Cystic liver disease

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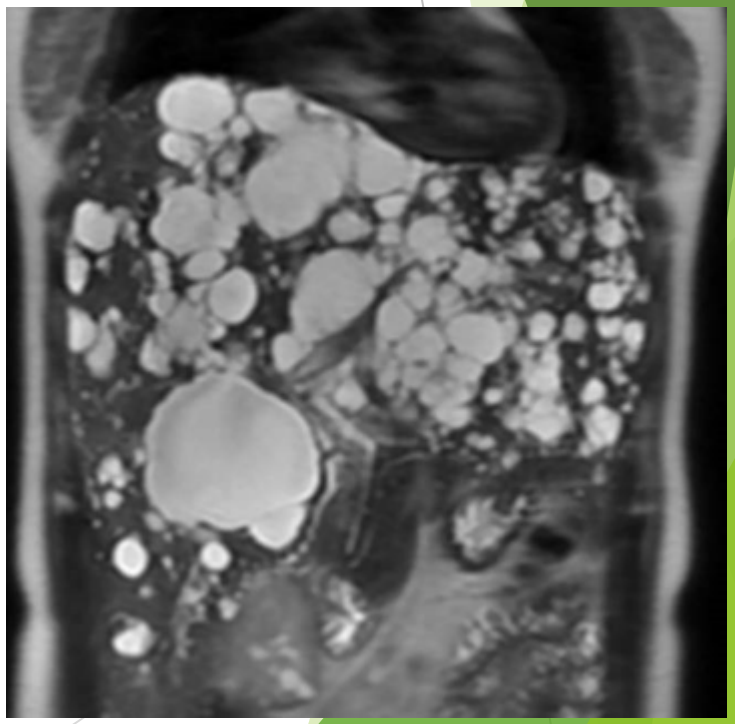
Learning objectives

- *Ductal plate malformations & cystic liver disease*
- *Complications of simple cysts*
- *Simple vs complex cystic lesions*
- *Biliary cystadenoma & biliary cystadenocarcinoma*
- *Polycystic liver diseases (concise overview)*

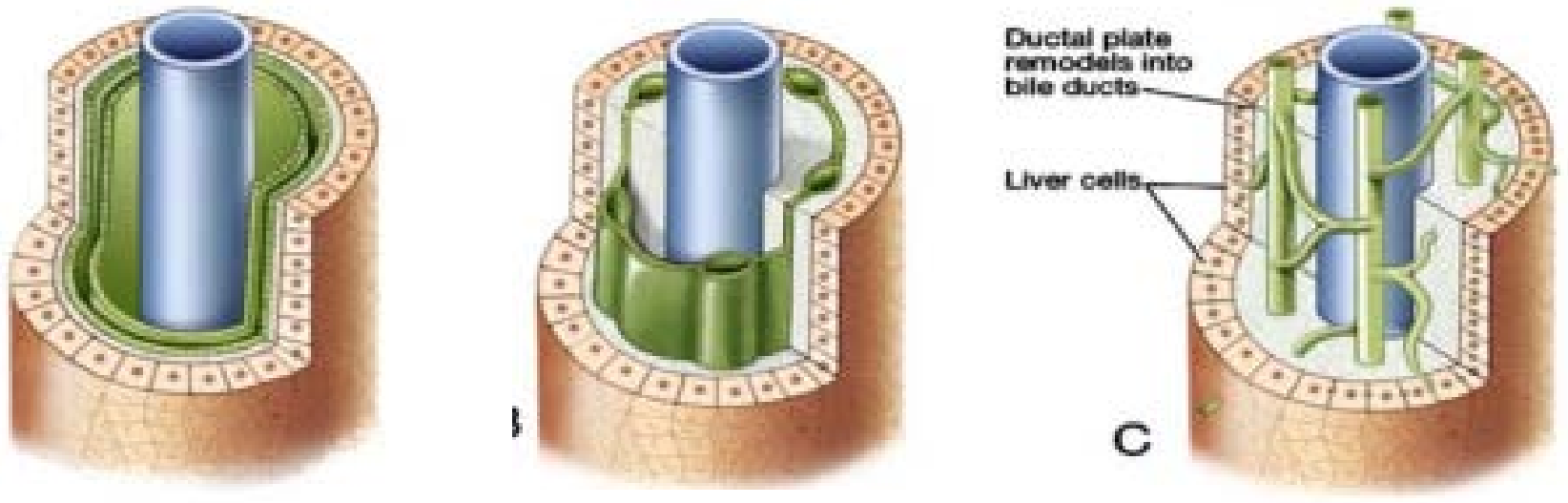
- *Your help with a case*



Origin of biliary system: the ductal plate

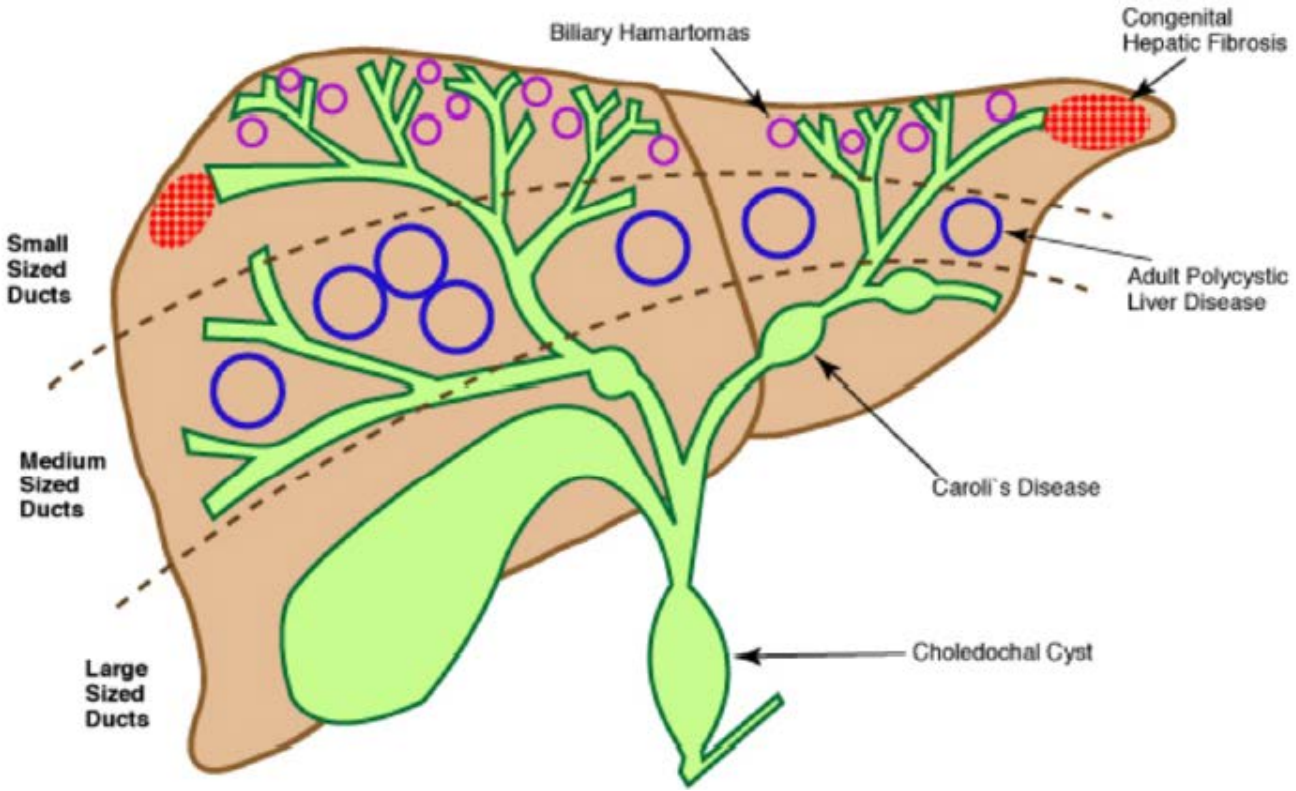
(don't worry, just one slide on embryology)

Ductal plate: cylindric (double) layer of biliary epithelium surrounding portal vein ramifications. Undergoes remodeling and involution.



Remodeling starts at week 6-7 and proceeds from hepatic hilum to liver periphery

Ductal plate malformations



Late stage > smaller ducts
Biliary hamartoma's (VMC)
Congenital hepatic fibrosis

Middle stage: medium ducts
PCLD

Early stage > large ducts
Choledochus cysts
Caroli's disease

NB: in case of liver cysts and hamartomas the connection with bile ducts is lost!!

Image: Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine - Kyoto/JP

Solitary cystic lesions

(Incidental) finding of a cystic liver lesion

and then…?

(Incidental) finding of a cystic liver lesion

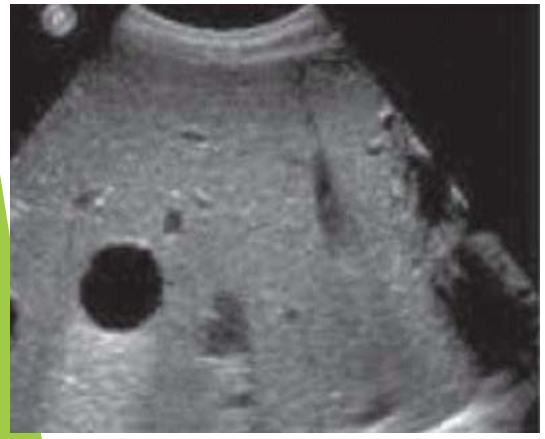
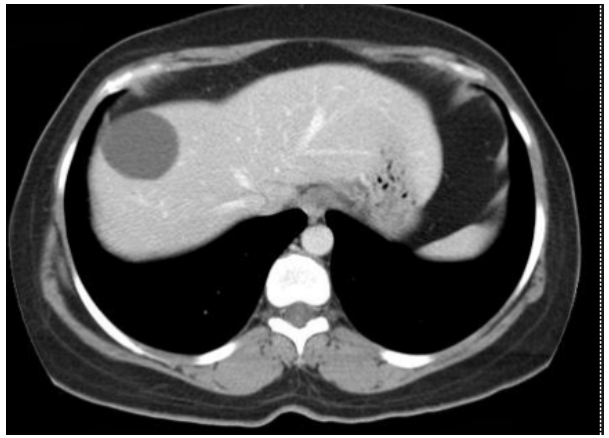
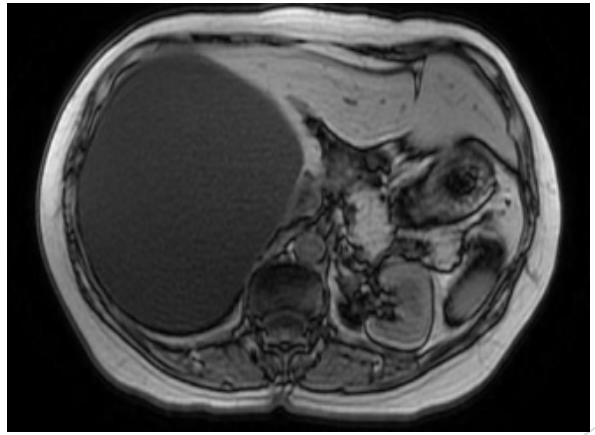
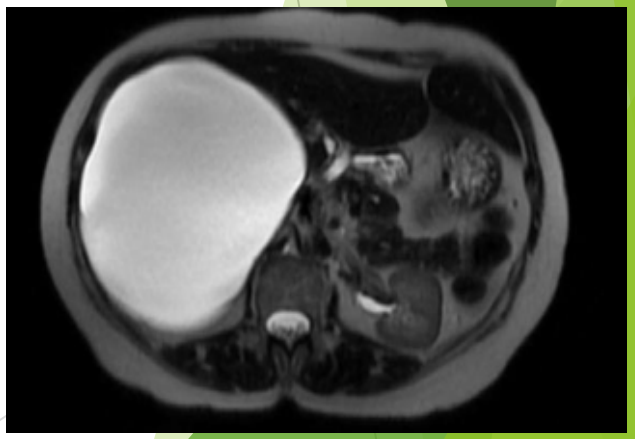
and then…?

Simple cyst?

Complex cyst?

