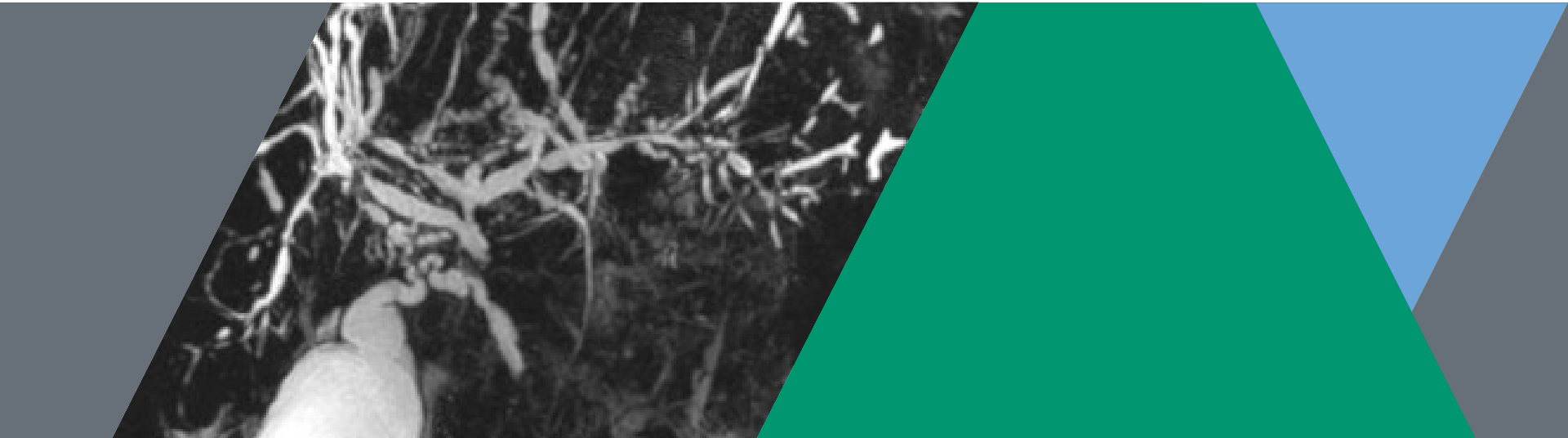
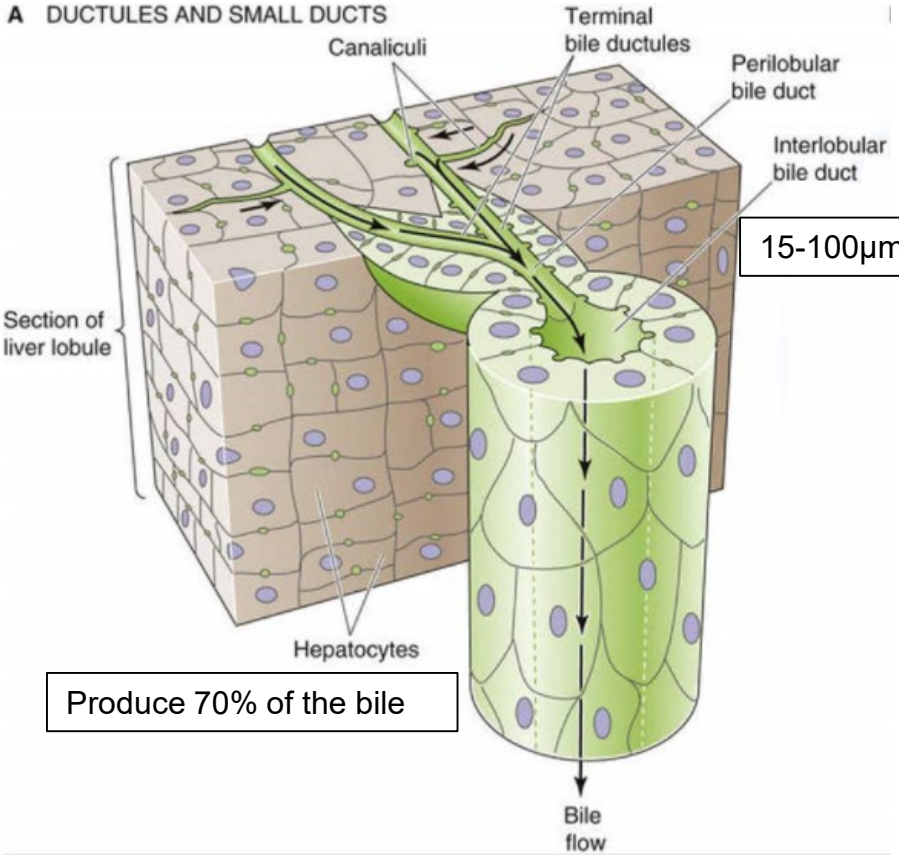
INSELGRUPPE

Bible Class
PSC and IgG4 cholangiopathy

25.03.2022, M. Knecht

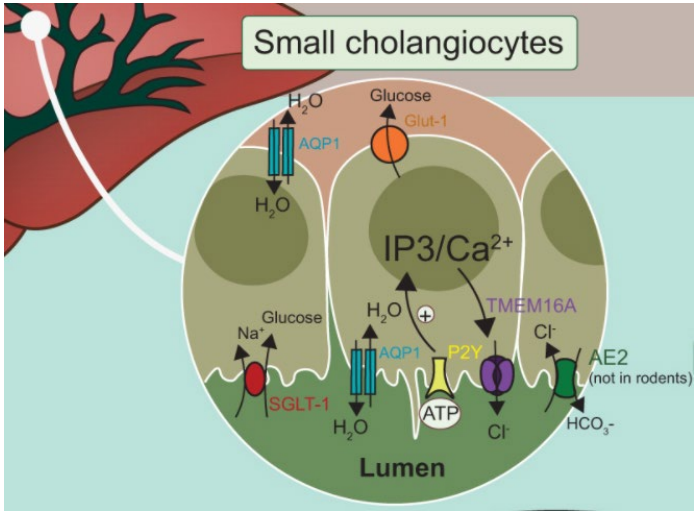


Anatomy and function of the bile ducts

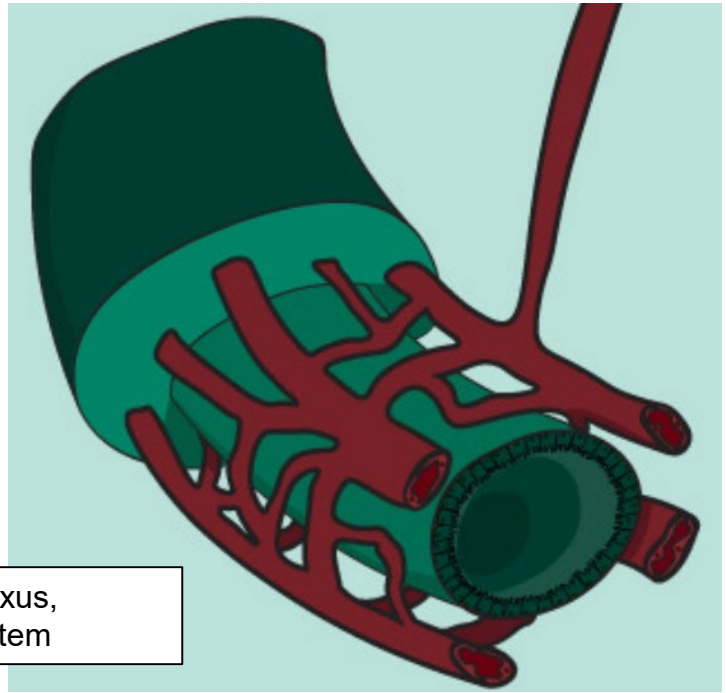


15-100µm

Produce 70% of the bile

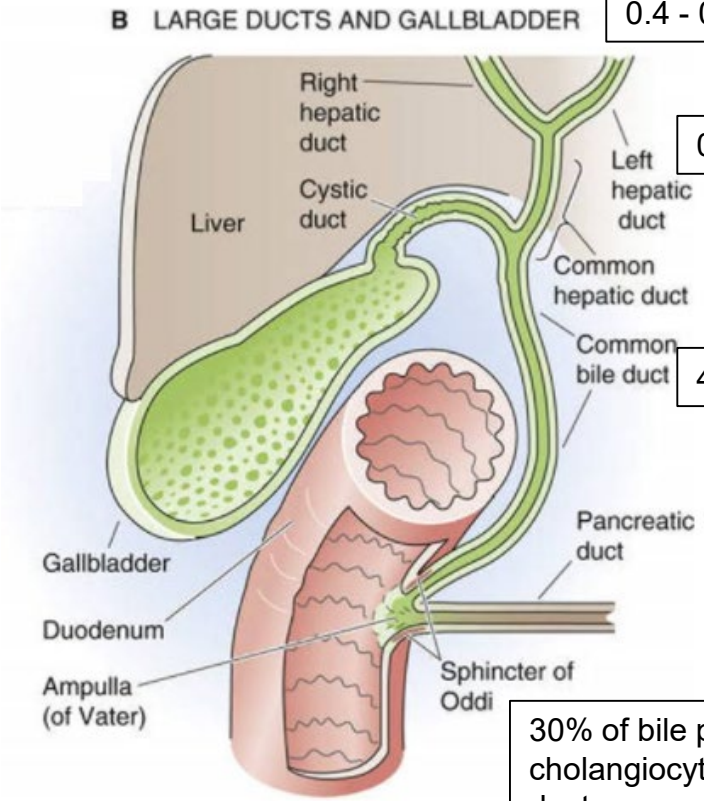


Borron WF. Functional Anatomy of the Liver and Biliary Tree. Medical Physiology, 3rd Edition. Elsevier 2017
De Jong IEM. J Hep 2021



