13th Paris Hepatology Conference

Cholestatic Liver Diseases and Cholangiocarcinoma

Paris

January 14, 2020

U. Beuers
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Tytgat Institute for Liver and Intestinal Research
Amsterdam University Medical Centers
Location AMC
Amsterdam, The Netherlands

Amsterdam UMC
University Medical Centers

Disclosures

2010-2019

Grant support

German, Norwegian, American and South-African PSC patient foundations
Netherlands Foundation for Gastroenterology & Hepatology (MLDS)
EU Program 'LIVERHOPE'

Lecture fees

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

Consulting agreements

Intercept, NGM, Novartis

Support for investigator-initiated studies

Falk, Intercept

Case report

♀ 80 yrs

2019 (7): Jaundice, itch (9/10), gray feces, dark urine, fatigue, disgust at eating, weight loss 12 kg (19%)

2019 (6): Fall from bicycle (nose fracture, no surgery)

No relevant diseases in the past

Family: 2/7 brothers with jaundice in the past, 4 healthy sisters

Work (past): funerals, gastronomy, chicken farm

Traveling: no tropical countries

Toxins: no alcohol, drugs, smoking

Medication: 2x tetanus vaccination

Physical Examination

♀ 80 yrs

- Exhausted, icteric elderly lady with scratch lesions on arms and legs
- RR 109/55 mm Hg, P 57/min, L 160 cm, W 51,5 kg, BMI 20 kg/m²
- No other relevant diagnostic findings

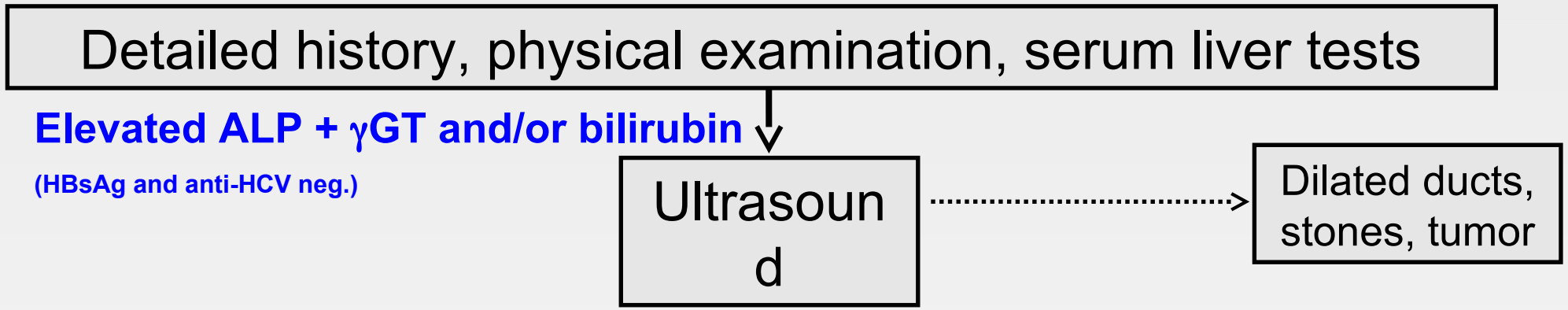
Lab

♀ 80 yrs

		2019 (8)
Bilirubin	(≤ 17 μmol/l)	253 (223 conj.)
ALT	(≤ 45 U/l)	113
AST	(≤ 40 U/l)	56
γGT	(≤ 40 U/l)	383
ALP	(≤ 120 U/l)	288
Ferritin		493
Transferrin saturation		41%

Negative/normal findings: HAV/HBV/HCV/HEV, leptospirosis
IgG/IgA/IgM, AMA, ANA, ASMA, LKM-1
α_1-antitrypsin
Hemoglobin, leucocytes, platelets, PT

Diagnostic approach to cholestasis



EASL CP Guidelines Cholestasis, J Hepatol 2009;51:237
EASL CP Guidelines PBC. J Hepatol 2017; 67:145-172

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Abdominal Imaging I

♀ 80 yrs

Ultrasound:

-Normal aspect of the liver, no focal lesions

-No stones in the gallbladder

-No bile duct obstruction (by stones or mass)

Fibroscan: 7.1 kPa (IQR 3.3, success rate 100%)

CAP: 154 dB/m (IQR 23)