Simple liver cysts

- Highly prevalent (2.5%-18%)
- Size: from small to very large
- Lined with cuboidal biliary-type epithelium (with secretory function)
- Contains serous fluid
- Often asymptomatic, unless very large or complications

Lantinga et al, World J Gastroenterol 2013; Borhani et al, AJR 2014; www.radiopaedia.org

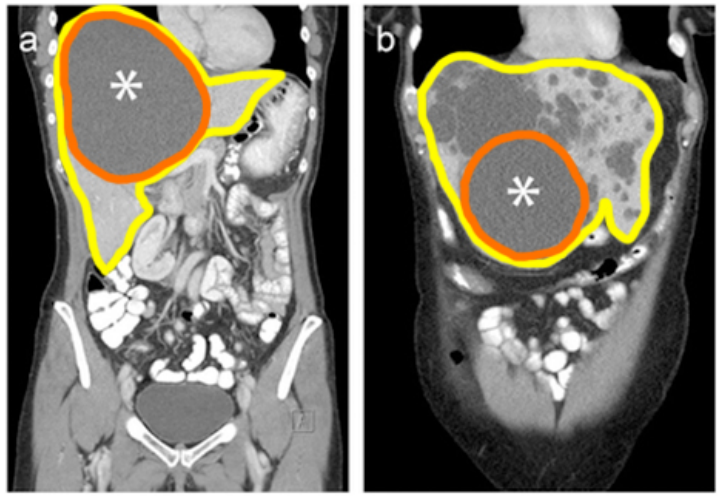
When do liver cysts cause problems?

H Haemorrhaging

I Infection

V Very large

Very large cysts

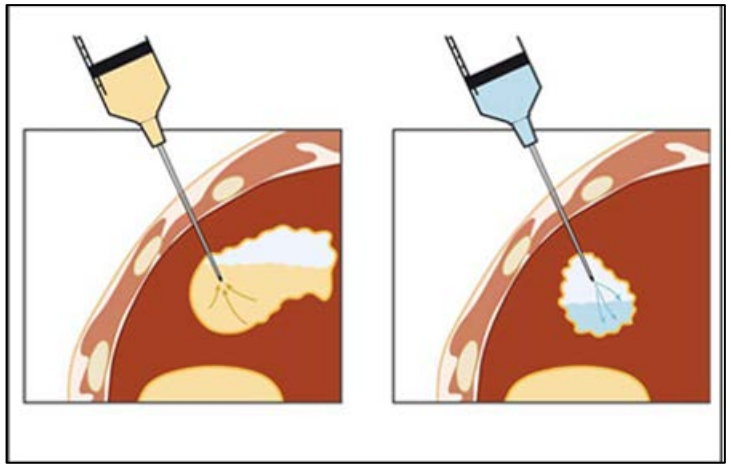


Problems:

Pain, dyspnea, early satiety.
Decreased quality of life.

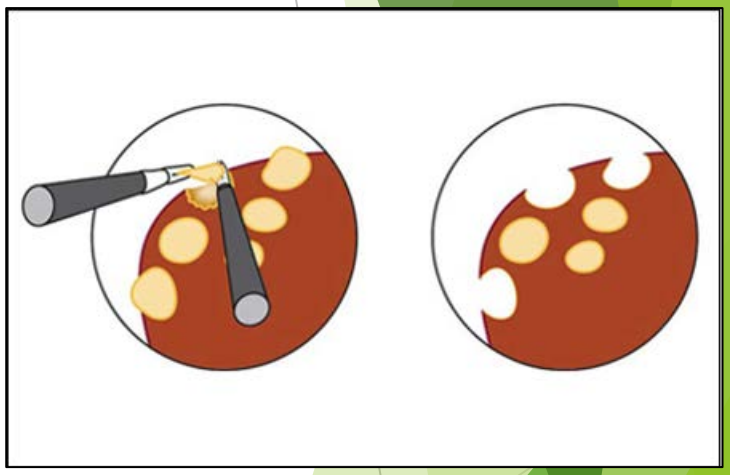
Treatment options

Aspiration sclerotherapy



Ethanol
Polidocanol
Acetic Acid

Fenestration



Wijnands et al, Efficacy and safety of aspiration sclerotherapy, a systematic review, AJR 2017
Bernts et al, Clinical response after fenestration of symptomatic hepatic cysts, systematic review and meta-analysis, Surgical Endoscopy 2019

Effect of aspiration sclerotherapy

Reference	Year	No. of Patients	No. of Cysts	Volume Reduction (%)	Follow-Up (mo)
Benzimra et al. [27]	2014	57	58	94.0[a] (58.0–100)[b]	27.3[a]
Chrispijn et al. [28][c]	2012	106	106	75.6[d] (NS)	2.4[2]
Jusufovic and Serem [36]	2011	20	20	96.3[d] (74.9–100)[e]	24.0[d]
Larssen et al. [37]	1997	10	10	90.8[d] (77.0–100)[e]	17.3[d]
Nakaoka et al. [10]	2009	13	17	93.1[a] (47–100)[e]	54.0[d]
Nido and Wong [24][c]	2012	14	19	84.4[d] (24.8–100)[e]	8.5[a]
Radjokovic et al. [39][c]	2012	57	57	92.5[d] (NS)	18.0[a]
Souftas et al. [40]	2015	10	14	100 (68.9–100)[e]	12.0[d]
Spârchez et al. [41]	2014	13	13	88.0[a] (3.0–99.2)[e]	1.0[d]
Yan-Hong et al. [25]	2012	67	67	96.2[d] (NS)	30.0[a]
Yang et al. [30]	2006	27	31	98.1[d] (83.6–100)[e]	29.6[a]
Zerem et al. [26]	2008	20	23	90.2[d] (76.9–100)[e]	24.0[d]
Range		10–106	10–106	76–100	1.0–54.0

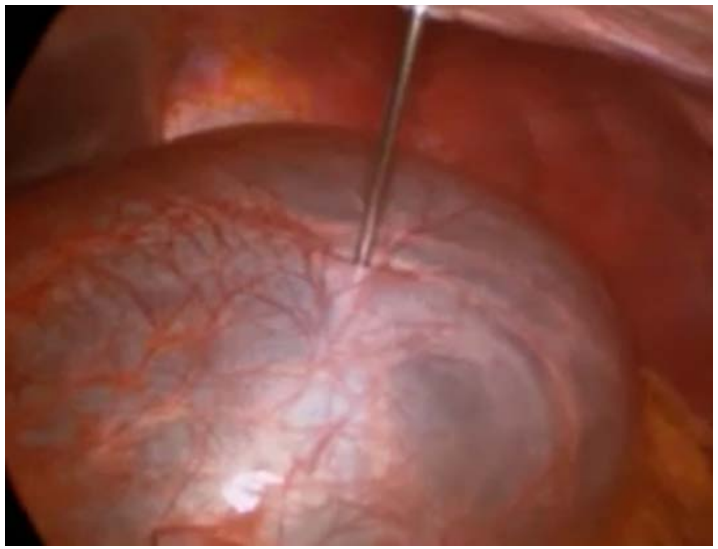
Reference	Year	No. of Patients With Symptoms	Percentage With Symptom Reduction
Benzimra et al. [27]	2014	57	94.7
Choi et al. [35][b]	2009	21	85.7
Chrispijn et al. [28][b]	2012	106	72.6
Larssen et al. [37]	1997	10	80.0
Montorsi et al. [38]	1994	21	100
Nakaoka et al. [10]	2009	13	100
Nido and Wong [24][a]	2012	14	100
Souftas et al. [40]	2015	10	100
Tikkakoski et al. [29]	1996	25	72.0
Yan-Hong et al. [25]	2012	44	86.4
Range		10–106	72.0–100

Safe and effective procedure (Radboudumc: semi-outpatient procedure).
Pain most common complication.
Ethanol intoxication (mainly in studies with high volume, long duration).

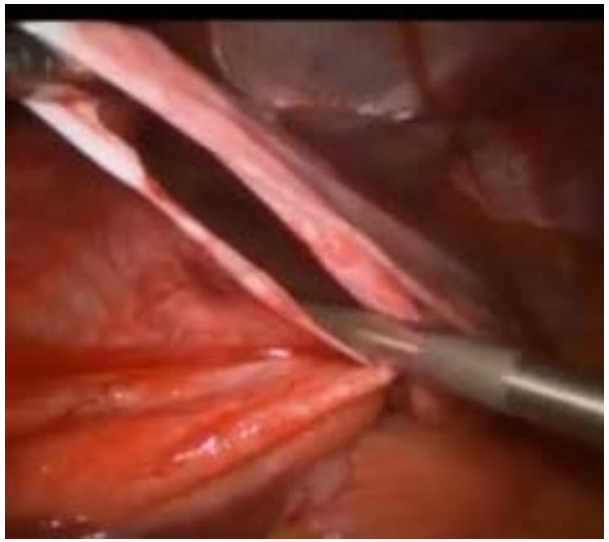
16 studies
526 patients
PLD and non-PLD

Wijnands et al, Efficacy and safety of aspiration sclerotherapy, a systematic review, AJR 2017

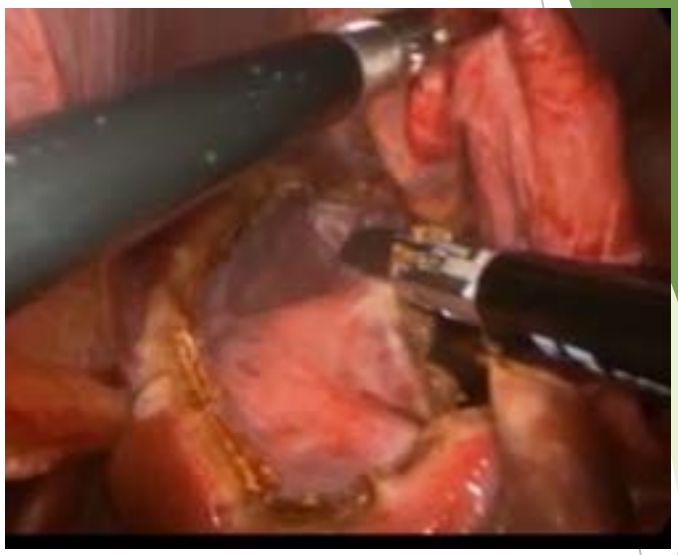
Fenestration: procedure and effect



Laparoscopic approach
Puncture and aspiration



Cyst emptied



Deroofing of cyst

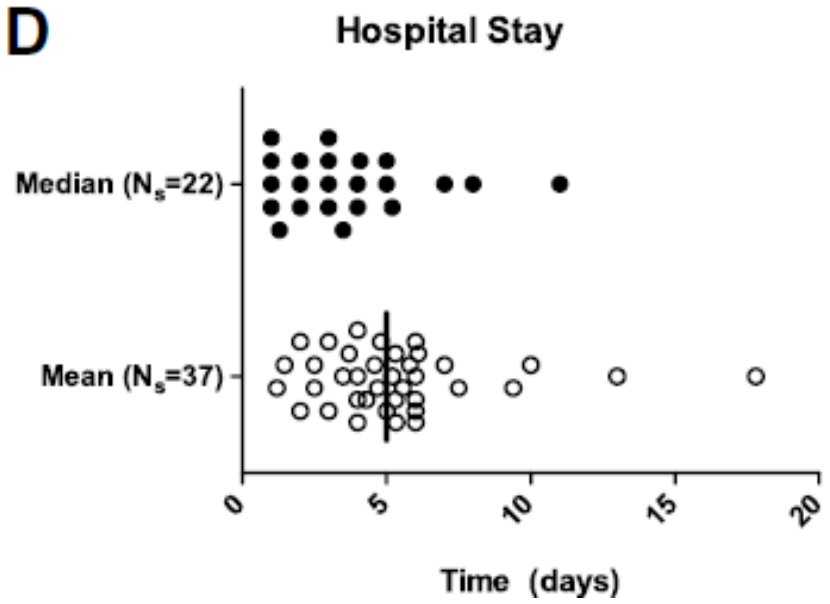
Symptomatic relief (pooled) 90.2%

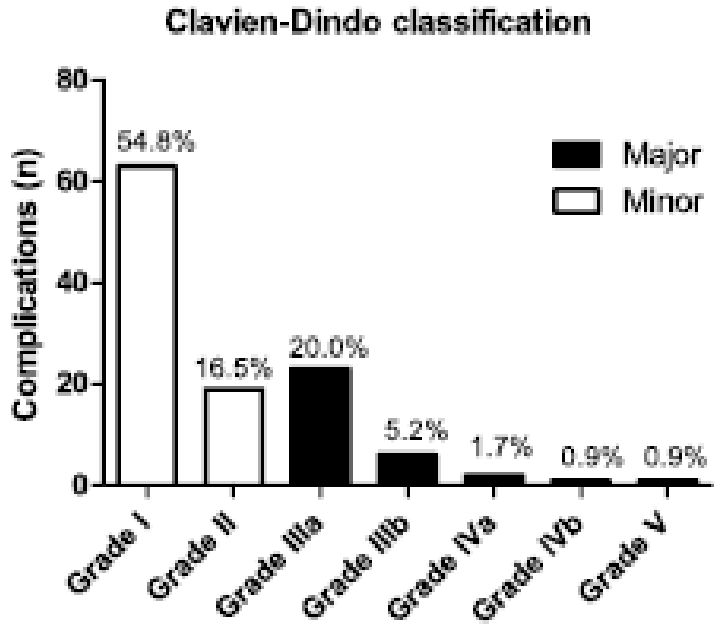
Symptomatic recurrence 9.6%

62 studies
1314 patients
PLD and non-PLD

Bernts et al, Clinical response after fenestration of symptomatic hepatic cysts, systematic review and meta-analysis, Surgical Endoscopy 2019

Fenestration: hospital stay & safety





Median hospital stay 5 days.
Overall post-operative complication rate 10.8% (71.3% minor).
Costs?