Single layer of vascular plexus, communicates with PV-system

De Jong IEM. J Hep 2021

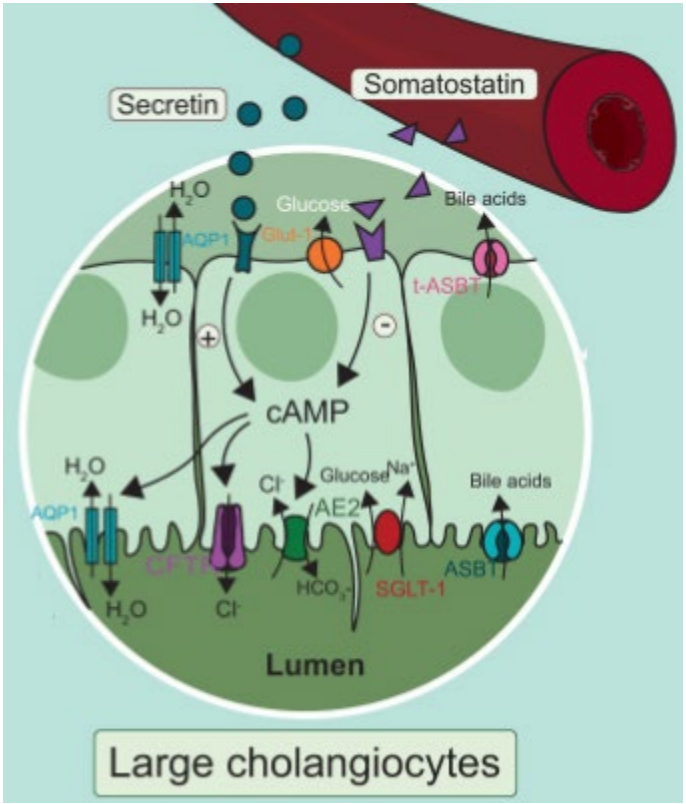


Segmental ducts
0.4 - 0.8mm

0.8 - 4mm

4 - 7mm

30% of bile production via large cholangiocytes lining large bile ducts



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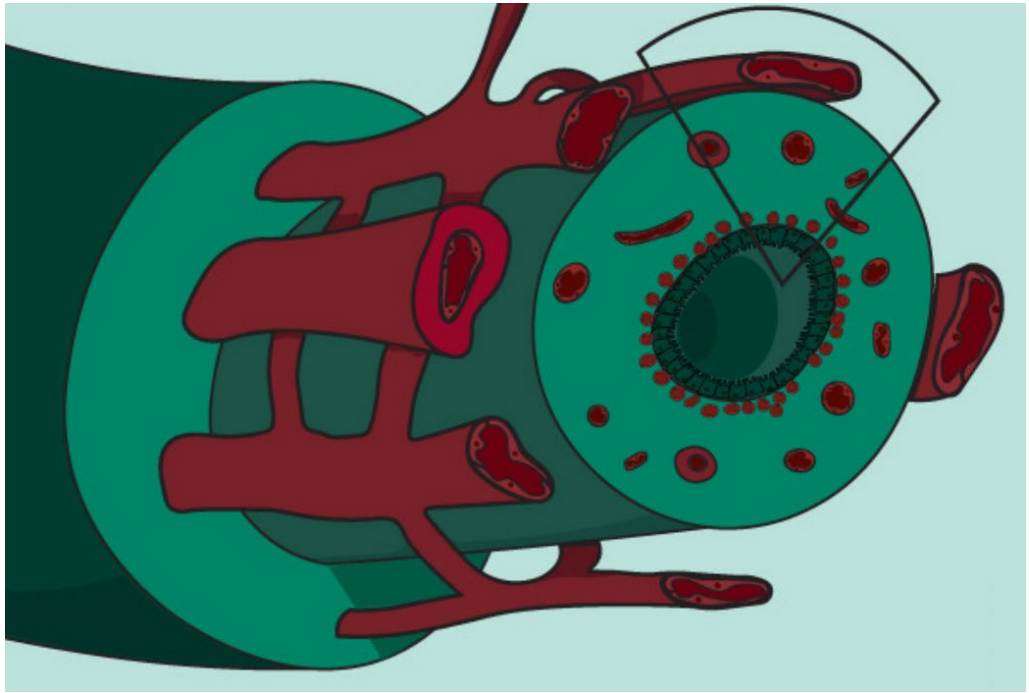
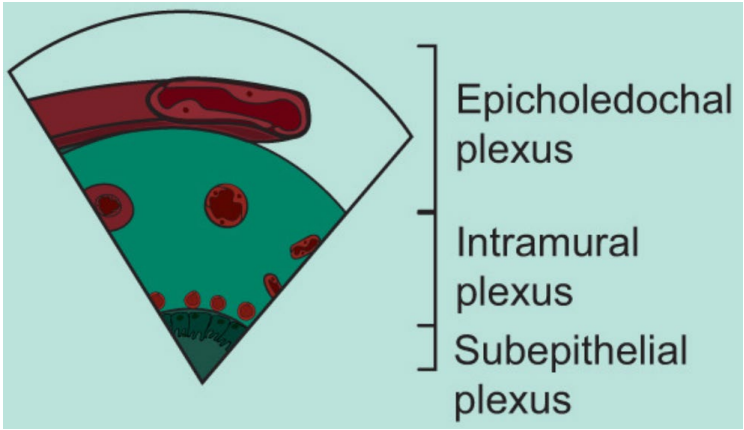
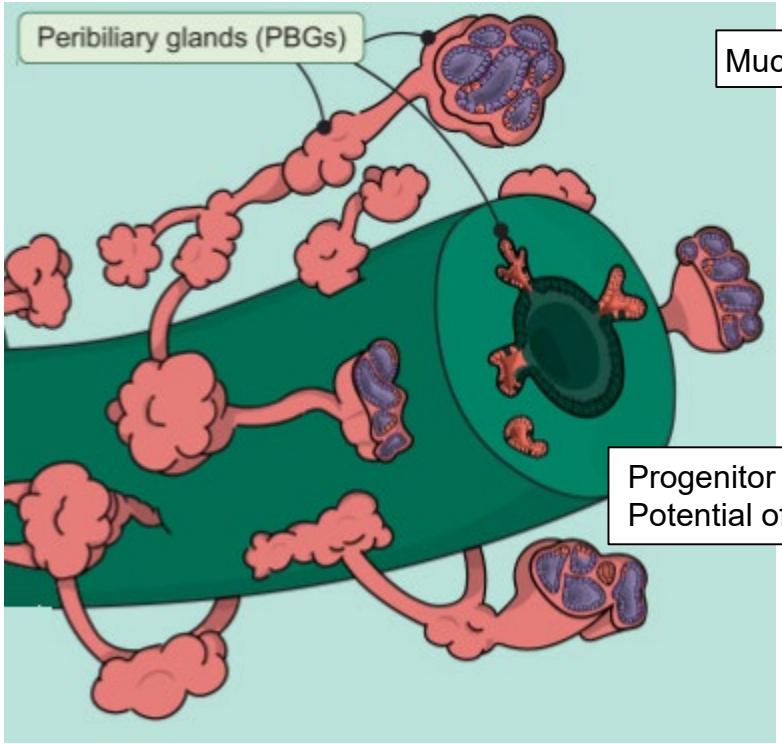


Feeding via GDA and AH



De Jong IEM. J Hep 2021



Mucus secretion

Progenitor cells for biliary epithelial
Potential of differentiating to pancreatic tissue

Igarashi S et al. WJG. 2013
De Jong IEM et al. Hepatology. 2019 Apr

Causes of sclerosing cholangiopathies

- PSC
- IgG4-related

Secondary sclerosing cholangiopathies

- Neoplastic: CCC, metastasis, mastocytosis, LHC Histiocytosis
- Recurring infection: Pyogenic, parasitic (opisthorchis, clonorchis)
- Autoimmune: eosinophilic/neutrophilic, Sarkoidosis, GvHD
- Vascular/Ischemic: Shock, PH-Biliopathy, dissection, trauma, PNH
- Immunodeficiency: HIV/AIDS a.o.
- Toxic/mechanical: stones, surgery, trauma, chemotherapy
- Other: Caroli, CF, ABCB4, HHT