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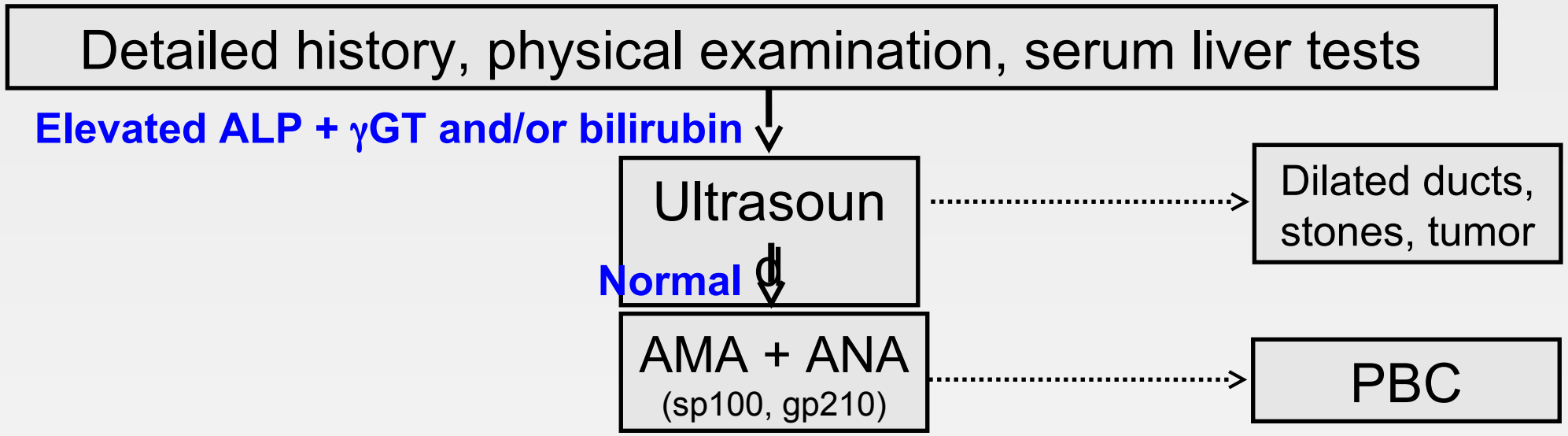

EASL CP Guidelines Cholestasis, J Hepatol 2009;51:237
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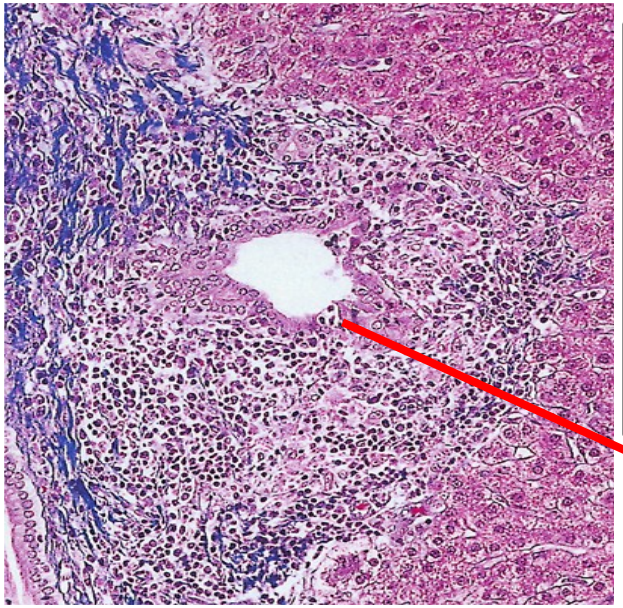
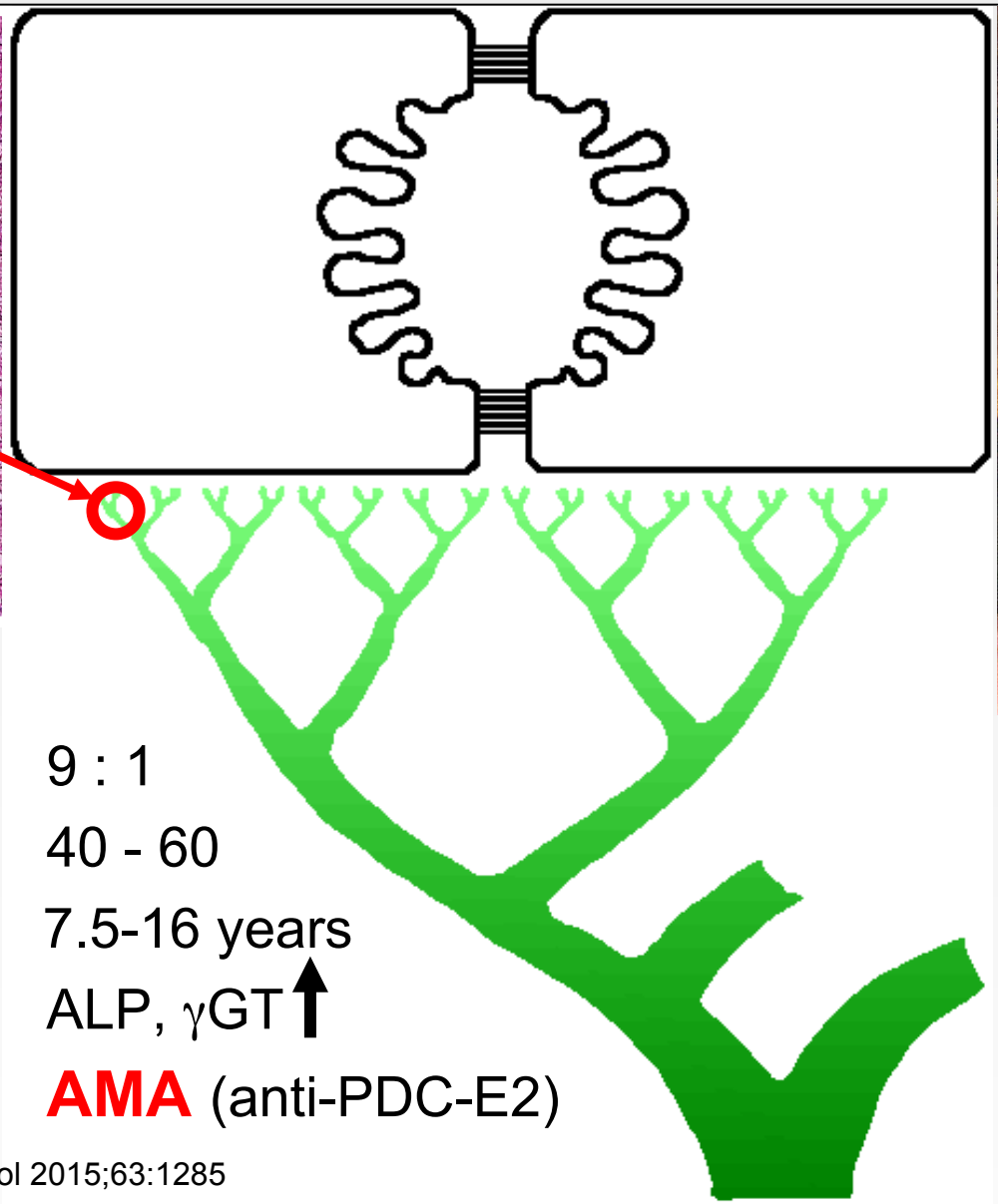
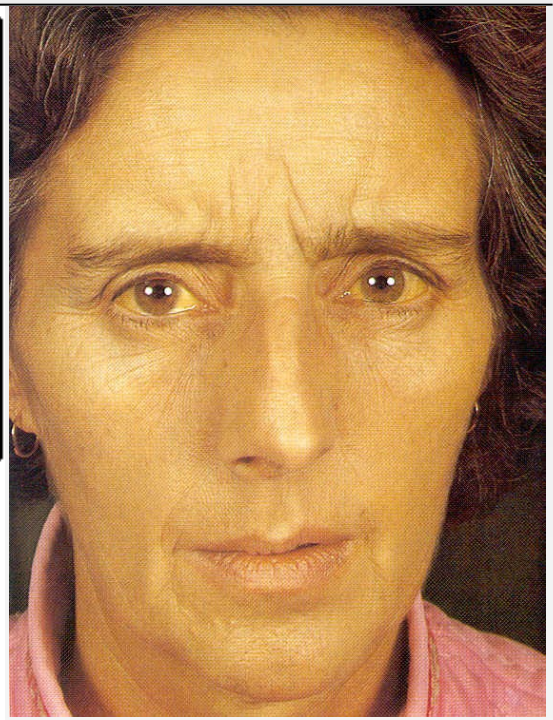
Primary biliary cholangitis* (PBC)