Bernts et al, Clinical response after fenestration of symptomatic hepatic cysts, systematic review and meta-analysis, Surgical Endoscopy 2019

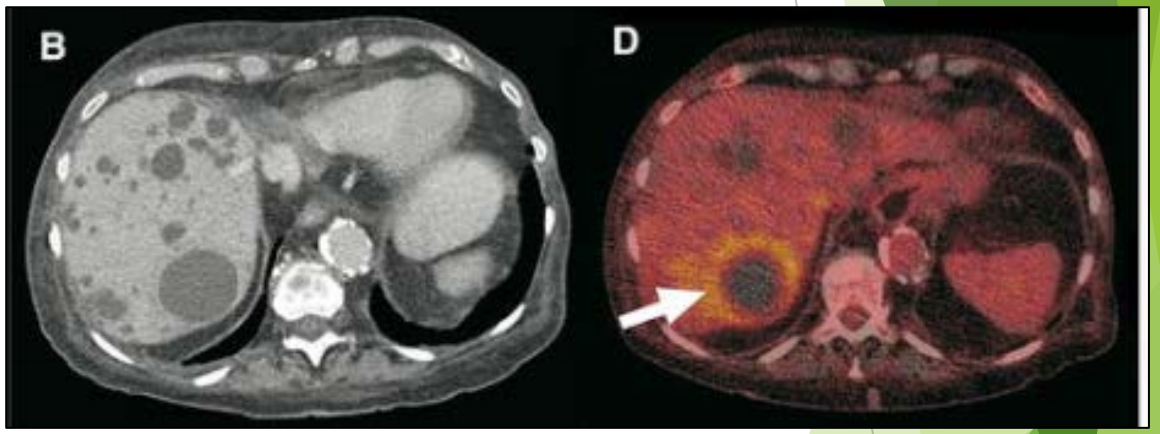
Infection of liver cysts

- Gold standard: cyst aspirate with leucocytes or + culture
- Other criteria poorly validated and variable in literature

Pain 59-100%
Fever 100% *

Analyzed in only 40% of studies

CRP median 120-220
Leucocytes not reliable



US and conventional CT less reliable
FDG-PET CT highly sensitive!

Lantinga et al, Nephrol Dial Transplant 2015; Lantinga et al, Nephron 2016; Lantinga et al, AP&T 2014

Which bugs?

E. coli (18)
K. pneumonia (9)
E. faecium (6)
E. cloacae (4)
Enterococcus species (4)
P. aeruginosa (3)
H. parainfluenzae (2)
Staphylococcus species (2)
Citrobacter freundii (2)
S. marcescens (1)
A. baumannii (1)
C. perfringens (1)
E. aerogenes (1)
S. maltophilia (1)
A. baumannii (1)
Salmonella typhi (1)
Salmonella ajiobo (1)
Salmonella paratyphi A (1)
Klebsiella oxytoca (1)
Bacteroides species (1)
Gram-positive cocci (1)
Anaerobic Gram-negative rods (1)

77% of cyst cultures positive

<u>Top 3 micro-organisms</u>:

E.Coli (30,5%)

K. Pneumoniae (15%)

E. Faecium (10%)

Lantinga et al, Nephrol Dial Transplant 2015

Management of cyst infection

Extremely heterogeneous approach in literature

Initial and final therapy for hepatic cyst infection (n = 54)	All therapies	Antimicrobial						
		All	Mono	Dual	Triple	Missing	Percutaneous	Surgical
Initial therapy, n (%)	54 (100)	30 (56)	12 (40)	6 (20)	5 (17)	7 (23)	17 (31)	7 (13)
Initial therapy outcome, n (%)								
Success	27 (50)	9 (30)	5 (42)	2 (33)	2 (40)	0 (0)	11 (65)	7 (100)
Failure	27 (50)	21 (70)	7 (58)	4 (67)	3 (60)	7 (100)	6 (35)	NA

Optimal therapy?

Consider early percutaneous approach when response to AB is incomplete.

Lantinga et al, AP&T 2014

Cyst haemorrhage and rupture

- Rare complication
- Sometimes asymptomatic, most common symptom is pain
- Management: conservative if possible
- If severe/HD instable: most experience with surgery

Fong et al, J Gastrointest Surg 2012,

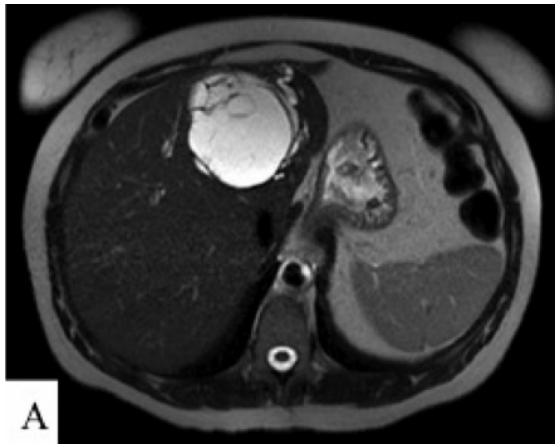
Complex liver cysts

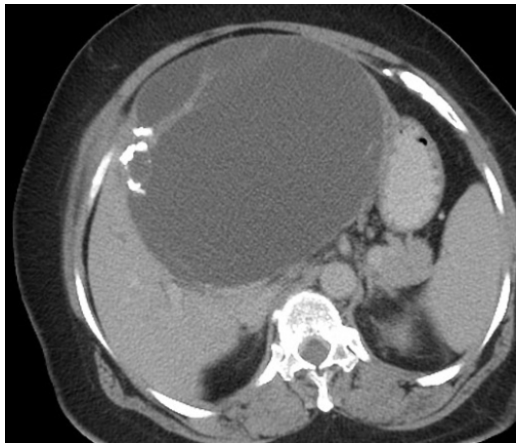
Complex liver cysts

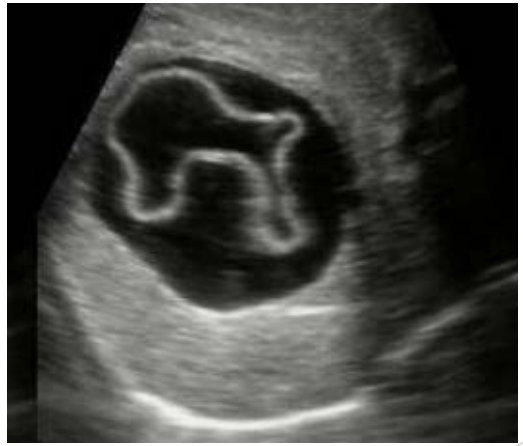
Complex cyst ≠ simple cyst

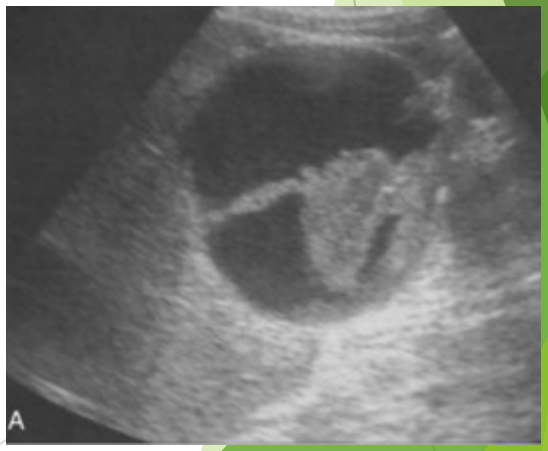
Table 2. Appearance of simple versus complex hepatic cysts with various imaging modalities

	US	CT	MRI	CEUS
Simple cyst	Anechoic, homogeneous, aseptate, thin and smooth margins[1,3,6]	Nonenhancing, hypodense, smooth margins[1,3]	Nonenhancing T1: low signal T2: high signal[3,12]	Nonenhancing[6]
Complex cyst	Irregular border, hyperechogenic septations, loculations, shadowing beyond calcifications[1,3]	Multilocular, mural and septal enhancement, mural thickening and/or nodules, calcifications, debris containing fluid[12,15]	T1: hypointense cyst contents T2: hyperintense with low signal border[1,23]	Mural and septal enhancement[6]









Mavilia et al, J Clin Transl Hepatol 2018; Arnaoutakis et al, Ann Surg 2015; Farges & Vilgrain (ClinicalGate.com, chapter 69)

Complex cystic lesions

Haemorrhagic simple cyst

Biliary cystadenoma

Biliary cystadenocarcinoma

Infectious cysts

Cystic metastasis (GIST, pancreas, ovary, melanoma)

Cystic HCC

Lesions mimicking cysts (hematoma, biloma)

How to differentiate?

History (general, travel, pain)

Imaging characteristics

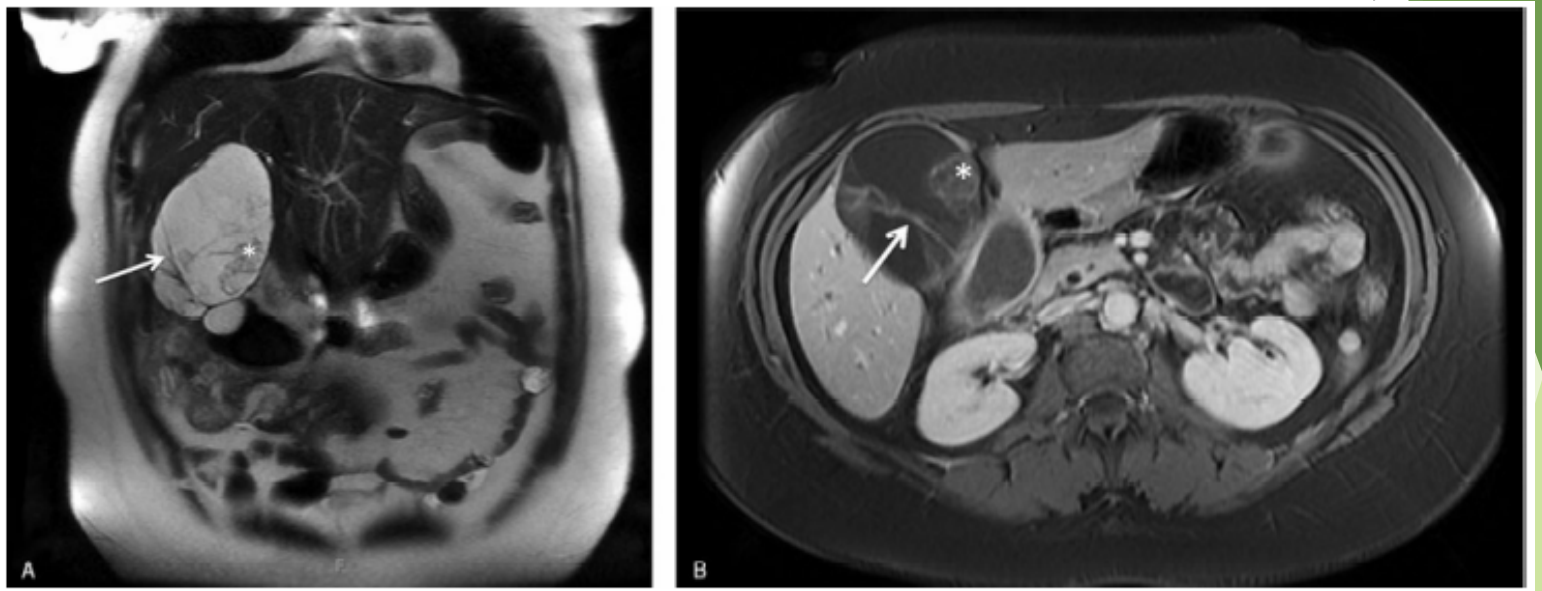
Previous malignancy?

Cirrhosis?

Trauma? Surgery?

Biliary Cystadenoma (BCA)

85-90%



- BCA is a complex liver cyst (see image)
- Risk of cystadenocarcinoma (BCAC) > how to distinguish?
- Mostly in middle-aged females (NB > biliary cystic lesions in males more often BCAC (33% vs 7.4%))

Bakoyiannis et al, World J Gastroenterol 2013; Arnaoutakis et al, Ann Surg 2015; Cannella et al, Curr Probl Diagn Radiol 2019

Differentiation between BCA and BCAC?

N = 248
10 centers
USA, Europe, Australia

SIZE?

Size	BCA (n=221, 89.1%)	BCAC (n=27, 10.9%)	p
median, cm (IQR)	10 (7-12)	10.5 (7-15)	0.056

LAB?