Primary sclerosing cholangitis

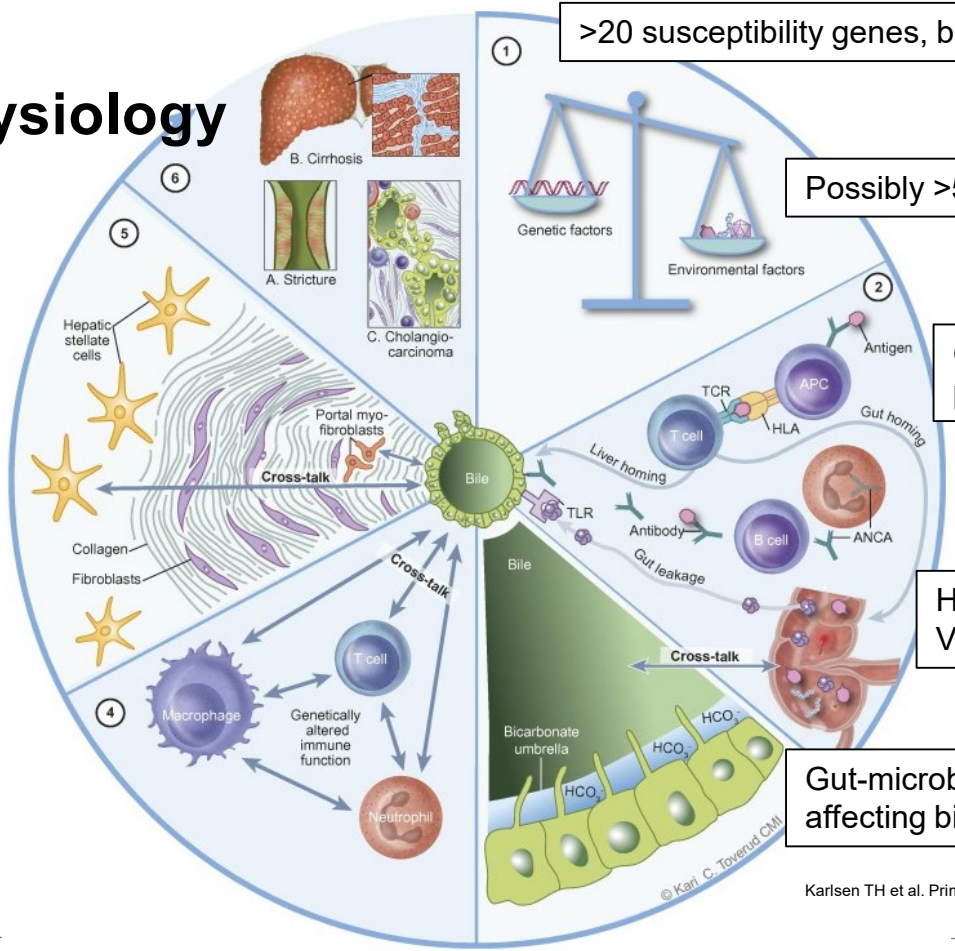
PSC

Epidemiology

- Male predominance 2:1
- Mostly between 30 and 40y
- Incidence
  - PSC 0.92 – 1.3/100‘000 person-years
- Increasing incidence over time

Boberg KM et al. Scand J Gastroenterol. 1998
Kaplan GG et al. Am J Gastroenterol 2007.
Molodecky NA et al. Hepatology 2011

Etiopathophysiology



>20 susceptibility genes, but impact <10%

Possibly >50% of liability

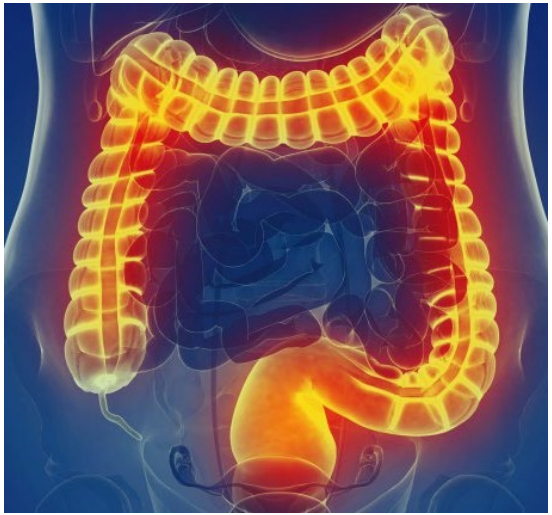
Gut derived antigens presented to T cells

Homing via MadCAM-1, VCAM-1 and CCL25

Gut-microbial co metabolism affecting bile composition

Karlsen TH et al. Primary sclerosing cholangitis – a comprehensive review. J Hep. 2017

PSC and IBD



- 70% of PSC with IBD

de Vries AB, Janse M, Blokzijl H, Weersma RK. World J Gastroenterol. 2015 Feb

- 80% of PSC-IBD are UC
  - 10% IBD-U and CD each
  - More pancolitis, possibly more rectal sparing and backwash ileitis

Loftus EV et al. Gut. 2005 Jan

- ~5% of IBD patients develop PSC
- Reduced risk of PSC in current (OR 0.31) and former smokers (OR 0.52)

Wijarnpreecha K. UEG. 2018 May

Symptoms

- Mostly asymptomatic! (~50%)
- Abdominal pain 20%
- Pruritus 10%
- Jaundice 6%
- Fatigue 6%
- Fever, chills, weight lsos

Kaplan GG, Laupland KB, Butzner D, et al. The burden of large and small duct primary sclerosing cholangitis in adults and children: a population-based analysis. Am J Gastroenterol 2007;102:1042–9.

Diagnostics

Labs

- Abnormal LFTs in about ¾ of patients
- Mostly cholestatic pattern (AP>GGT>Bili)
- ASAT/ALAT can be elevated (IgG/Aktin positive in AIH overlap)

- De Ritis >1, low Tc, INR and albumin suggest ACLD

Diagnosis

- IgG4 elevati

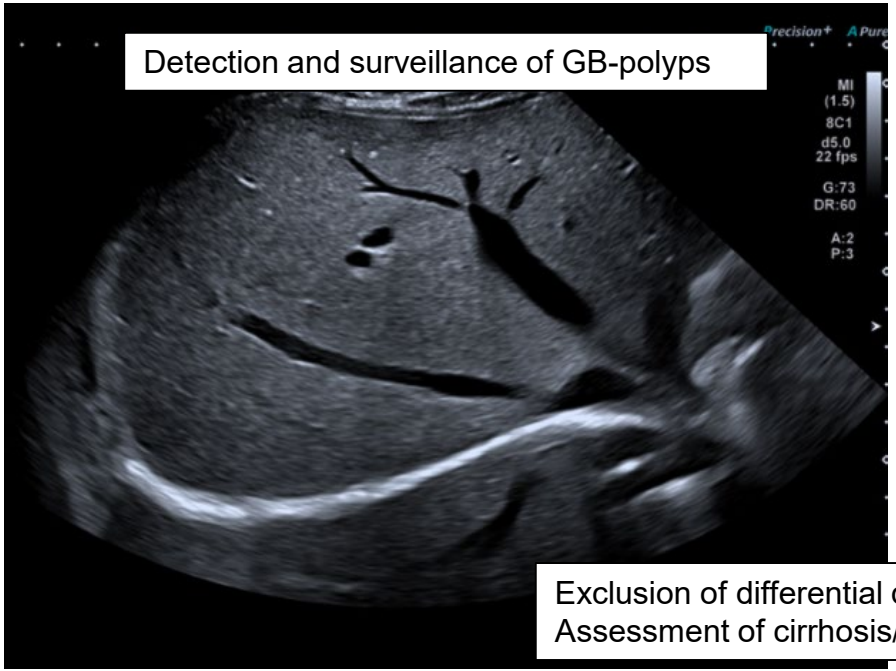
Antibody	Prevalence (%)	(Median)	No. of patients	(Median)
Anti-BEC	63	(63)	30	(30)
pANCA	26-94	(68)	13-86	(30)
AMA	0-9	(0)		
Anti-LKM	0	(0)		
Anti-SLA/LP	0	(0)	10-37	(25)
ANA[1]	8-77	(30)	13-73	(35)
SMA[1]	0-83	(17)	10-73	(36)
ASCA	44	(44)	25	(25)
Anti-cardiolipin	4-63	(27)	23-73	(41)
Rheumatoid factor	15	(15)	71	(71)
AECA	35	(35)	20	(20)
Anti-TPO	16	(16)	73	(73)
Anti-GBM	17	(17)	24	(24)
Anti-sulfite oxidase	33	(33)	39	(39)
Anti-GSTT1	5	(5)	58	(58)

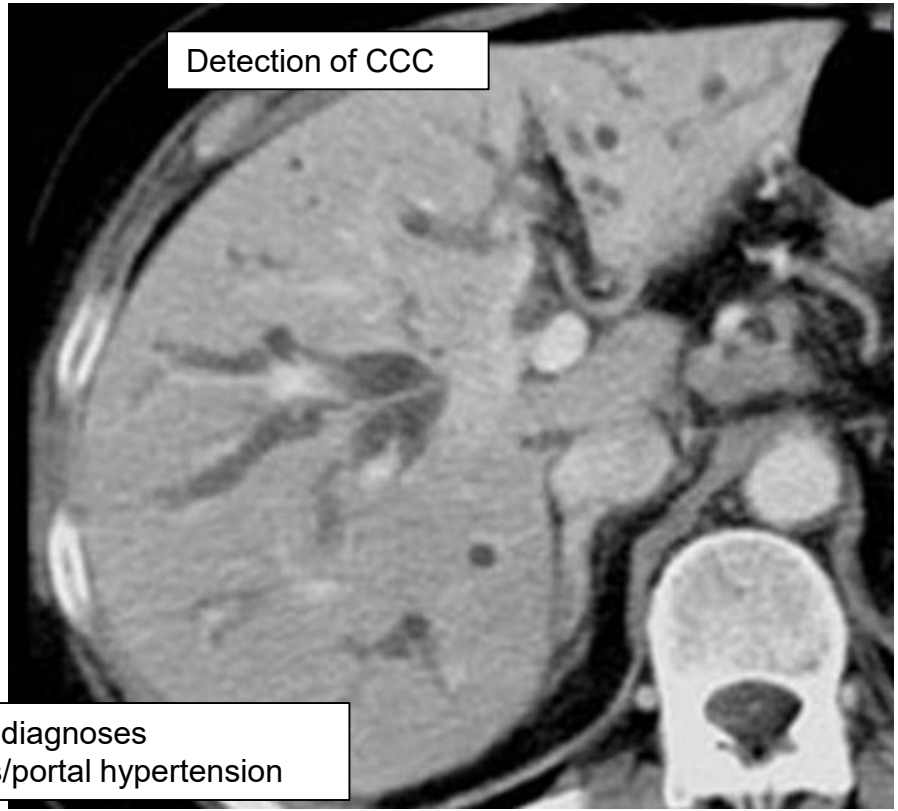
Best in patients without IBD (present in UC, AIH and PBC)

agnosis?)