Characteristics



Florid, non-suppurative, destructive cholangitis





Sherlock and Summerfield, 1991

Women : Men	9 : 1
Age at diagnosis	40 - 60
Survival without treatment	7.5-16 years
Cholestasis	ALP, γGT ↑
Autoantibodies	**AMA** (anti-PDC-E2)

Symptoms

- Fatigue
- Pruritus
- Sicca syndrome
- …

* Beuers , Gershwin, …Poupon. J Hepatol 2015;63:1285

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Primary biliary cholangitis:

Potential pathogenetic mechanisms

Immune-mediated bile duct injury

↓

Aggravation of bile duct injury by hydrophobic bile acids

↓

Cholestasis with retention of hydrophobic bile acids in liver

↓

Fibrosis, cirrhosis

↓

Liver failure

Genetic Predisposition

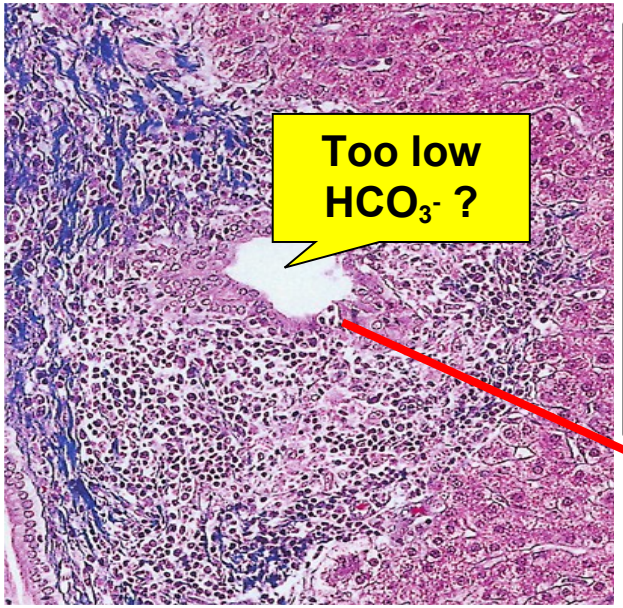
Environmental factors
(molecular mimicry)

Cellular/humoral immune response

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

Primary biliary cholangitis (PBC)