	Total (n = 248)	BCA (n = 221, 89.1%)	BCAC (n = 27,10.9%)	*P*
Preoperative laboratory data				
Total Bilirubin (mg/dL), median (IQR)	0.6 (0.4–0.8)	0.6 (0.4–0.7)	0.7 (0.5–1.0)	0.844
CA 19–9 (U/mL), median (IQR) (n = 210)	15 (7.1–94.0)	15 (6.0–63.1)	210 (37.1–280.0)	0.647
CEA (ng/mL), median (IQR) (n = 210)	2.7 (1.0–4.6)	2.4 (0.9–4.6)	4.3 (1.9–90.0)	<0.001

CA19.9 elevation in BCA vs BCAC (30% vs 70%)

Size, laboratory or tumor markers are unsufficient to differentiate between BCA and BCAC.

Bakoyiannis et al, World J Gastroenterol 2013; Arnaoutakis et al, Ann Surg 2015; Cannella et al, Curr Probl Diagn Radiol 2019
ACG Guideline Focal Liver Lesions, 2014;

Differentiation between BCA and BCAC?

N = 248
10 centers
USA, Europe, Australia

IMAGING?

	Total (n = 248)	BCA (n = 221, 89.1%)	BCAC (n = 27,10.9%)	*P*
Multilocular cyst	141 (56.9)	123 (55.7)	18 (66.7)	0.093
Septa	163 (65.7)	145 (65.6)	18 (66.7)	0.913
Mural nodularity	41 (16.5)	24 (10.9)	17 (63.0)	<0.001
Calcification	25 (10.1)	16 (7.2)	9 (33.3)	<0.001
Hypervascular	19 (7.7)	10 (4.5)	9 (33.3)	<0.001
Enhancement after contrast	42 (16.9)	31 (14.0)	11 (40.7)	<0.001
Biliary ductal dilatation	44 (17.7)	36 (16.3)	8 (29.6)	0.087

Nodularity, calcification, contrast enhancement and hypervascularity are more ***common in BCAC, but are found in BCA as well***

Abcence *of ALL these features suggests BCA*

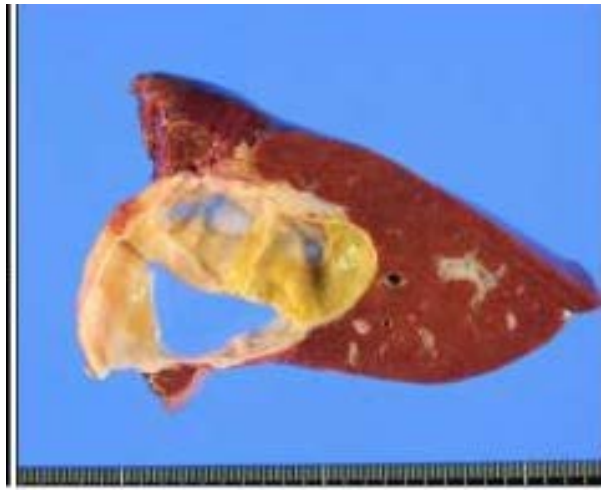
Bakoyiannis et al, World J Gastroenterol 2013; Arnaoutakis et al, Ann Surg 2015; Cannella et al, Curr Probl Diagn Radiol 2019
ACG Guideline Focal Liver Lesions, 2014;

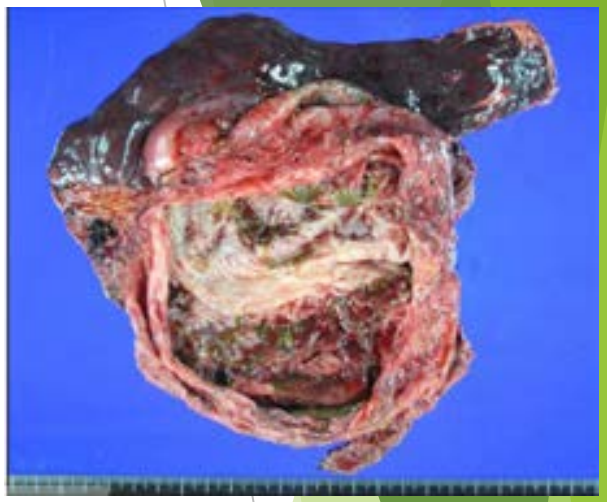
So what to do with a BCA?

Multidisciplinary approach

Often resection

(depending on patient and localisation)





Formal resection! High recurrence with deroofing or fenestration (≈ 50%)

Polycystic liver diseases

Polycystic liver diseases

Biliary hamartomas (Von Meyenburgh complex), 1: 40/167

Autosomal dominant polycystic kidney disease (ADPKD), 1 : 400/2700

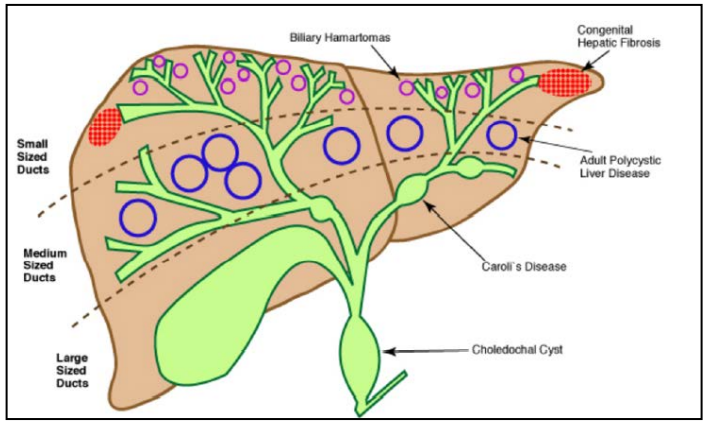
Autosomal recessive polycystic kidney disease (ARPKD), 1 :10.000/26.500

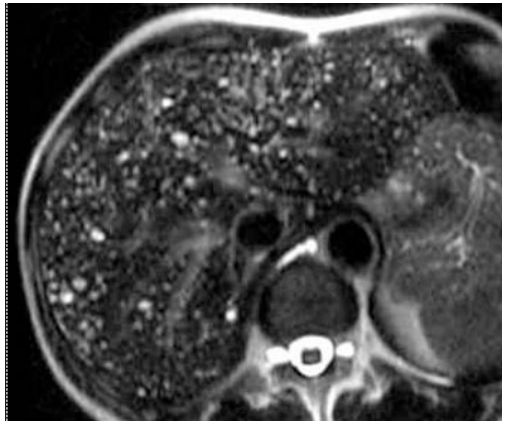
Autosomal dominant polycystic liver disease (ADPLD), 1 : 100.000/1000.000

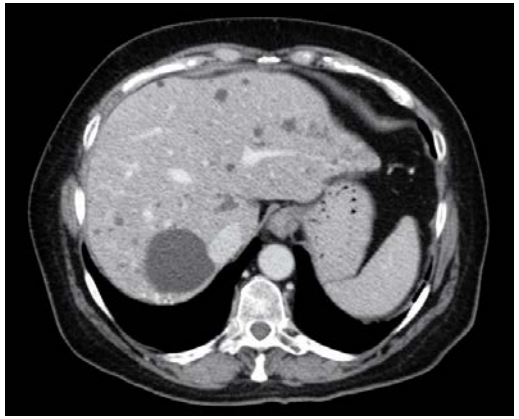
Caroli disease, 1:1000.000

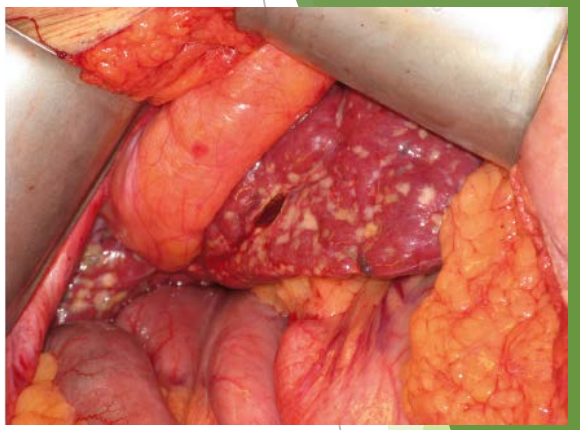
Bergmann et al, Nature Rev Primers, 2018; Cnossen et al, Orphanet J Rare Dis 2014; Borhani et al, AJR 2014, Canella et al, CPD Radiology 2019)

Biliary hamartomas (VMC)









Late stage DPM
Subcapsular/interlobular cysts

MRI/MRCP
“Starry sky”
NO bile duct connection

Sometimes subtle

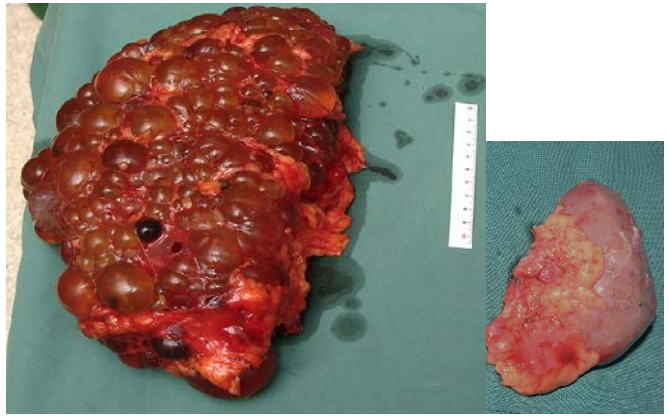
May resemble metastases
(Van Baardewijk et al, NTvG 2010)

Mostly uncomplicated course

No intervention or follow up necessary

Bergmann et al, Nature Rev Primers, 2018; Cnossen et al, Orphanet J Rare Dis 2014; Borhani et al, AJR 2014, Canella et al, CPD Radiology 2019)

ADPKD



Genes	disease	Disease liver phenotype
PRKCSH	ADPLD	Variable, usually multiple large cysts (>1 cm)
GANAB	ADPLD or ADPKD	Variable, usually multiple large cysts (>1 cm)
SEC63	ADPLD	Variable, usually multiple large cysts (>1 cm)
SEC61B	ADPLD	Innumerable small liver cysts
ALG8	ADPLD	Variable, usually multiple large cysts (>1 cm)
LRP5	ADPLD or ADPKD	Variable, usually multiple large cysts (>1 cm)
PKD1	ADPKD	Similar to ADPLD but less and smaller cysts than seen in ADPLD[a]
PKD2	ADPKD	Similar to ADPLD but less and smaller cysts than seen in ADPLD[a]
PKHD1	ARPKD or ADPLD[b]	Innumerable small liver cysts[b]

Primary renal disease

BUT: 83% has PLD

Δ PKD1 & PKD2

Protein: Polycystin

Role in cilia function

Role in Ca-influx

HT (50-70%)

i.c. aneurysms (< 8%)

MV/AoV defects (<25%)

ESRD (dialysis) in 50% of patients by 60 years

Bergmann et al, Nature Rev Primers, 2018; Cnossen et al, Orphanet J Rare Dis 2014

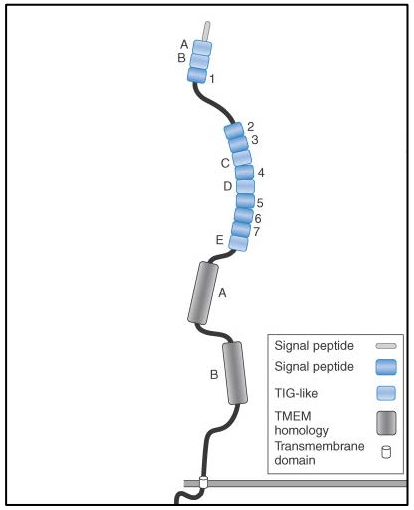
ARPKD

Severe phenotypes

Young age

High mortality when early presentation

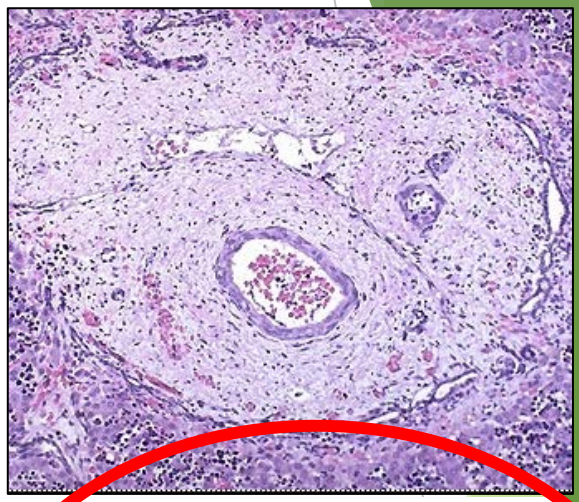
Early ESR



Δ in PKHD-1

Protein: fibrocystin

Role in: cilia function, gene expression?