Hov JR et al. WJG. 2008 Jun
Zhang L et al.. Am J Surg Pathol 2010:

US/CT



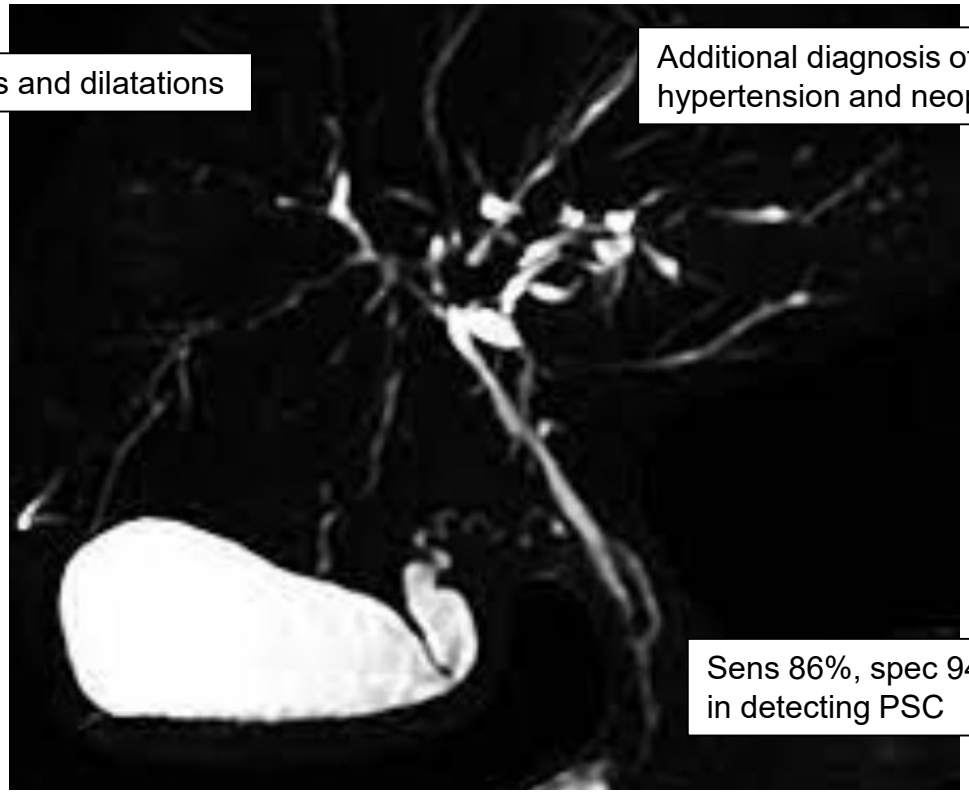


Exclusion of differential diagnoses
Assessment of cirrhosis/portal hypertension

MRCP

Strictures and dilatations

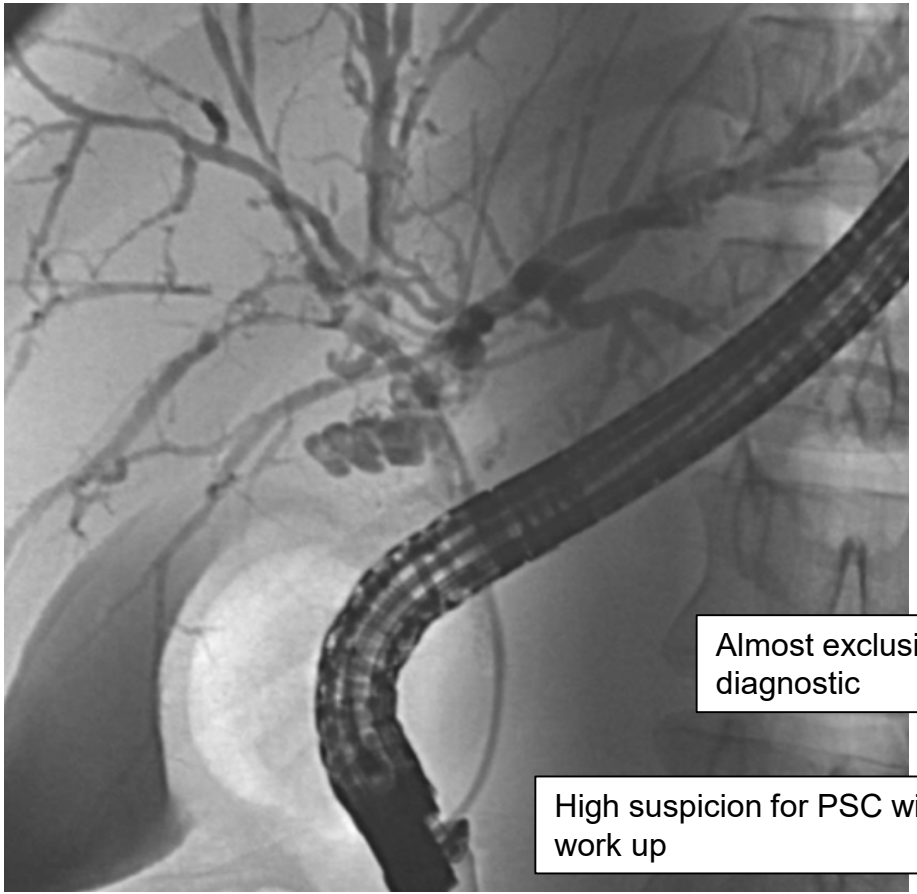
Additional diagnosis of cirrhosis, portal hypertension and neoplasia



Sens 86%, spec 94% in detecting PSC

Dave M et al. Radiology. 2010

ERCP



Almost exclusively therapeutic, rarely diagnostic

High suspicion for PSC with negativ diagnostic work up

Inconclusive cases

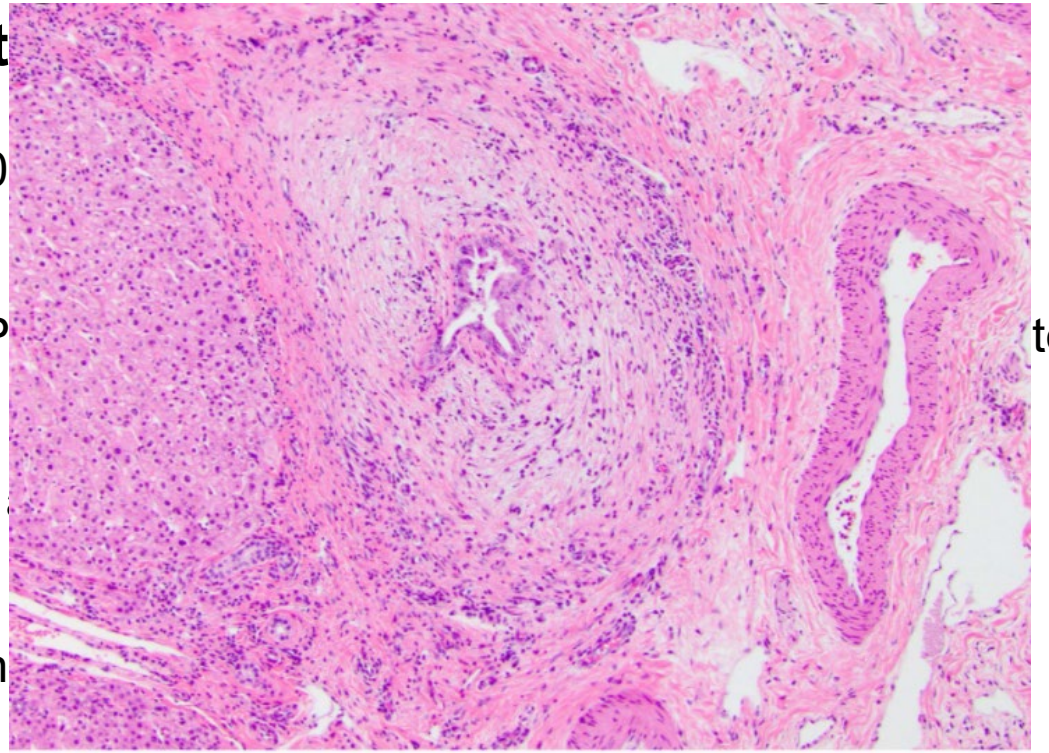
- Patient with symptoms
- Cholestatic patt
- Normal MRI