Characteristics



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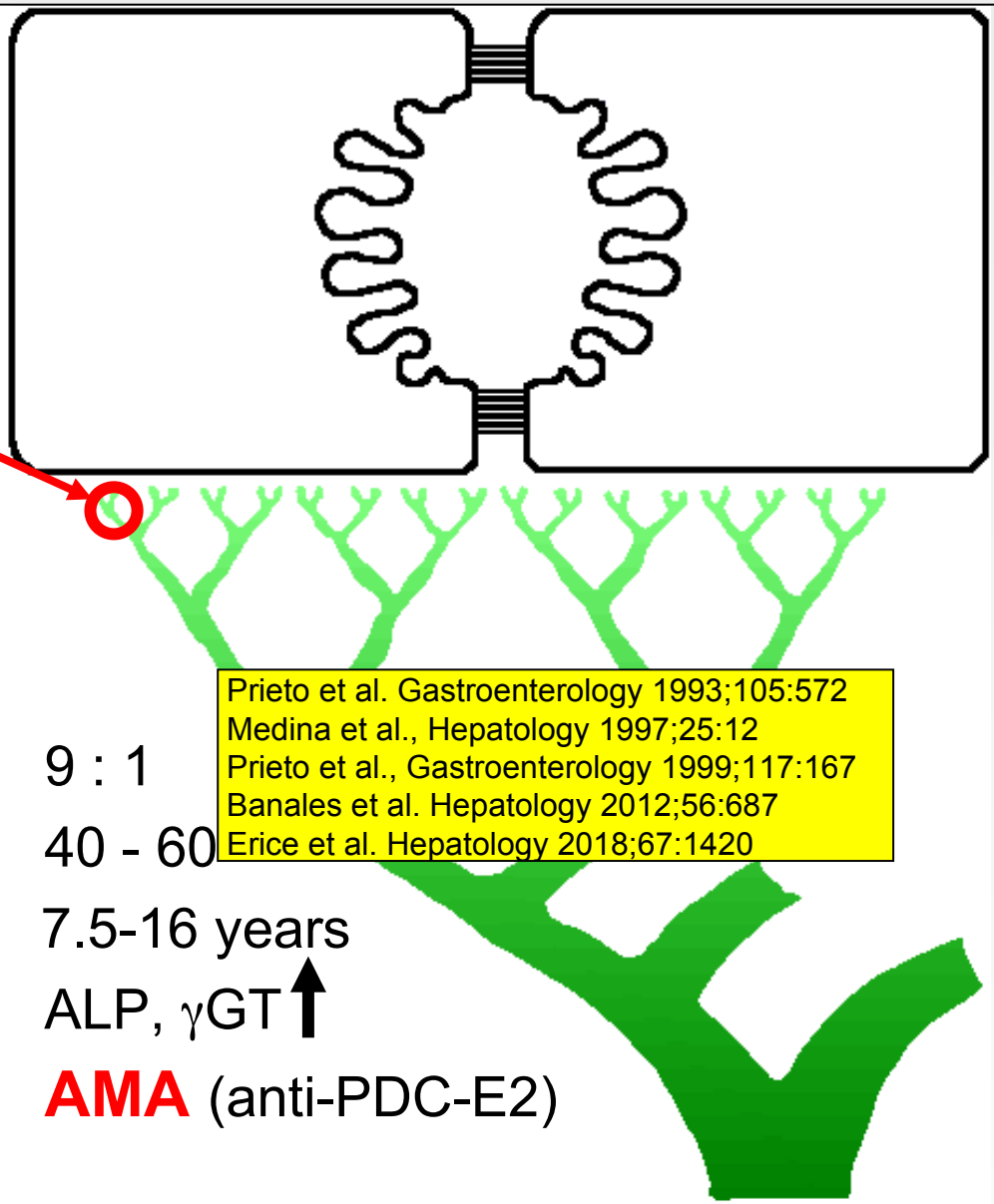

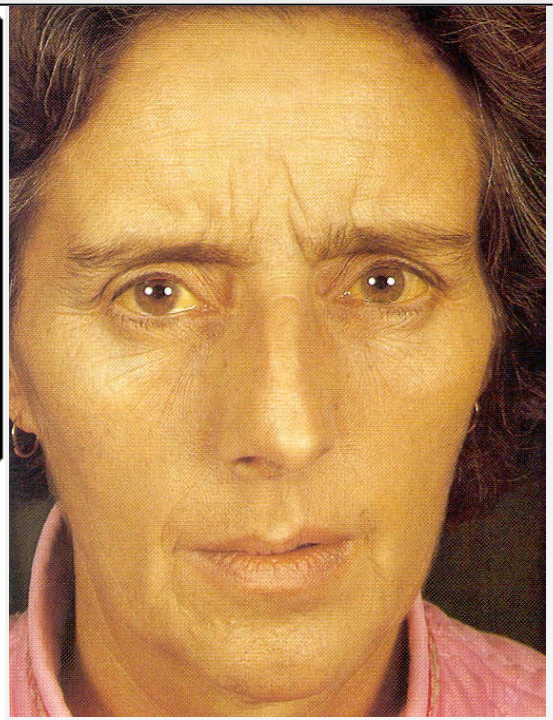

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Prieto et al. Gastroenterology 1993;105:572
Medina et al., Hepatology 1997;25:12
Prieto et al., Gastroenterology 1999;117:167
Banales et al. Hepatology 2012;56:687
Erice et al. Hepatology 2018;67:1420