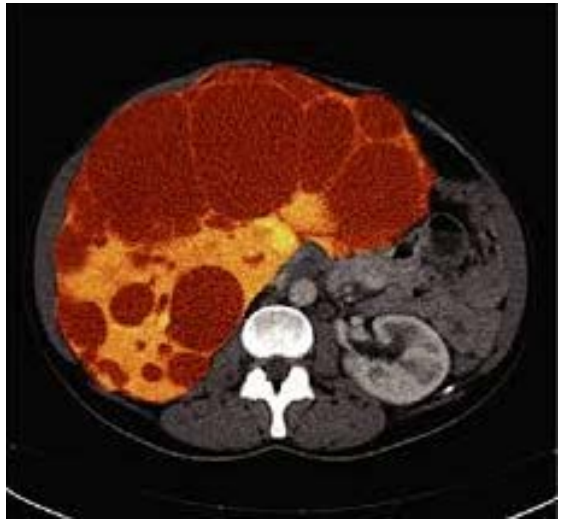
Congenital hepatic fibrosis

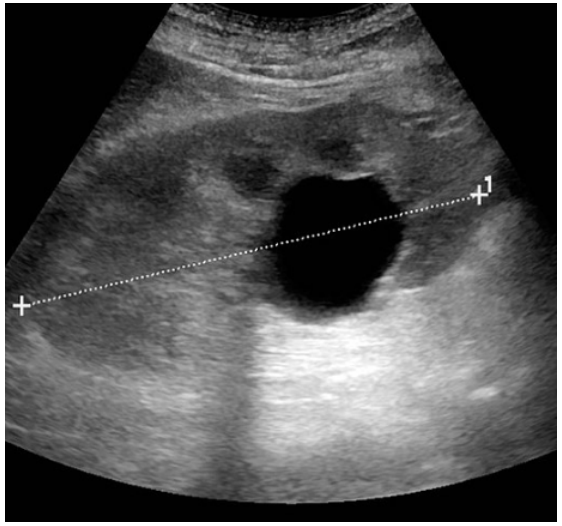
Portal hypertension

Biliary duct ectasia

Bergmann et al, Nature Rev Primers, 2018; Cnossen et al, Orphanet J Rare Dis 2014

ADPLD





Genes	Proteins	Localization	Function	Associated disease
PRKCSH	Glucosidase II subunit β or hepatocystin	ER	N-glycan metabolism	ADPLD
GANAB	Glucosidase II subunit α or PKD3	ER	N-glycan metabolism	ADPLD or ADPKD
SEC63	Translocation protein SEC63 homolog	ER	Protein translocation	ADPLD
SEC61B	Protein transport protein Sec61 subunit β	ER	Protein translocation	ADPLD
ALG8	α-1,3-glucosyltransferase	ER	Protein glycosylation	ADPLD
LRP5	Low density lipoprotein receptor-related protein 5	Plasma membrane	Receptor in canonical Wnt pathway	ADPLD or ADPKD

Hepatic disease

Segmental or diffuse

Women more affected than man.

Some renal cysts possible

NO renal disease!

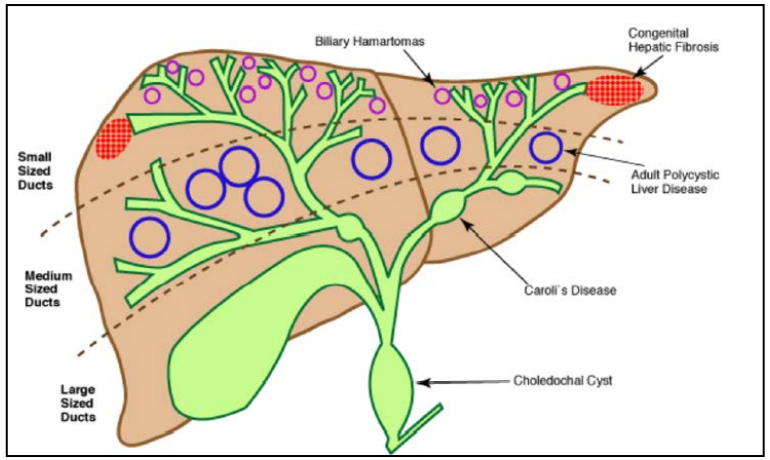
Multiple genes involved (PRKCSH, SEC63, LRP5 etc)

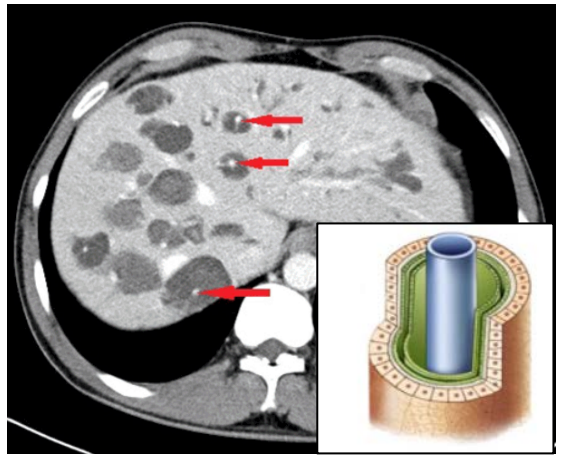
In 50% unknown (genetic) cause

Second hit hypothesis (somatic mutation important for disease phenotype)

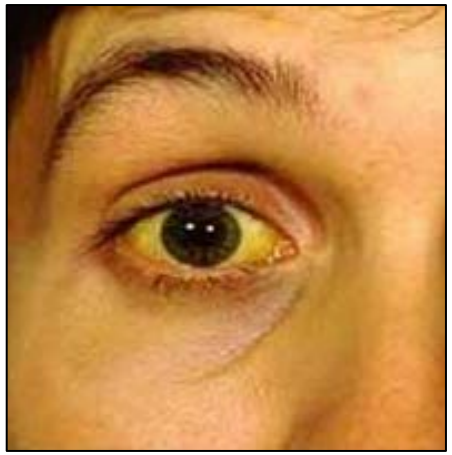
Bergmann et al, Nature Rev Primers, 2018; Cnossen et al, Orphanet J Rare Dis 2014; Borhani et al, AJR 2014, Canella et al, CPD Radiology 2019; Lee-Law et al, Curr Op Gastroenterol 2019

Caroli disease & syndrome

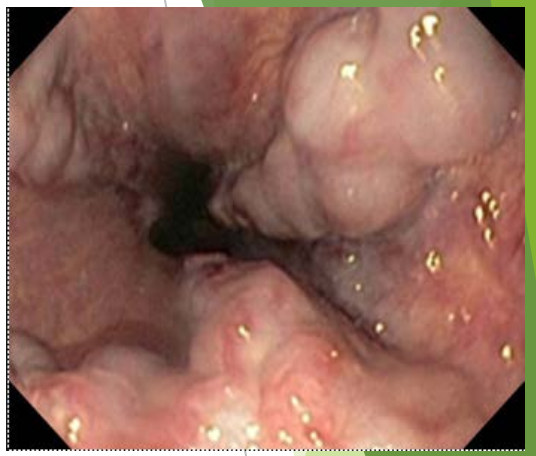




Cystic dilatation or intrahepatic biliary tract.
Central dot sign.



Bile stasis, stones
Cholangitis
Cholangiocarcinoma



Portal hypertension

Caroli disease = cystic dilatation of intrahepatic biliary tract, 1:1000.000

Caroli syndrome = cystic dilation of intrahepatic biliary tract + congenital hepatic fibrosis (often in patients with ARPKD).

Canelli's et al, Curr Probl Diagn Radiol. 2019; Bakoyiannis et al, World J Gastroenterology 2013

Take home messages

- Large symptomatic cyst: aspiration sclerotherapy or fenestration
- Diagnosis of cyst infection: FDG-PET might help, try to obtain culture, AB treatment often not enough
- Complex cysts: use multidisciplinary approach!
- Reliable differentiation between BCA and BCAC is difficult, consider resection in fit patients
- Polycystic liver without renal cysts: think ADPLD, management dependent on phenotype

Your help with a case…

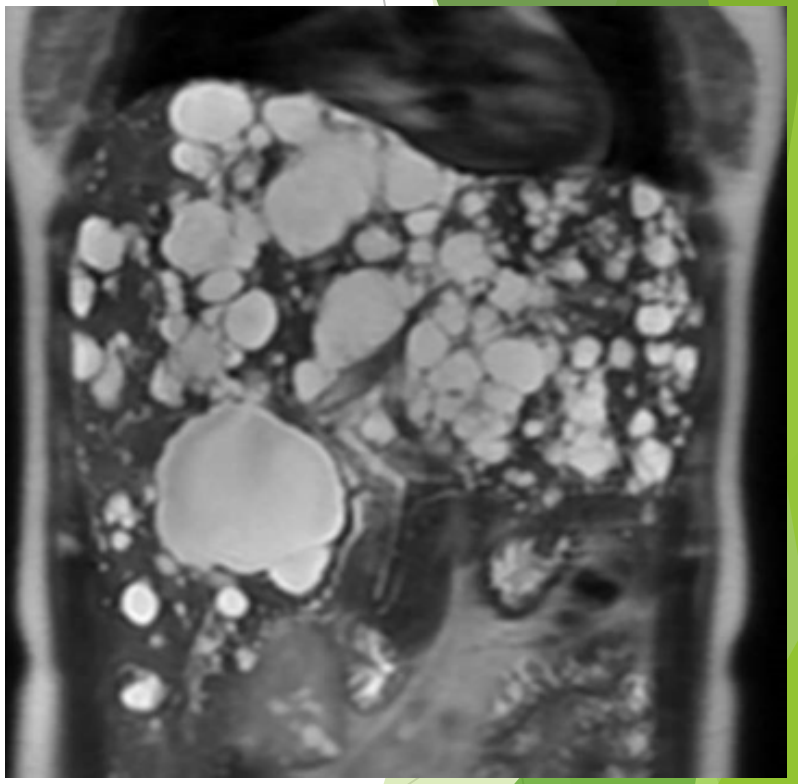
Vrouw, 30

VG: appendectomie, hooikoorts
Med: cetirizine, orale anticonceptie
FA: onbekend (pleegkind)

A/ Buikpijn/vol gevoel, verminderde eetlust, geen koorts/pijnaanval

AO/ Beeld van PLD op beeldvorming, CRP 8, niet suggestief voor bloeding of infectie

B/ Uitleg over ziekte



Your help with a case…

Vrouw, 30

VG: appendectomie, hooikoorts
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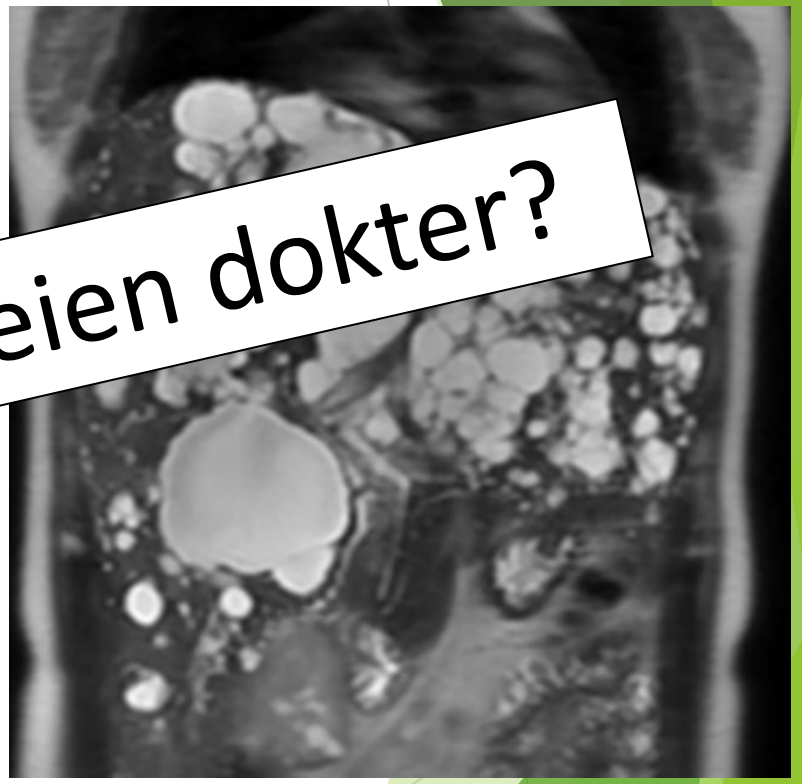
FA: onbekend (pleegkind)

A/ Buikpij[illegible]

[illegible]beeld van PLD op beeldvorming, CRP 8, niet suggestief voor bloeding of infectie

B/ Uitleg over ziekte

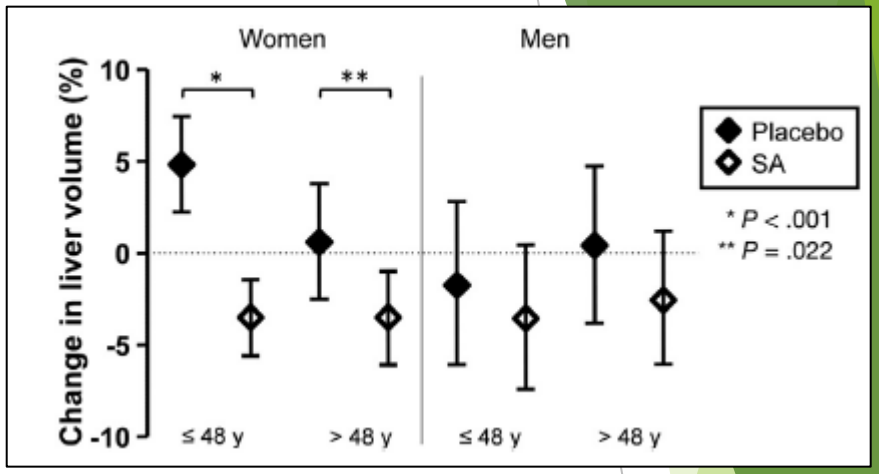
Gaan die cysten nog verder groeien dokter?



