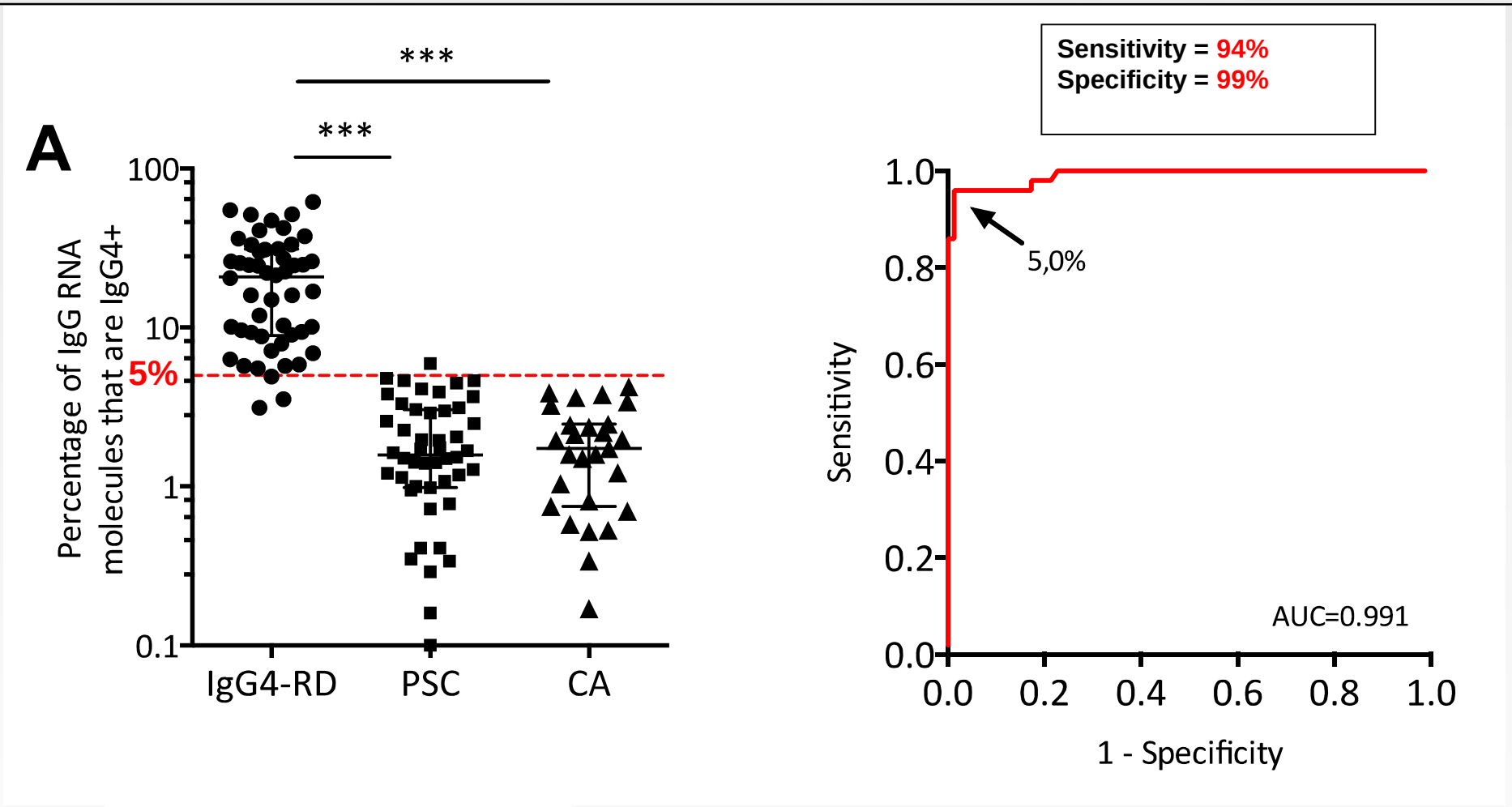
Doorenspleet, Hubers et al. Hepatology 2016; 64: 501