Symptoms

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- Pruritus
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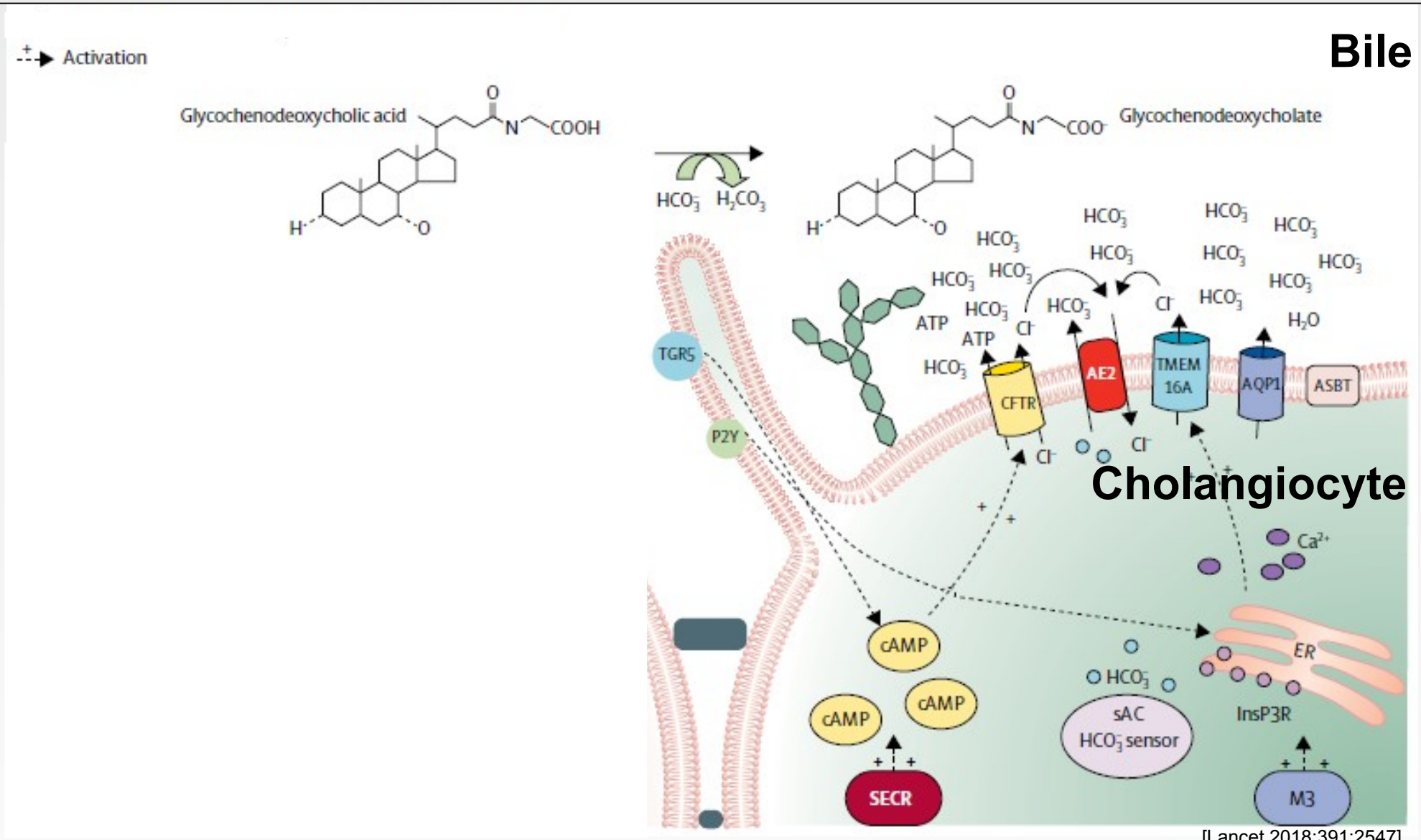
The 'Biliary HCO_3^- Umbrella' Hypothesis



[Lancet 2018;391:2547]