Also when suspicion of AIH-Overlap

ff

Small-duct

- Incidence 0
- Variant of P tology
- More often
- Longer tran

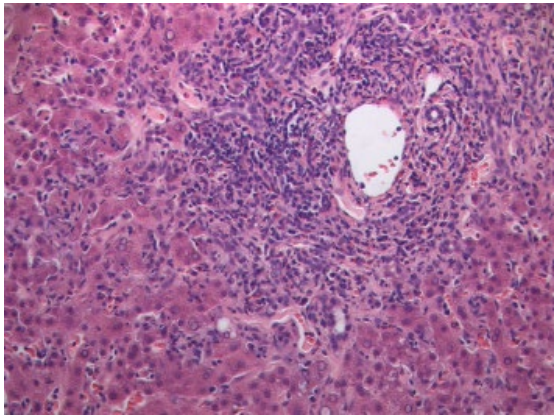


Periductal “onion skin” fibrosis surrounding an injured but intact bile duct in a liver transplanted for primary sclerosing cholangitis

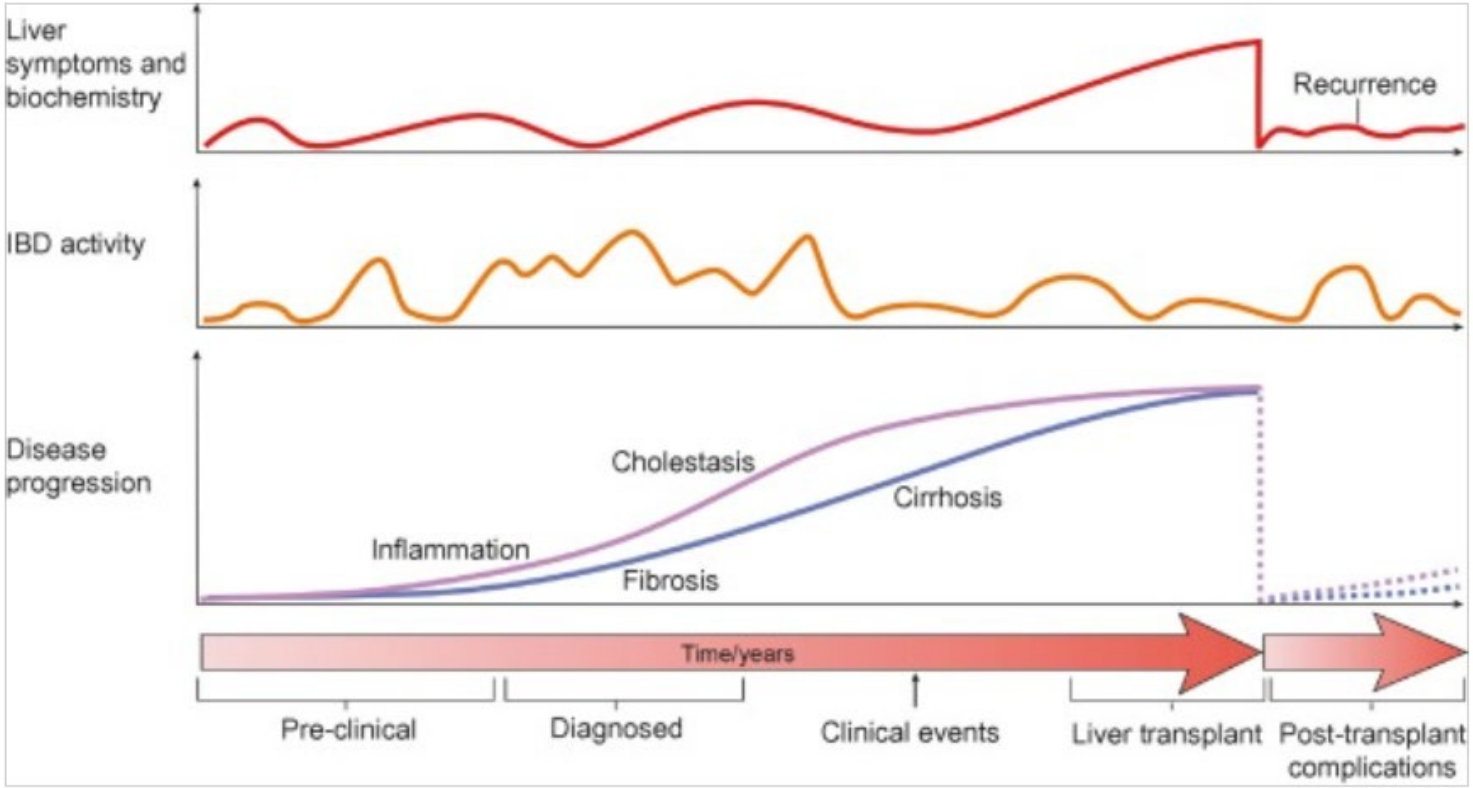
Björnson E et al. Gastroenterology. 2008

AIH-PSC Overlap

- Up to 7-14% of PSC patients
  - More common in children (so called autoimmune sclerosing cholangitis)
- ALT >5xULN, IgG >2xULN, ANA, SMA, LKM, LP
- Always biopsy!



Prognosis and natural course


Liver symptoms and biochemistry
Recurrence
IBD activity
Disease progression
Cholestasis
Cirrhosis
Inflammation
Fibrosis
Time/years
Pre-clinical
Diagnosed
Clinical events
Liver transplant
Post-transplant complications

Prognosis in peds

- Chronic relentless course
  - Event-free survival 53% at 10y
  - After 10y 38% portal-hypertensive and 25% biliary complications
  - CCC in 1%
  - High risk in patients with high bilirubin, GGT or APRI

Survival with native liver 2.8y and 3.5y respectively

Deneau MR et al. Hepatology. 2017

Prognosis in adults

- Median time from diagnosis to death or OLT varies substantially
  - 21.3y population-based cohort vs. 13.2y in transplant-centers

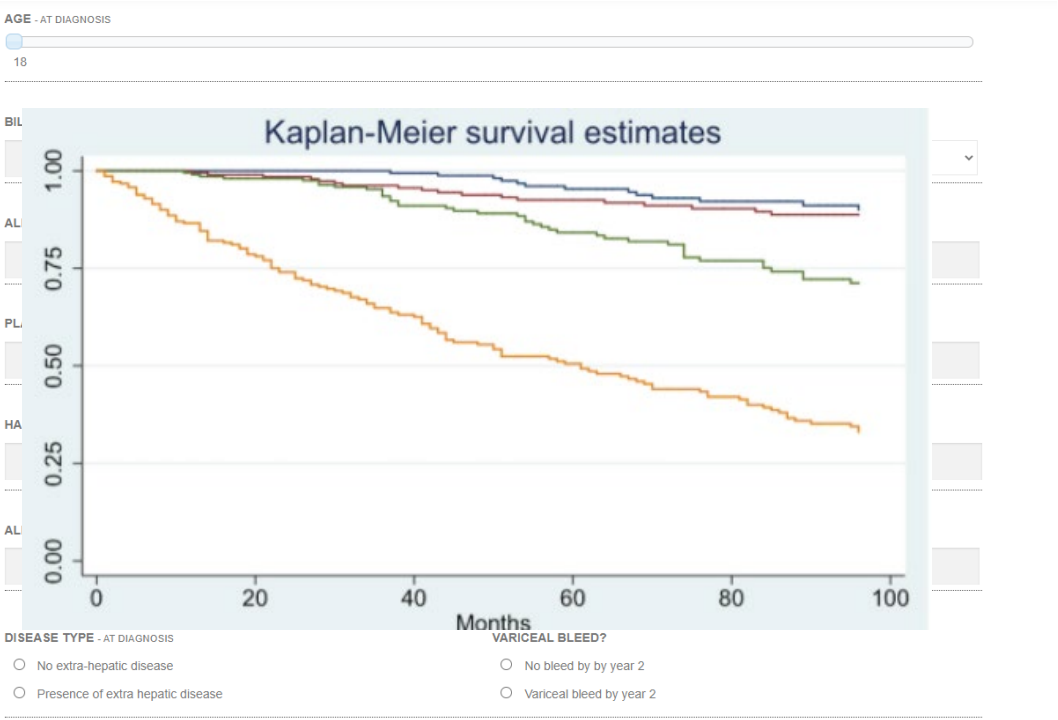
- Death mostly due to cholangiocarcinoma (32%)
  - Liver failure 18%, OLT complications 9%, CRC 8%

- Increase cancer risk
  - CCC (HR 28.46), HCC (HR 21.00), pancreatic (HR 5.26) and gallbladder (HR, 9.19)

Boonstra K et al. Hepatology 2013
Triveid PJ et al. Gastroenterology. 2020

Prognosis in adults

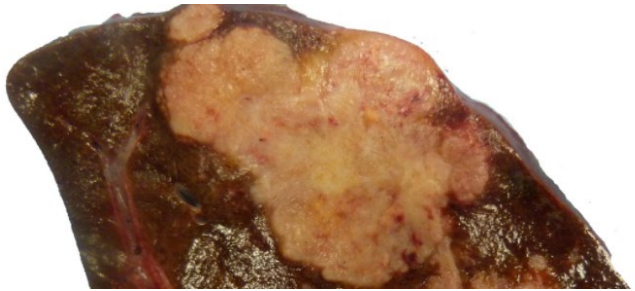
- UK-PSC risk score calcu
- Mayo risk score calculat
- MELD Score



Goode E. Hepatology 2018.