Natural course

Highly variable, even with same germline mutation.

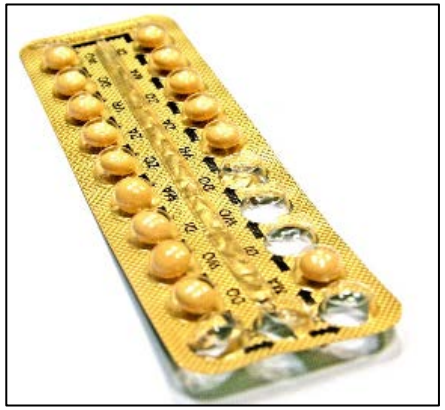
In prone subpopulation: 1-5 % volume ↑ per year.



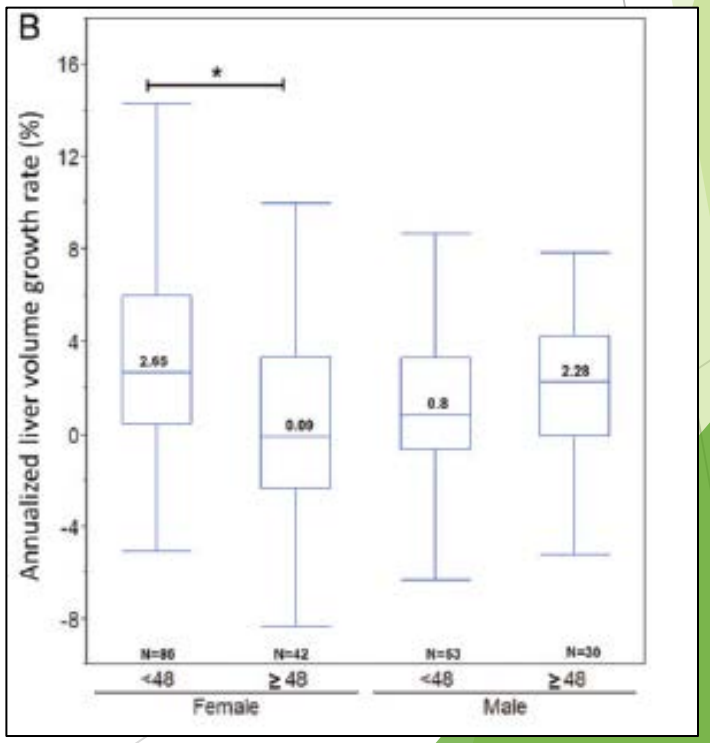
Risk factors

Young women

Old men



Oral contraceptives



Patients with ADPLD and ADPKD combined!

Gevers et al, Gastroenterology 2013; Chebib et al, NDT 2016

Your help with a case…

Vrouw, 30

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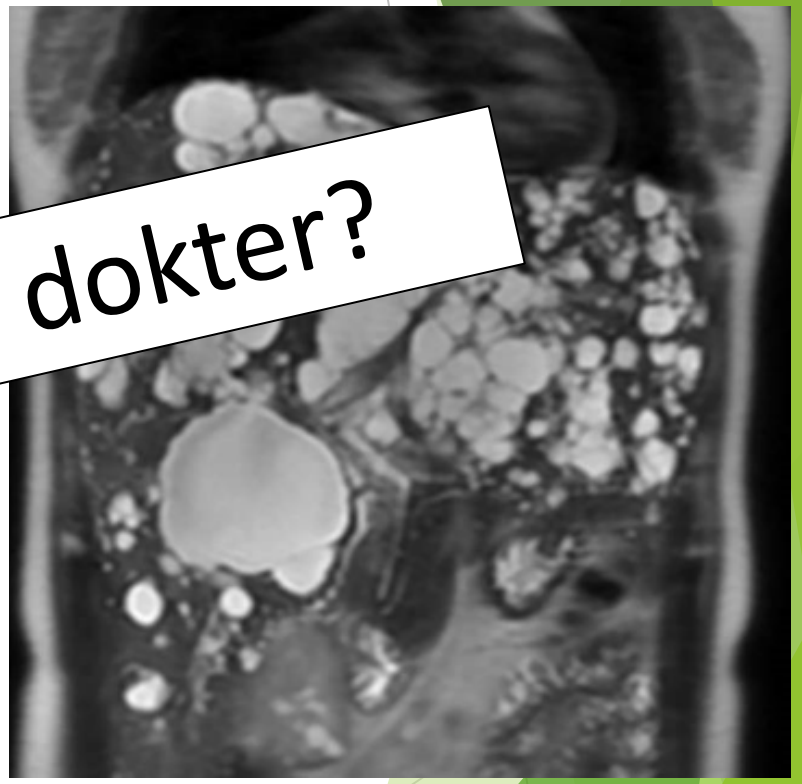
A/ Buik
jnaanval

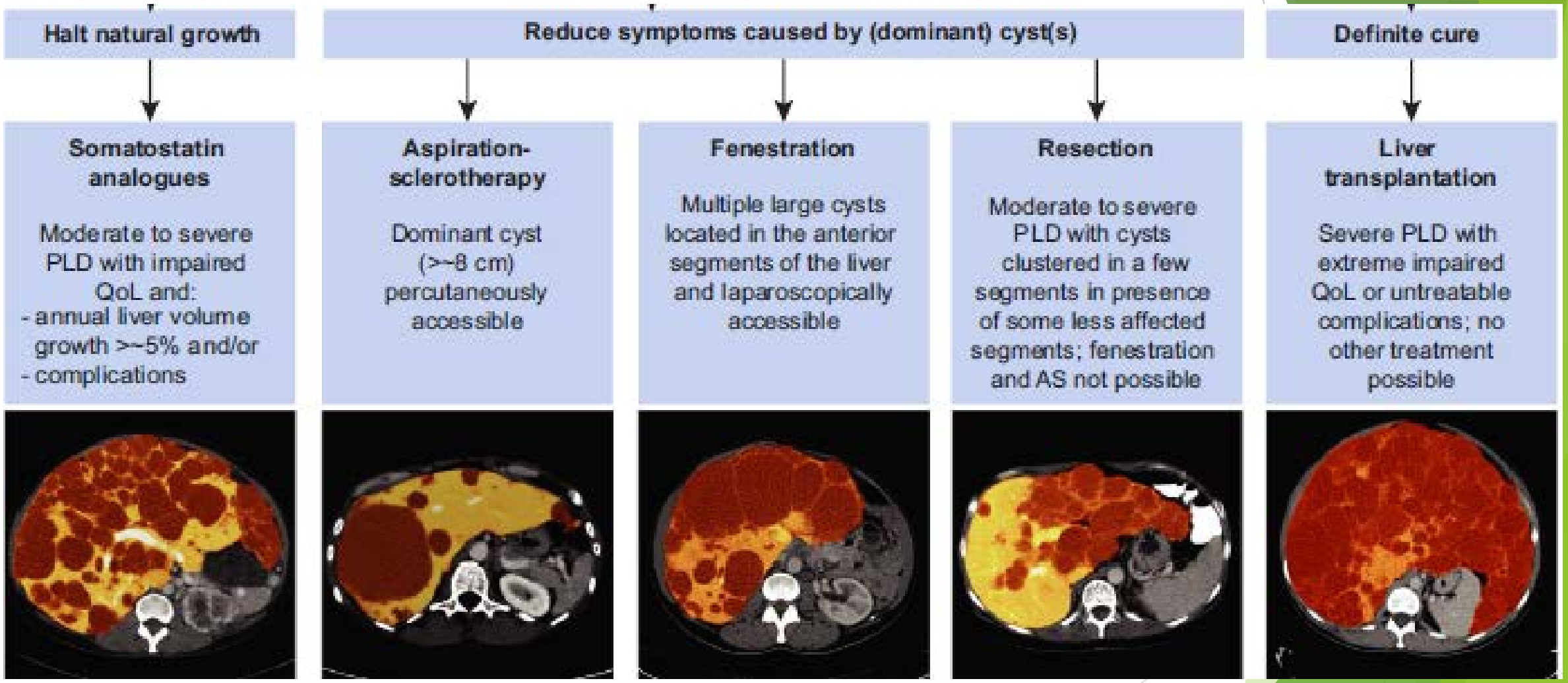
A/ Beeld van PLD op beeldvorming, CRP 8, niet suggestief voor bloeding of infectie

B/ Uitleg over ziekte

Wat kunnen we eraan doen dokter?

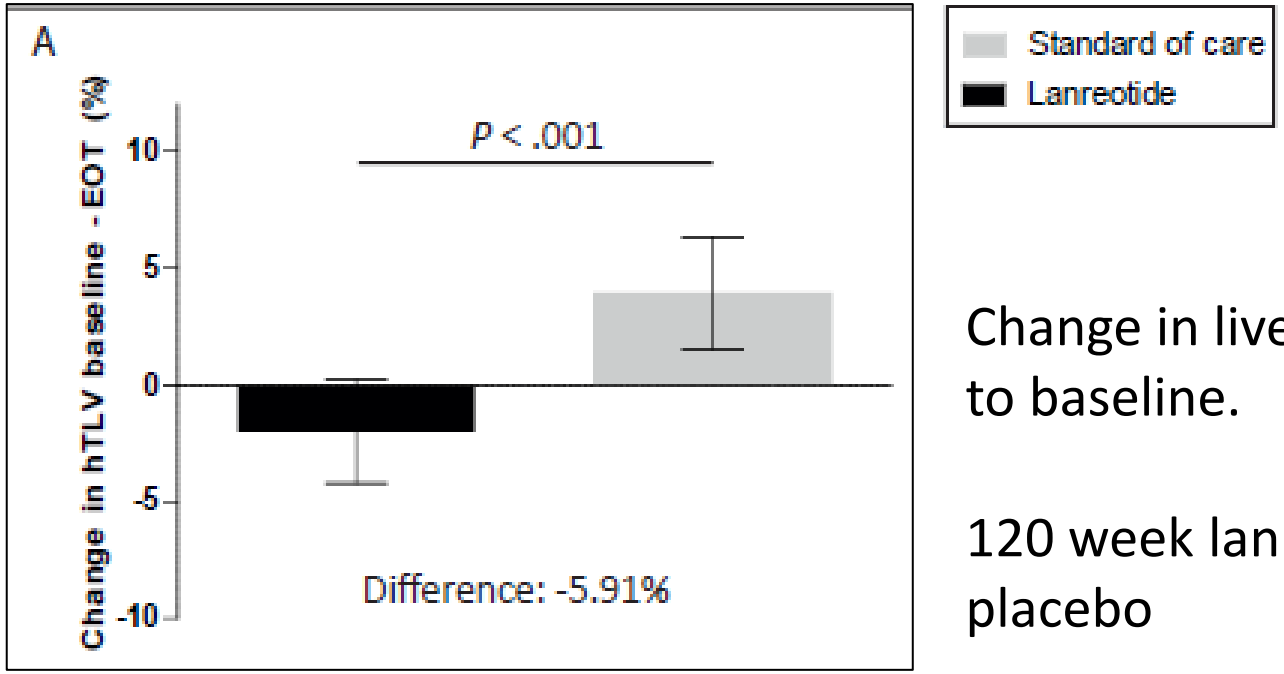


Tailor made management



Van Aerts et al, J Hep 2018; Van Aerts et al, Gastroenterology 2019

Effect of long acting SA



Change in liver volume compared to baseline.