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

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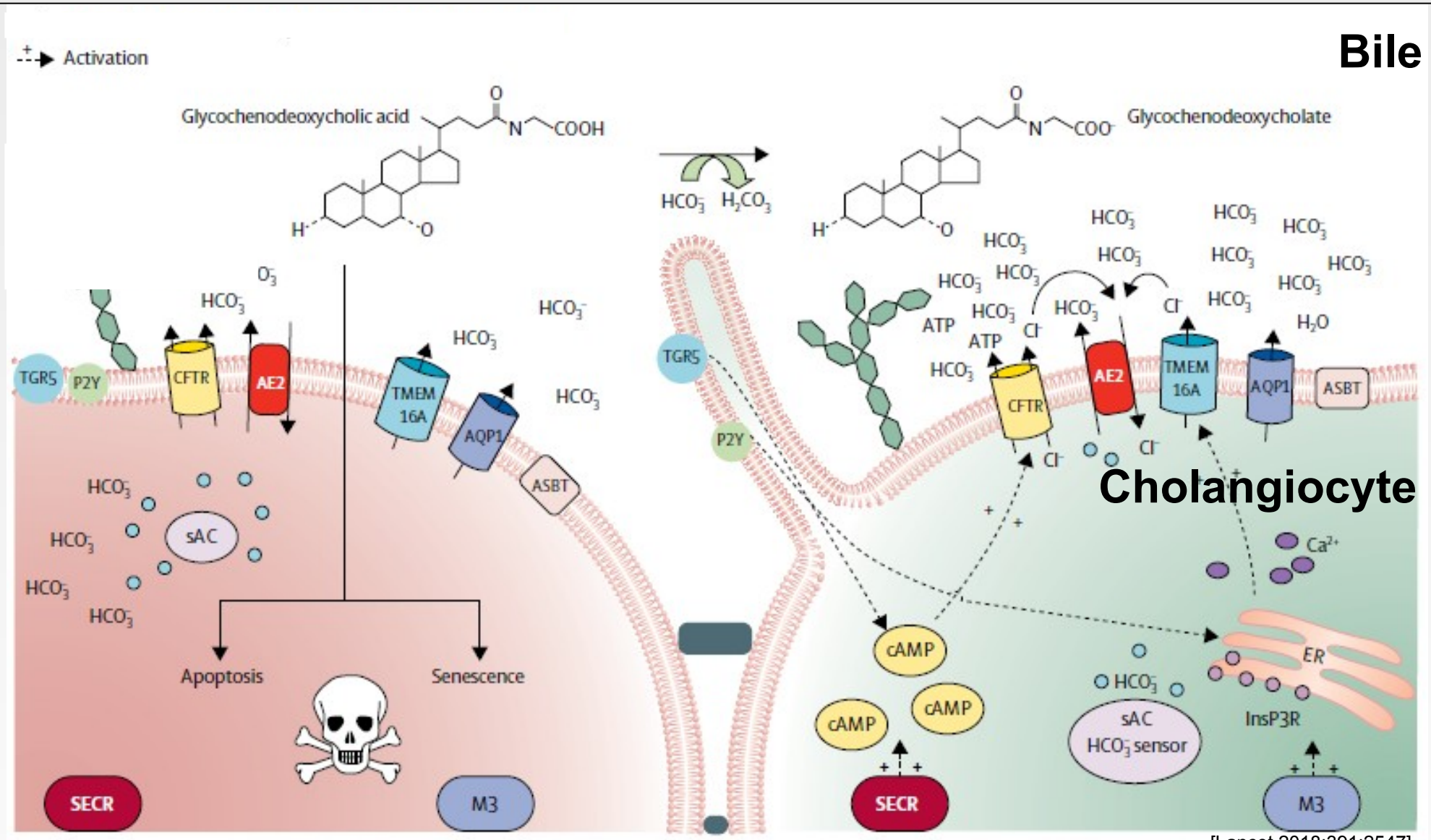