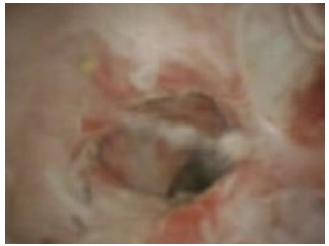
Complications

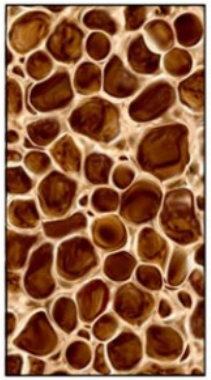
Most common complications



- Cancer

- Biliary strictures
  - Cholestasis and pruritus
  - Infection
  - Fibrosis





- Hepatic osteodystrophy/osteoporosis

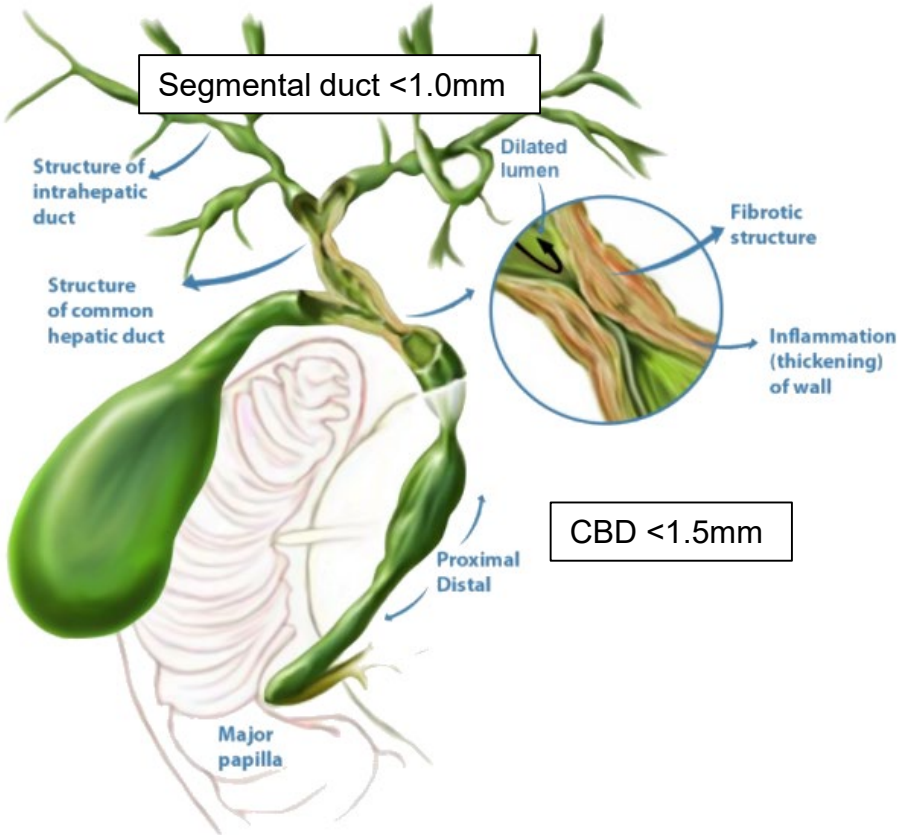
Boonstra K et al. Hepatology 2013

Dominant strictures

- Worsening LFTs or pruritus
- Fever and chills (cholangitis)
- Pain, weight loss, fatigue as warning signs of CCA
- In up to 62.5% of patients

Chapman M. Eur J Gastroenterol Hepatol. 2013

Dominant strictures



Strictures

▶ **Table 2** Amsterdam classification of cholangiographic changes in primary sclerosing cholangitis (PSC) [23].

Type	Intrahepatic	Extrahepatic
0	No visible abnormalities	No visible abnormalities
I	Multiple caliber changes; minimal dilatation	Slight irregularities of duct contour; no stricture
II	Multiple strictures; saccular dilatations, decreased arborization	Segmental strictures
III	Only central branches filled despite adequate filling pressure; severe pruning	Strictures of almost entire length of duct
IV	–	Extremely irregular margins; diverticulum-like outpouchings

Strictures

- High risk of CCA in dominant strictures (7-26%)

Chapman M et al. Eur J Gastroenterol Hepatol. 2013
Boyd S et al. Endoscopy. 2014

- Perform always brush sampling, biopsy when possible

- Ballon dilatation perferred, repeated if necessary (1-4w)
  - Goal 8mm CBD, 6mm DHL/DHR
- Higher rate of AE in stenting (pancreatitis, cholangitis, perforation)

Ponsioen C et al. Gastroenterology. 2018

- Routine antibiotics!

Cholangiocellular carcinoma

- Median time from PSC to CCC diagnosis is 6y
  - Significant portion diagnosed in 1st year!
  - 80% die 1y after prognosis
- Cumulative risk of 20% in 30y

- Risk factors: Duration of IBD, colonic dysplasia
- CA 19-9 Sens 50-89%, Spec. 54-98%

High in cholestasis of any sort
No expression in Lewis-Ag negative patients (3-7%)

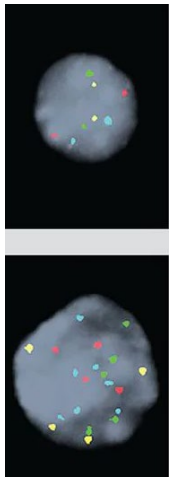
Boonstra K et al. Hepatology 2013
Gulamhusein AF et al. Am J Gastroenterol 2016
Takakura WR et al.. Curr Opin Gastroenterol. 2017

Cholangiocellular carcinoma

- Detection mostly via radiology (new mass or stricture, lymphadenopathy)

- Mostly invasive diagnostics (ERCP) necessary

Sens 43-52%
Spec 97-99%



Sens 68%
Spec 99.6%

Sens 65-99%
Spec 95.8-97%

Itoi T et al. CGH. 2010
Trikudanathan G. GIE 2014
Niej B. APT. 2016 Dec
Niej B. GIE. 2016 May

Gallblader carcinoma

- General increase in gallblader abnormalities (stones, polyps, cancer)
- 6-14% Gallbladder masses on ultrasound (55-56% malignancy)
- Lifetime risk of gallbalder cancer 3-14%

Cholecystectomy for masses >8mm

Buckels et al. Gastroenterol. 2022
Said K. J Hepatol 2008
Razumilava N et a. Hepatology 2017

Colorectal carcinoma

- Often right-sided colon

- HR 3.24-5.1

	10y risk	20y risk
PSC alone	2%	2%
PSC-IBD	14%	31%

- Screening colonoscopy recommend at time of diagnosis

Claessn MM. J Hepatol 2009
Broommé U. Hepatology. 1995
Boonstra K et al. Hepatology 2013
Zhen HH. Eur J Gastroenterol Hepatol. 2016

Surveillance

- Annual imaging reduces mortality (HR 0.43)

- MRCP superior to US, except gallbladder
  - If new, amenable dominant stricture go for ERCP

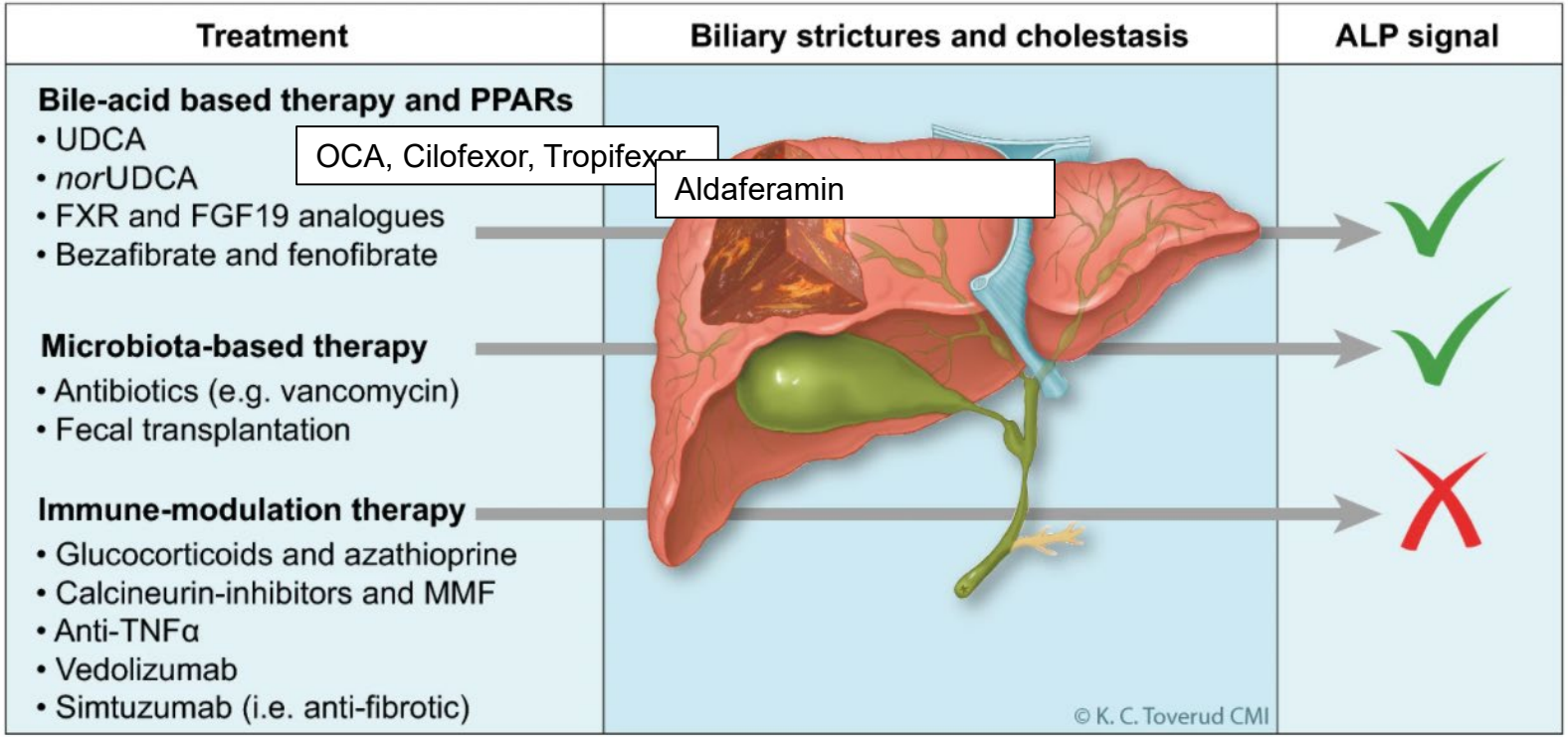
- PSC without IBD: Colonoscopy 5y-intervalls (colonic biopsies)
- PSC-IBD: Annual colonoscopy, even with J-pouch