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



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

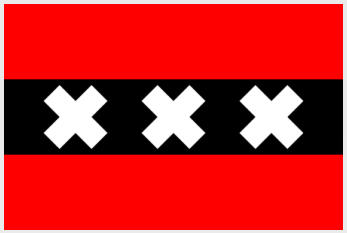
n=125

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



Job history (≥ 1 year)	Recalled regular occupational exposures (≥ 1 year)
1. Musician, painter, metal worker, carpenter	car paint, metal, solvents, pigments
2. Carpenter	sawdust, wood, chipboard, solvents
3. Glass worker, project manager at multinational	glass dust, glass components, lead, barium, cobalt, nickel, lead, silica, industrial dust, building sites
4. Plasterer	chalk dust, sawdust, wood, chipwood, solvents
5. Industrial fuel/waste oil laboratory, skipper	crude oil, ship waste oil, solvents, chemicals
6. Miner, tiler, bath superintendent	silica dust, mine dust, asbestos, solvents, glue, chlorine
7. Metal worker, textile worker	metal dust, solvents, textiles, pigments, paints
8. Shipping	solvents, asbestos, crude oil
9. Painter, army officer, flight arrangements, tomato farmer	paint, pigments, solvents, kerosene, pesticides, friction plate dust
10. Painter	paint, pigments, solvents, dust
11. Small machine factory owner	car paint, metal dust, solvents, asbestos, oils
12. Builder, plumber	plumbing materials, dust, sawdust, clipboard, glue, lead
13. Self-employed ophtometrician	lense glass dust, lense plastic dust, acetone
14. Carpenter	sawdust, clipboard, glue, solvents
15. Bricklayer, industrial cleaner of house walls	silica dust, concrete dust, brick dust, solvents, asbestos
16. Mud worker, shipping, mud industry manager	solvents, oil products, dust
17. Builder, painter	solvents, sawdust, clipboard, paints
18. Car industry worker	solvents, oil products
19. Historian, rebuilt 3 houses during last 20 years	sawdust, silica dust, solvents, paint
20. Builder, wall miller	silica dust, sawdust, dust, solvents
21. Hospital cleaner	cleaning products
22. Street builder, pigeon holder	silica dust, tar, pigeon antigens, pigeon faeces
23. Industrial warehouse forklift driver	*unknown (deceased)*
24. Teacher	*no known exposures*
25. Nurse	*no known exposures*

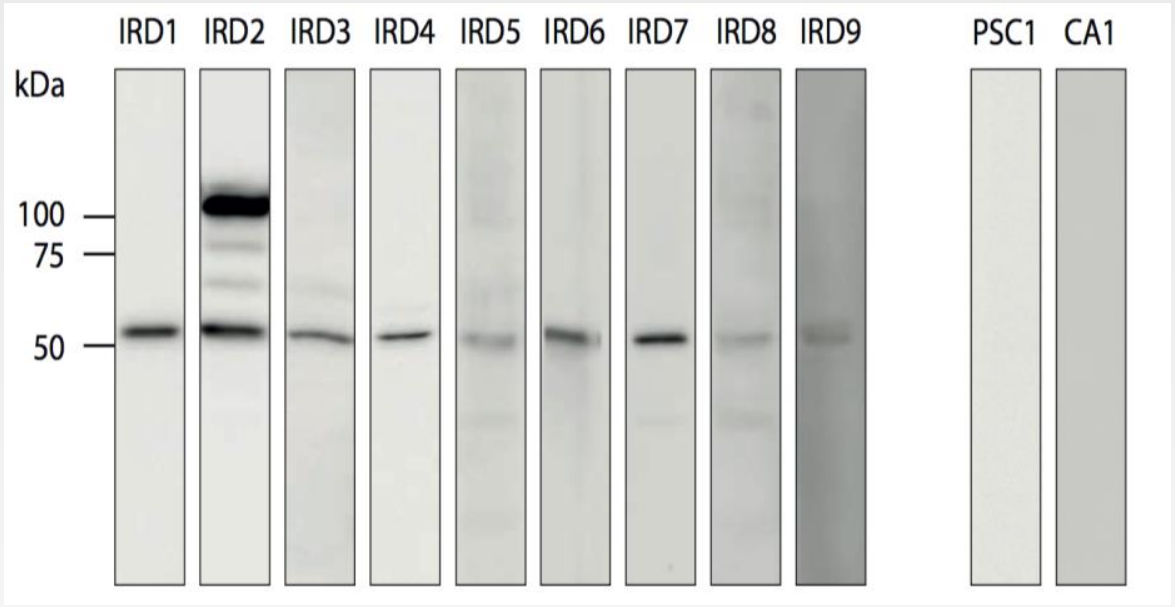
Maillette de Buy Wenniger, Curver, Beuers.

Hepatology 2014: 60:1453

Pathogenesis of IgG4-Related Disease

Are there specific auto-antigens in IgG4-RD?