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Beuers et al., Hepatology 2010;52:1489
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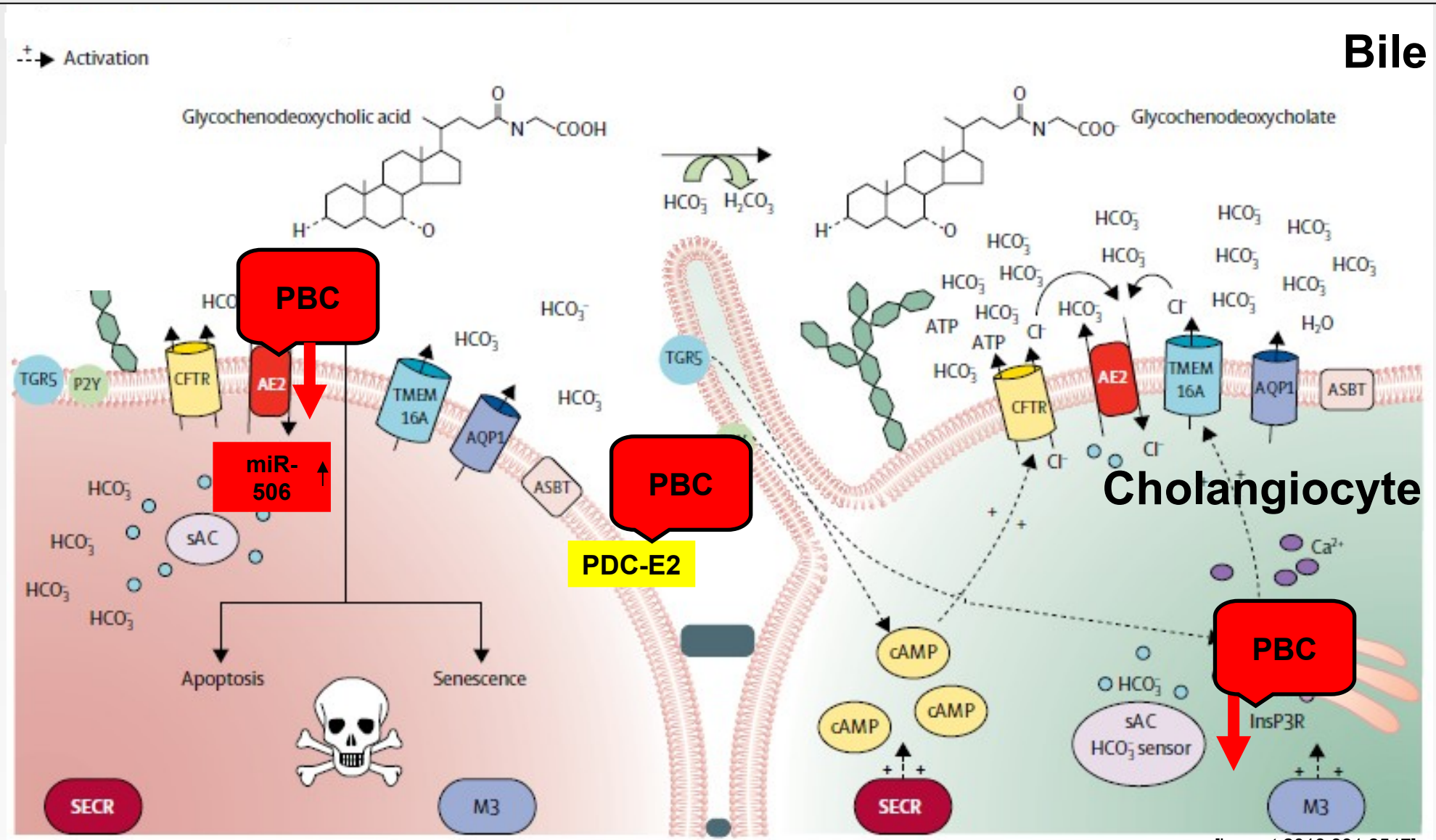
Defects of the 'Biliary HCO_3^- Umbrella' in PBC ?



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Banales et al. Hepatology 2012;56:687
Ananthananarayanan et al. JBC 2015;290:184
Erice et al. Hepatology 2018;67:1420

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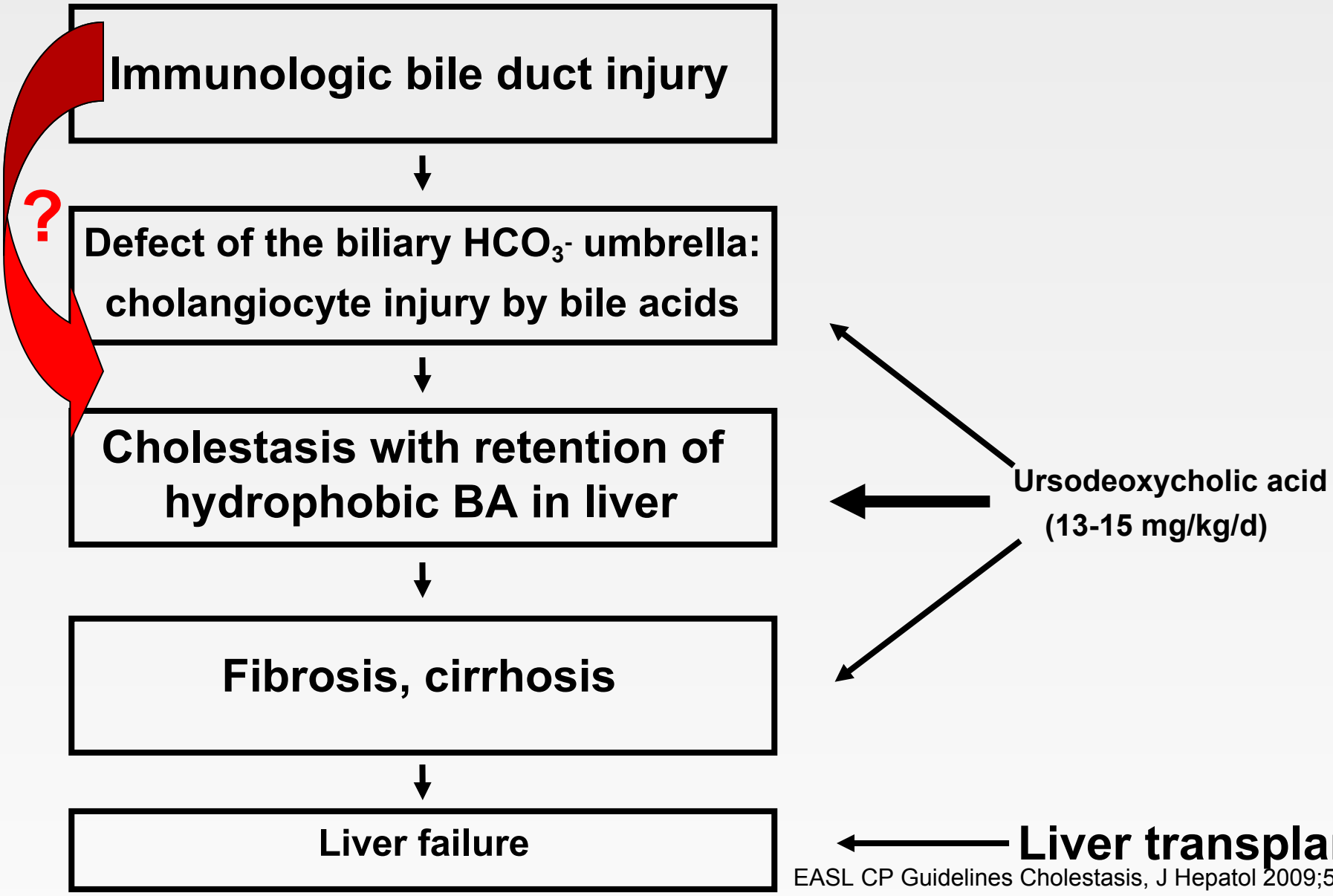
Primary biliary cholangitis: Therapy