Triveid PJ et al. Gastroenterology. 2020

Treatment

- No drug prolonging survival!
- UDCA often used due to lack of alternatives
  - But no evidence to support effect
  - High doses >28mg/kgKG even increase mortality
- Immunosuppressants without effect (except in overlap)

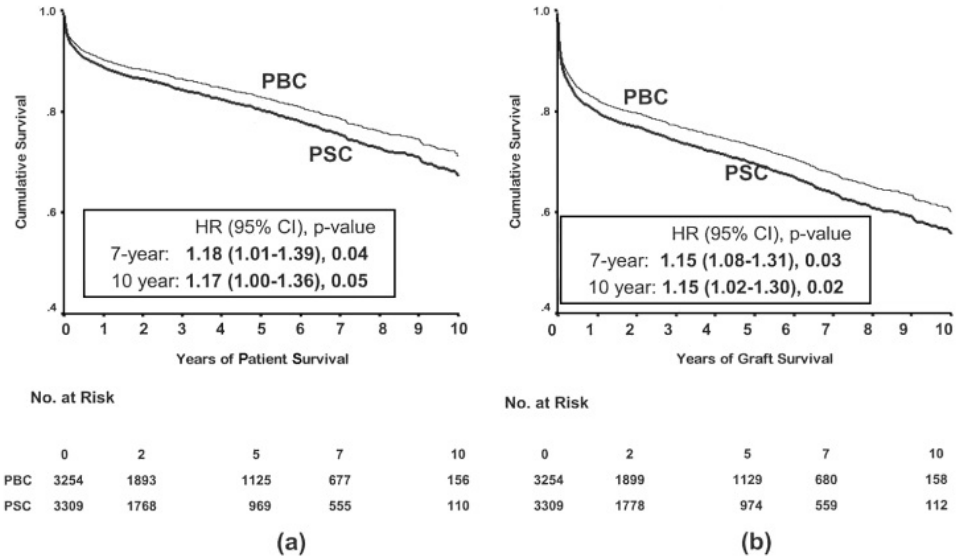
New horizons



OLT indications

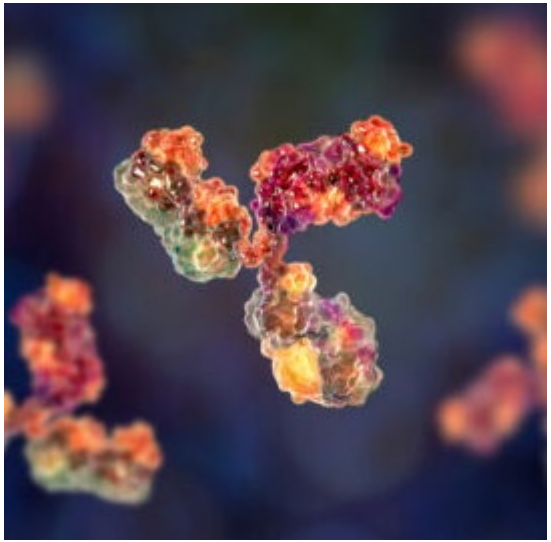
- Regular setting with cirrhosis and corresponding complications
- Recurring cholangitis
- Intractable pruritus
- Perihilar CCA (Mayo protocol)
  - Tumor <3cm, neoadjuvant RCx

OLT



- Recurrence of 20-45.8%
  - Risk factors are present IBD, high INR at OLT, high donor age
  - Unclear if colectomy is protective

Graziadei IW. Liver Transplant 2002
Hildebrand T. Liver Transplant 2015
Ueda Y. Transplant Direct 2017
Maheshwari A. AJG. 2004



IgG4-related cholangitis

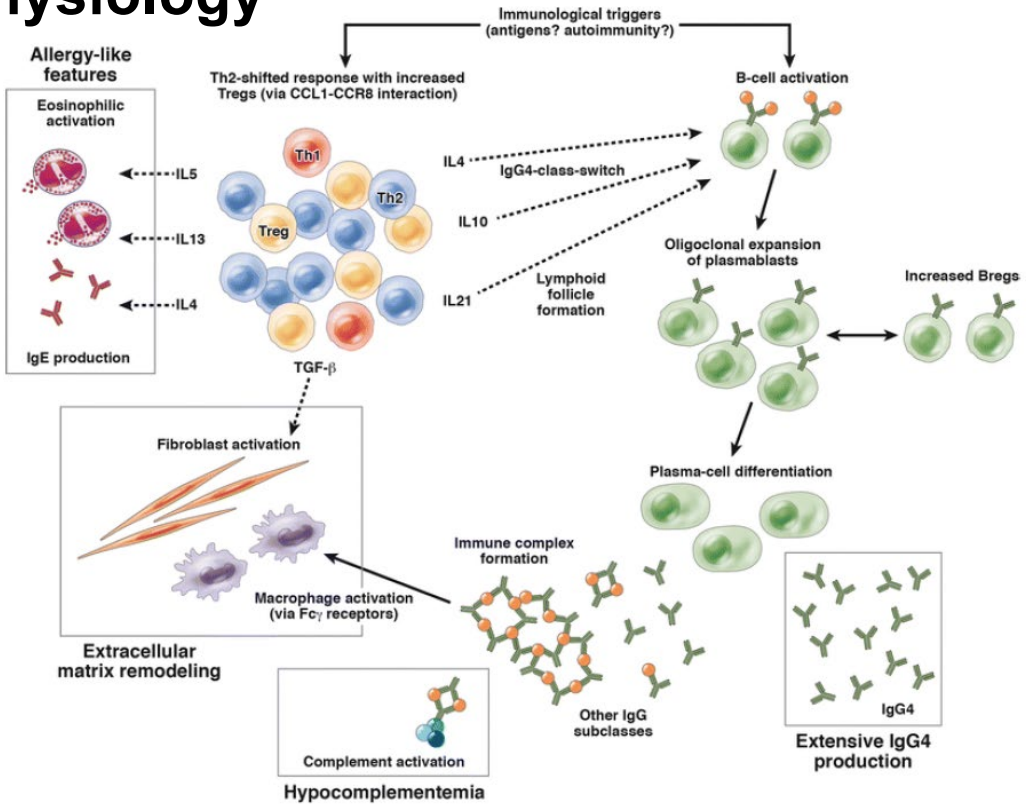
Epidemiology

- Male predominance 7:1
- >80% middle-aged to elderly men
- Risk factors
  - Blue collar workers (>1y exposure to toxins)
  - Autoimmune disease

68% of patients with pancreatobiliary IgG4 disease

Hubers LM et al. J Hep Reports. 2021

Pathophysiology



Kamisawa et al. Lancet 2015

Symptoms

- Jaundice (biliary and/or pancreatic involvement) in about 1/3
- Pruritus
- Weight loss
- Other organ involvement with incidental finding of cholangiopathy

- Cirrhosis and CCA rarely presenting symptoms

Tanaka A. Clin Gastroenterol Hepatol. 2017

Diagnosis

- H istology
- I maging
- S erology
- O rgan involvement (75% with ≥2 organs)
- R esponse to
- T herapy

HISORt

Hirotara O. J Hepatobiliary Pancreat Sci. 2012

Diagnosis

- O rgan involvement (75% with ≥2 organs)
  - pancreato-hepatobiliary tract 45%, in >80% combined
  - Major salivary glands 37%
  - Lacrimal gland 26%
  - Retroperitoneum 15%
  - Kidneys 15%
  - Lungs 14%
  - Aorta 10%

Wallace ZS et al. Ann Rheum Dis. 2019

Diagnostic items
1. Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the tickening of the bile duct wall
2. Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dl)
3. Coexistence of autoimmune pancreatiti, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis
4. Histopathological examination shows:
a. Marked lymphocytic and plasmacyte infiltration and fibrosis
b. Infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF
c. Storiform fibrosis
d. Obliterative phlebitis
Option: effectiveness of steroid therapy
A specialized facility, in which detailed examinations such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be administered, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out
Diagnosis
Definite diagnosis
1. + 3.
1. + 2. + 4.a., b.
4.a., b., c.
4.a., b., d.
Probable diagnosis
1. + 2. + option
Possible diagnosis
1. + 2.
It is necessary to exclude PSC, malignant diseases such as pancreatic or biliary cancers, and secondary sclerosing cholangitis caused by the diseases with obvious pathogenesis. When it is difficult to differentiate from malignant conditions, a patient must not be treated with facile steroid therapy but should be referred to a specialized medical facility.