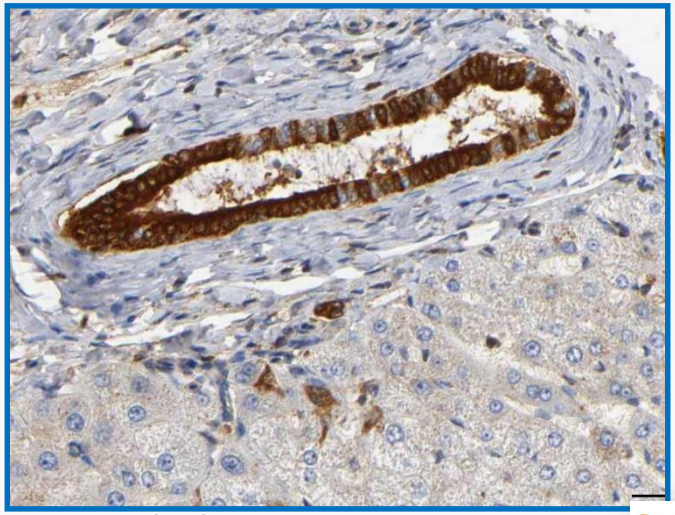
Serum IgG4 antibodies in IgG4 cholangiopathy recognize a ~56 kDa protein in human H69 cholangiocyte lysates



9 out of 50 IgG4-RD

0 out of 47 PSC/CA

- **IgG1 antibodies bind to the 56 kDa protein in 7/9 patients with IgG4-RD**
- **Mass-spectometry identified Annexin A11 as the 56 kDa protein**
- **IgG4 antibodies block binding of IgG1 antibodies to Annexin A11**



www.proteinatlas.com

Hubers et al. , Gut 2018

IRD = IgG4-RD *CA = biliary/pancreatic malignancies*

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):

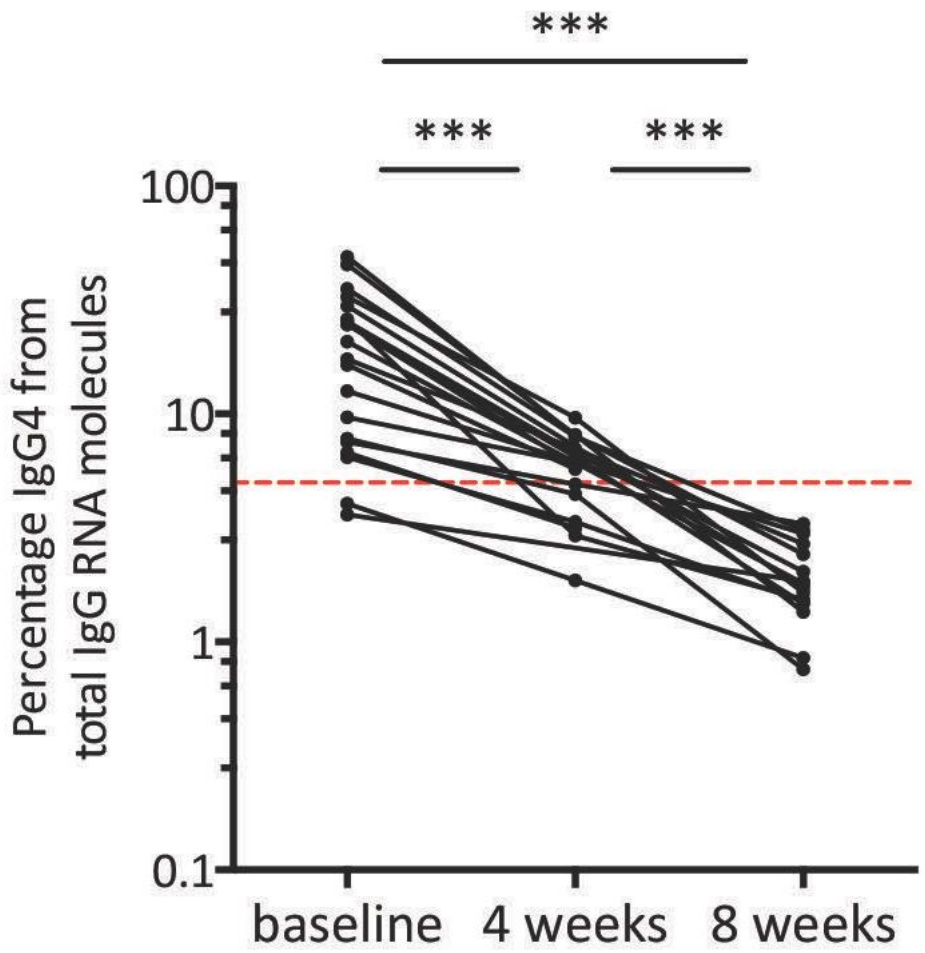
- 5(-10) mg/d Predniso(lo)ne
- ≤ 2 mg/kg/d Azathioprine

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.