120 week lanreotide treatment vs placebo

Van Aerts et al, J Hep 2018; Van Aerts et al, Gastroenterology 2019

Your help with a case…

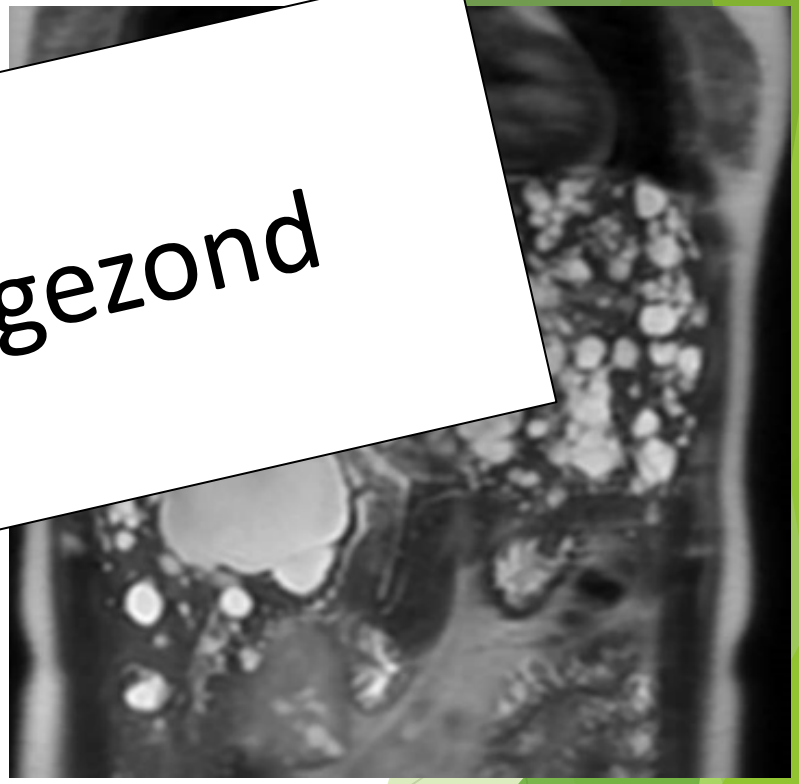
Vrouw, 30

VG: appendectomie, h

Med: cetiri

OK, cysten.
Is mijn lever verder wel gezond dokter?

ming,
ter voor bloeding of



B/ Uitleg over ziekte

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A/ Buik
jnaanval

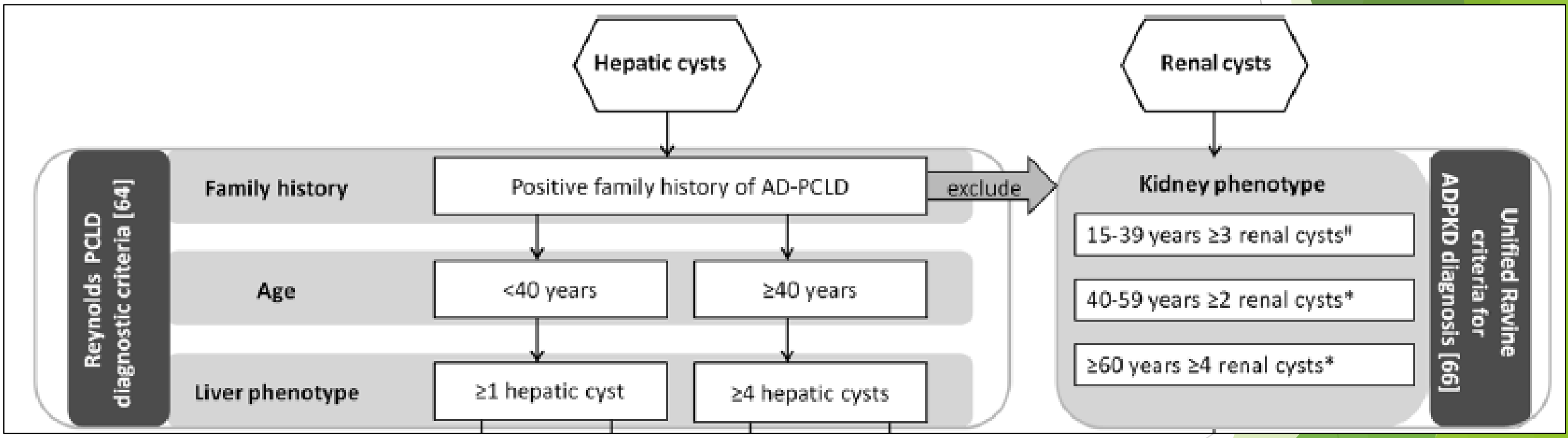
A/ Beeld van PLD op beeldvorming, CRP 8, niet suggestief voor bloeding of infectie

B/ Uitleg over ziekte

Moet ik mijn kind van 4 genetisch laten testen?

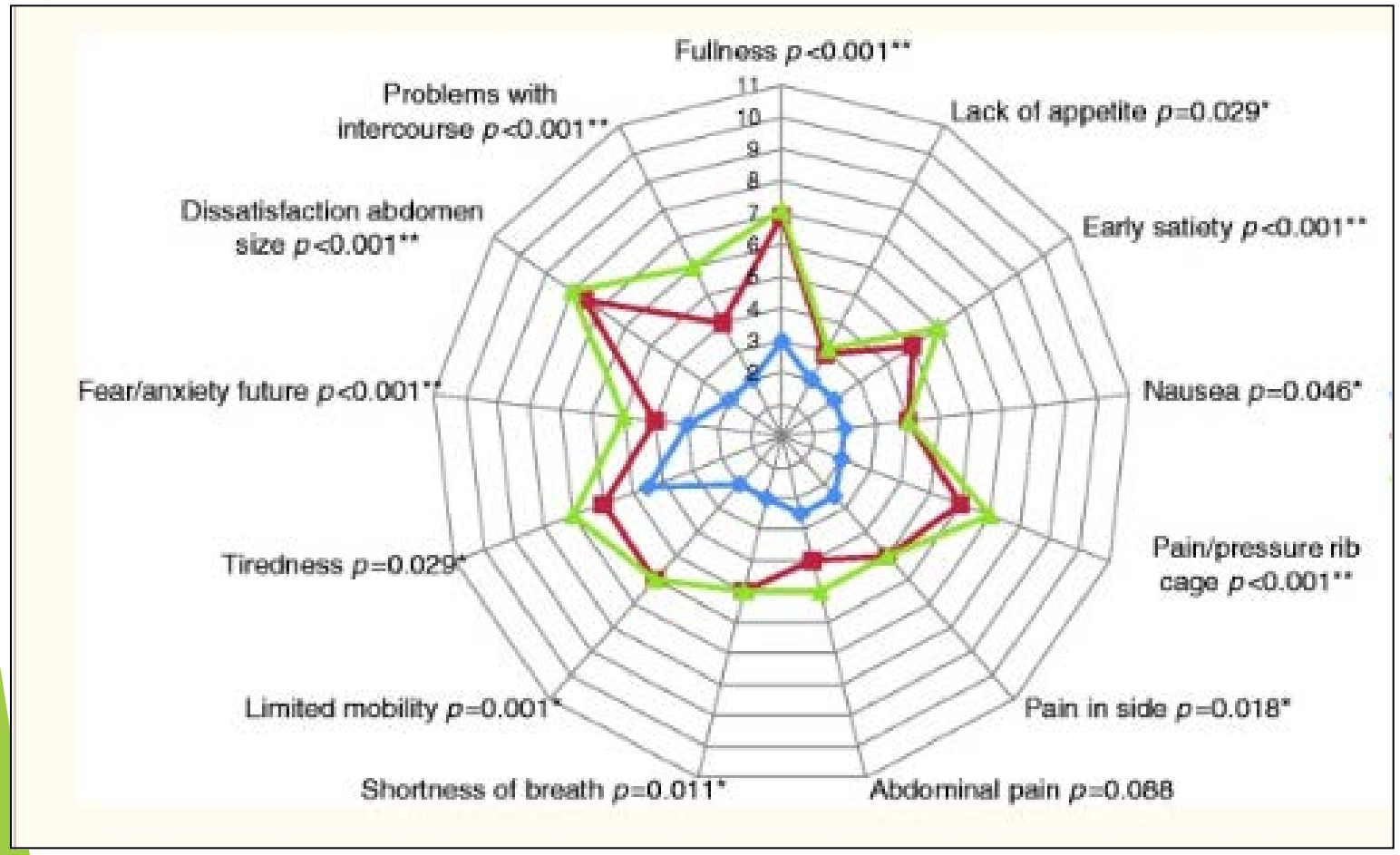
When to think of PLD?

Patients with more than 10-20 hepatic cysts….OR



Cnossen et al, Orphanet J Rare Dis 2014

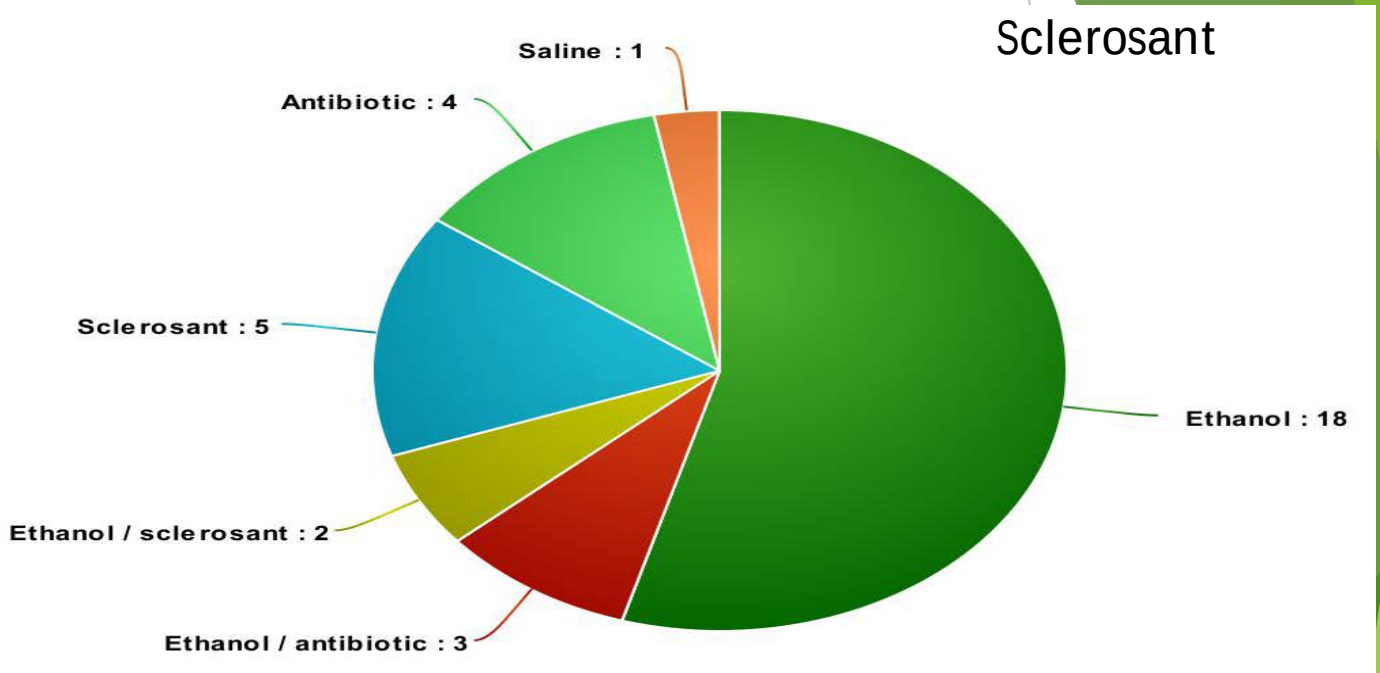
Quality of life in polycystic liver disease



Neijenhuis et al, United European Gastroenterol J 2018

Aspiration Sclerotherapy: methods

- **Systematic review**
  - 33 studies
  - 1989-2014
  - Total 1191 procedures

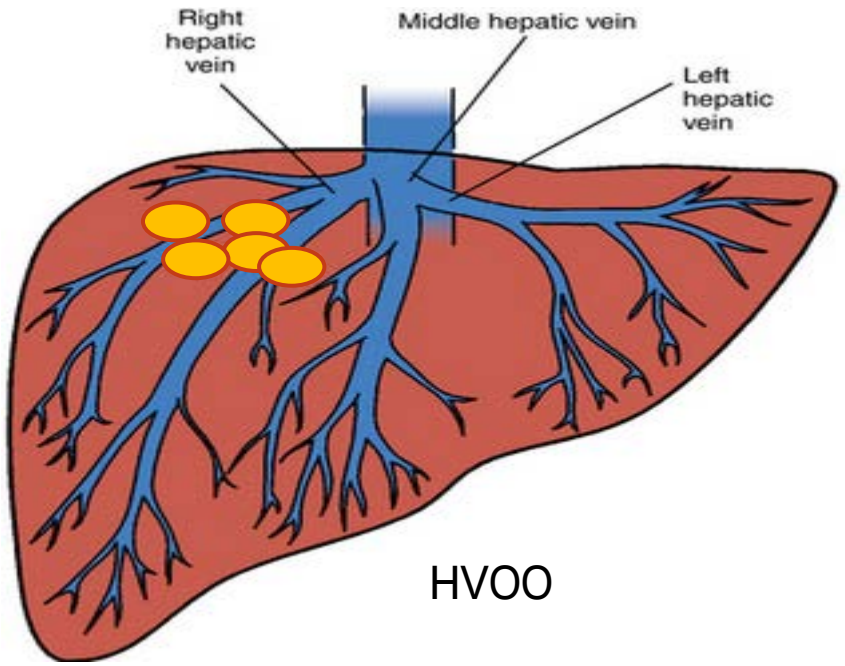


Antibiotic
Minocycline/Tetracycline
Sclerosant
Polidocanol / Acetic Acid / Ethanolamine