Hirotara O. J Hepatobiliary Pancreat Sci. 2012

INSELGRUPPE

Labs

- Cholestatic pattern (AP, GGT, bilirubin)
- Often diabetes due to AIP
- CA 19-9 regularly high, responding to steroids

Labs

- Serum IgG4
  - Elevated in 75-84% of IgG4-RD patients
  - Reliable when >4xULN
  - >1.4g/L → 22.4% have IgG4-disease, sens 82.8%, spec 84.7%
  - >2.8g/L → Sens 56.9%, spec 96.2%, PPV 44.5% , NPV 97.7%

  - High IgG4 (>2.8g/L) correlate with multiorgan involvement and relapse
  - IgG4 not reliable for disease course

Oseini AM et al. Hepatology 2011
Boonstra K et al. Hepatology 2014
Culver EL et al. Am J Gastroenterol 2016
Tanaka A et al. Clin Gastroenterol Hepatol. 2017

INSELGRUPPE

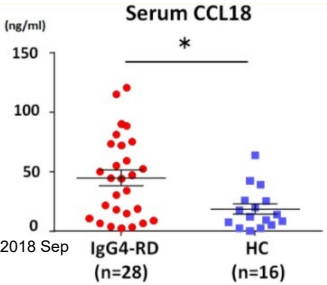
Labs

- IgG4/IgG RNA ratio >5% with equivocal results

Doorenspleet ME. Hepatology. 2016
De Vries E. J Hep Reports. 2020

- Circulating plasmablasts ($CD19^{+}CD24^{-}CD38^{hi}$)
  - Elevated in active disease, decrease after steroids

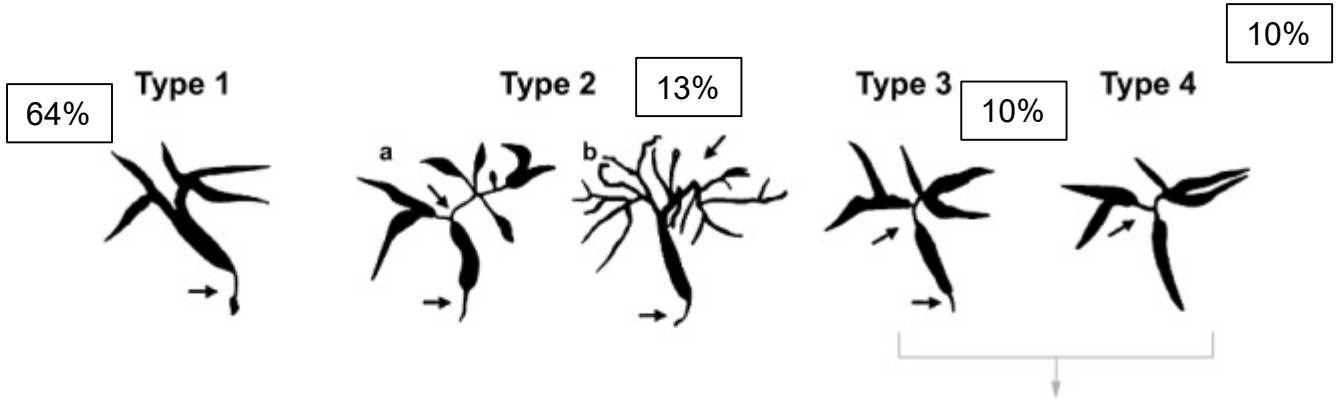
Lin W. Arthritis Res Ther. 2017 Feb



- CCL18
  - Elevated in active disease, decrease after steroids

Akiyama M. Ann Rheuma Dis. 2018 Sep

MRCP/ERCP



Differential diagnosis			
	Pancreatic cancer Bile duct cancer Chronic pancreatitis	Primary sclerosing cholangitis	Bile duct cancer Gallbladder cancer
Useful modalities			
	IDUS* (bile duct) EUS-FNA** (pancreas) Biopsy (bile duct)	Liver biopsy Colonoscopy (R/O co-existence of IBD***)	EUS (bile duct, pancreas) IDUS (bile duct) Biopsy (bile duct)

Differentiation IgG4-RD and PSC

IgG4-related sclerosing cholangitis

1. dilation after confluent stricture
2. stricture of lower common bile duct

Primary sclerosing cholangitis

3. band-like stricture
4. beaded appearance
5. pruned-tree appearance
6. diverticulum-like outpouching

Hirotara O. J Hepatobiliary Pancreat Sci. 2012

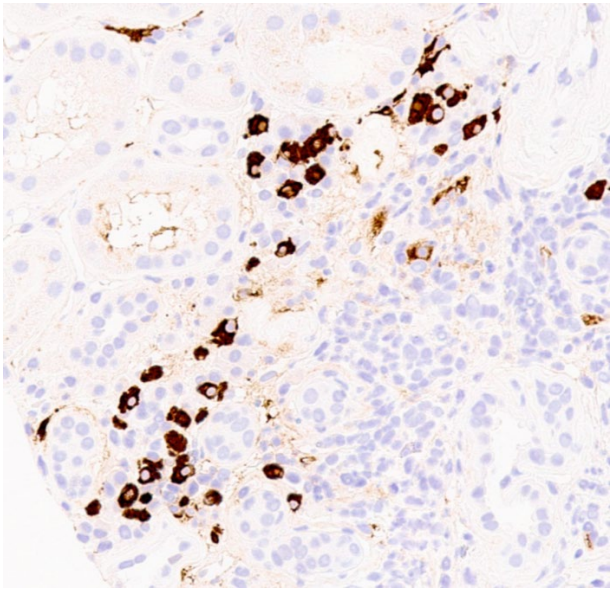
Histology

- Biopsy of papillae via duodenoscopy
  - 52-72% positive Kamisawa T et al. Gastrointest Endosc 2008
    Kawakami H et al. J Gastroenterol Hepatol. 2017

- Biopsy of bile ducts via cholangioscopy

Histologic criteria

- >10 IgG4+ plasma cells/hpf
- Lymphoplasmacytic infiltrates
- Storiforme fibrosis



- Minor criteria: partial obliterative phlebitis and eosinophilia


NOT SURE IF PSC
OR IG4-RD


They're the same picture.

	IgG4-RD	PSC
Organ involvement	Multiorgan involvement	Biliary tract ± GIT
Male predominance	7:1	2:1
Age	Older (~60yo)	Younger (30-40yo)
IBD	Rarely	Regularly (80%)
IgG4	Positive in ~75% >4xULN very specific	Positive 9-15%
Radiological	Longer stenosis, upstream dilatation	Duct pruning, biliary pseudodiverticula
Histology	>10 IgG4 positive plasma cells IgG4/IgG1 pc ratio >40%	Some plasma cells
Therapy	Responsive to PDN	No response

When to treat and with what

- Only patients that are symptomatic
  - 10-15% selflimited course

- Induction with prednison (0.6-0.8mg/kgKG, i.e. 30-40mg) for 4 weeks
- Taper 5mg EOW
  - Response rate of 62-100%

  - Goal is resolution of stenoses and reduction of LFTs

Treatment

- Often maintenance therapy necessary
  - High recurrence rate without maintenance in up to 30%

- Steroid-dependent/-refractory, relapse or high risk (multiple organs)
  - Common AZA or MMF

- Rituximab as ultima ratio

Complications and course

- Generally indolent course
  - 10-15% selflimited
  - Progression to cirrhosis in 7.7-9% with need for OLT in selected cases

- Cholangitis

- Equivocal data concerning cancer

Ghazale A et al. Gastroenterology. 2008
Hugett MT et al. Am J Gastroenterol. 2014
Tanaka A. Clin Gastroenterol Hepatol. 2017

Follow up

- Lifelong follow-up
- Serological with IgG4 level

- Radiological (US, CT, MRCP)
  - FDG-PET to distinguish inflammation from fibrosis

- IgG4 responder Index not routinely used

TAKE HOME MESSAGES

- Optimal diagnostic of sclerosing cholangiopathies with MRCP
- Think of SSC and exclude actively (history, labs, brush)
- If equivocal results go for biopsy, always if IgG4 suspected (papilla)
- HISORt (IgG4 levels only reliable if adequately high)
- Best treatment option in PSC is LTx for now (recurrence!), in IgG4 PDN
- Follow up patients to detect strictures amenable for ERCP and exclude cancer

INSELGRUPPE

Thanks for your attention