American Journal of Roentgenology. 2017;208: 201-207. 1

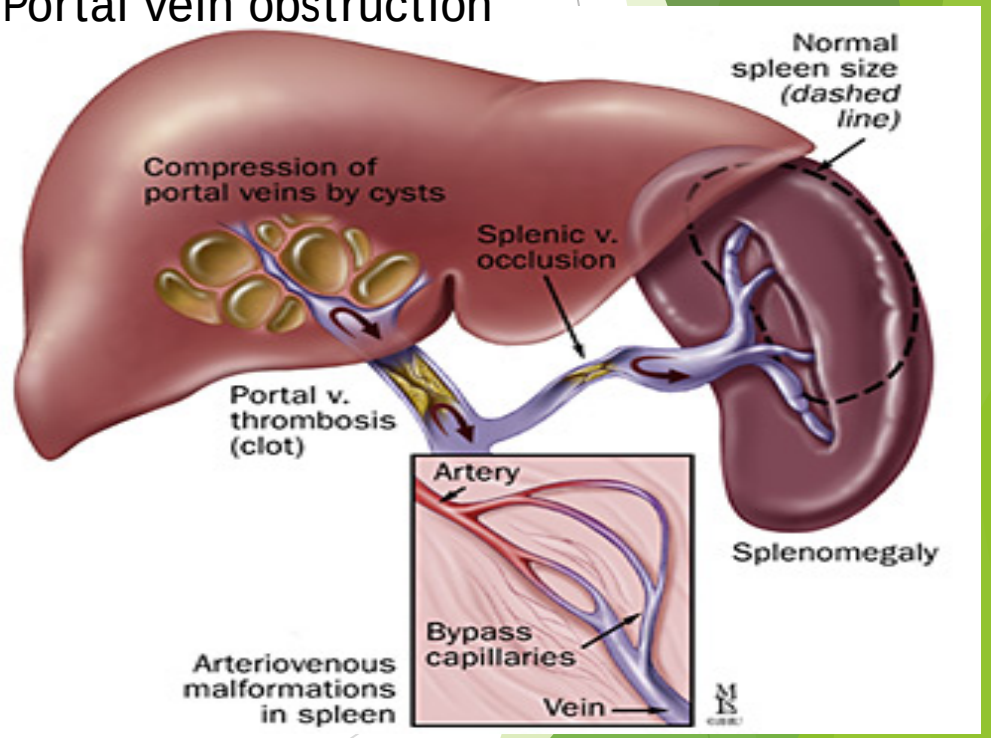
Portal Hypertension in PLD

- Obstruction of veins due to strategically located cysts
- Portal Vein
- Hepatic Vein (HVOO)



HVOO

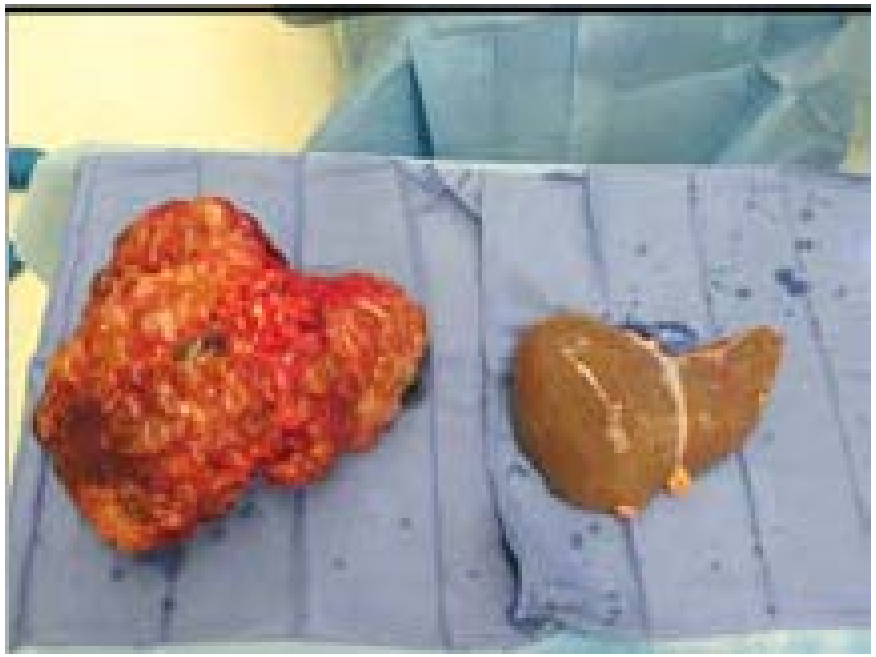
Portal vein obstruction



Hepatology. 2017 Oct 10. doi: 10.1002/hep.29582.

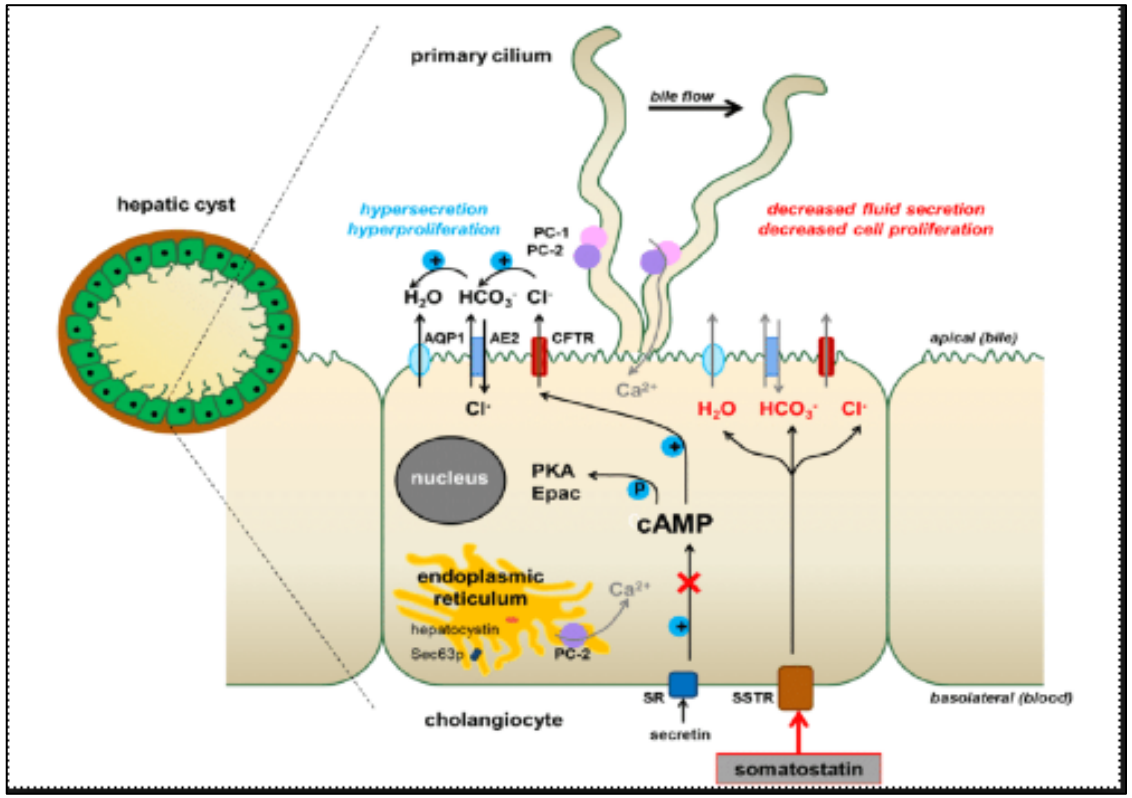
Liver transplantation

- Xxx
- *x*



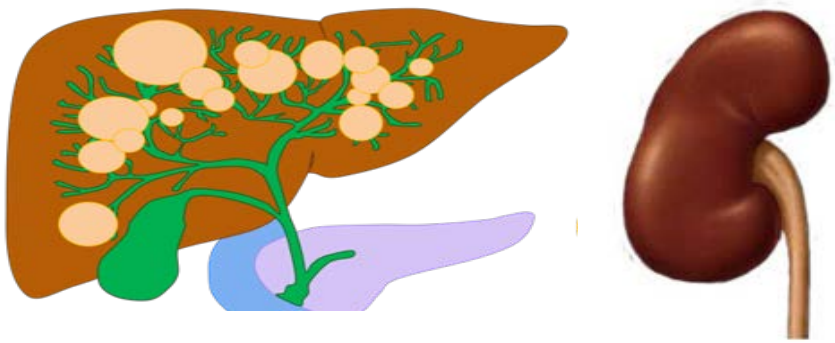
Courtesy Jacques Pirenne, UZ Leuven

cAMP as driver

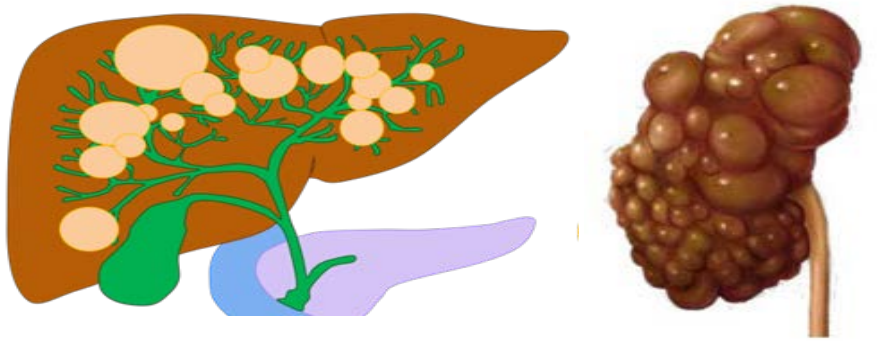


Cysts are lined with cholangiocytes
Cyst growth due to fluid secretion & proliferation
cAMP drives chloride & bicarbonate secretion + cholangiocyte proliferation
Somatostatin analogues (lanreotide/octreotide): cAMP inhibitors

Polycystic liver



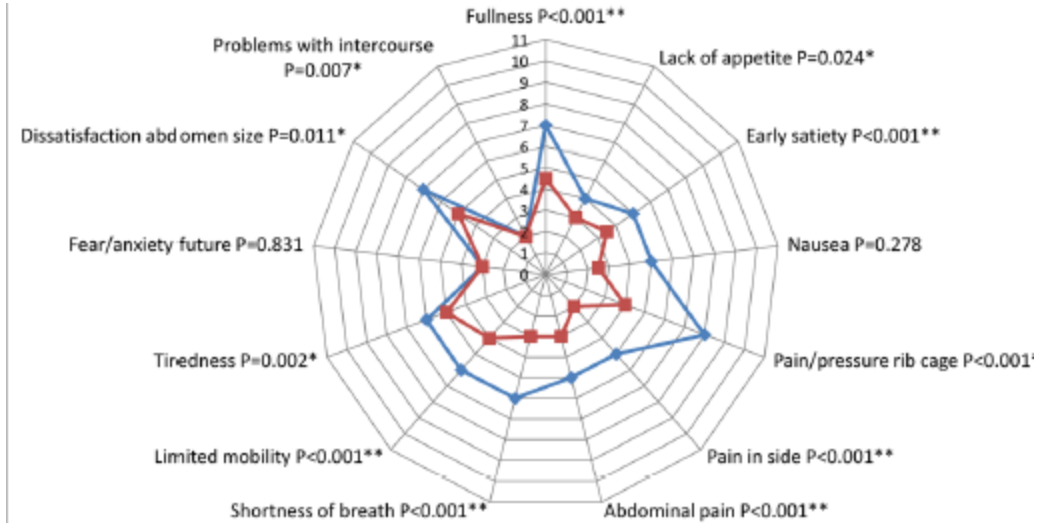
ADPLD
Autosomal dominant polycystic **liver** disease



ADPKD
Autosomal dominant polycystic **kidney** disease

Effect of aspiration/sclerotherapy

- Xxx
- *x*



Neijenhuis et al,