Potential pathogenetic mechanisms



EASL CP Guidelines Cholestasis, J Hepatol 2009;51
EASL CP Guidelines PBC. J Hepatol 2017; 67:145

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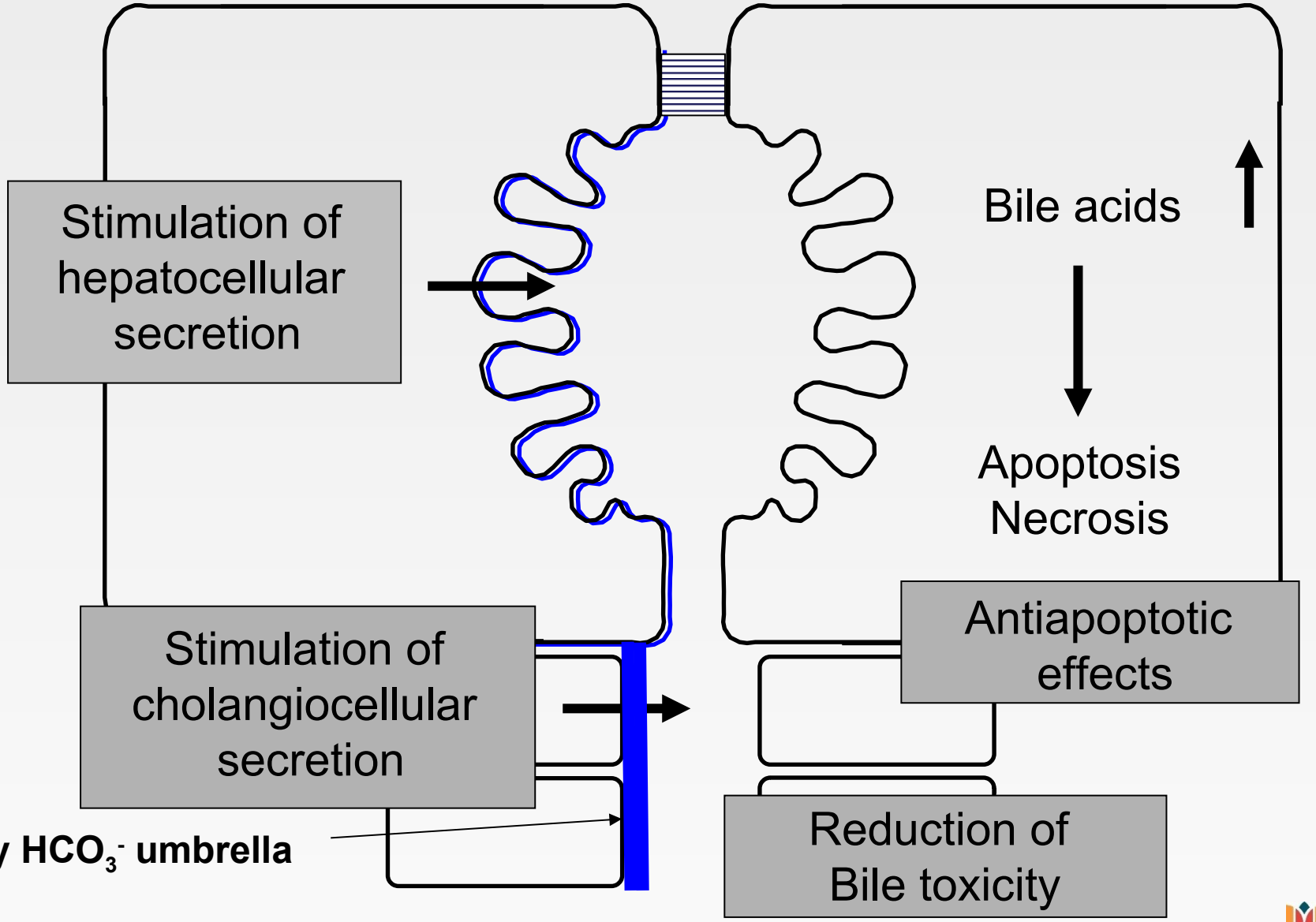
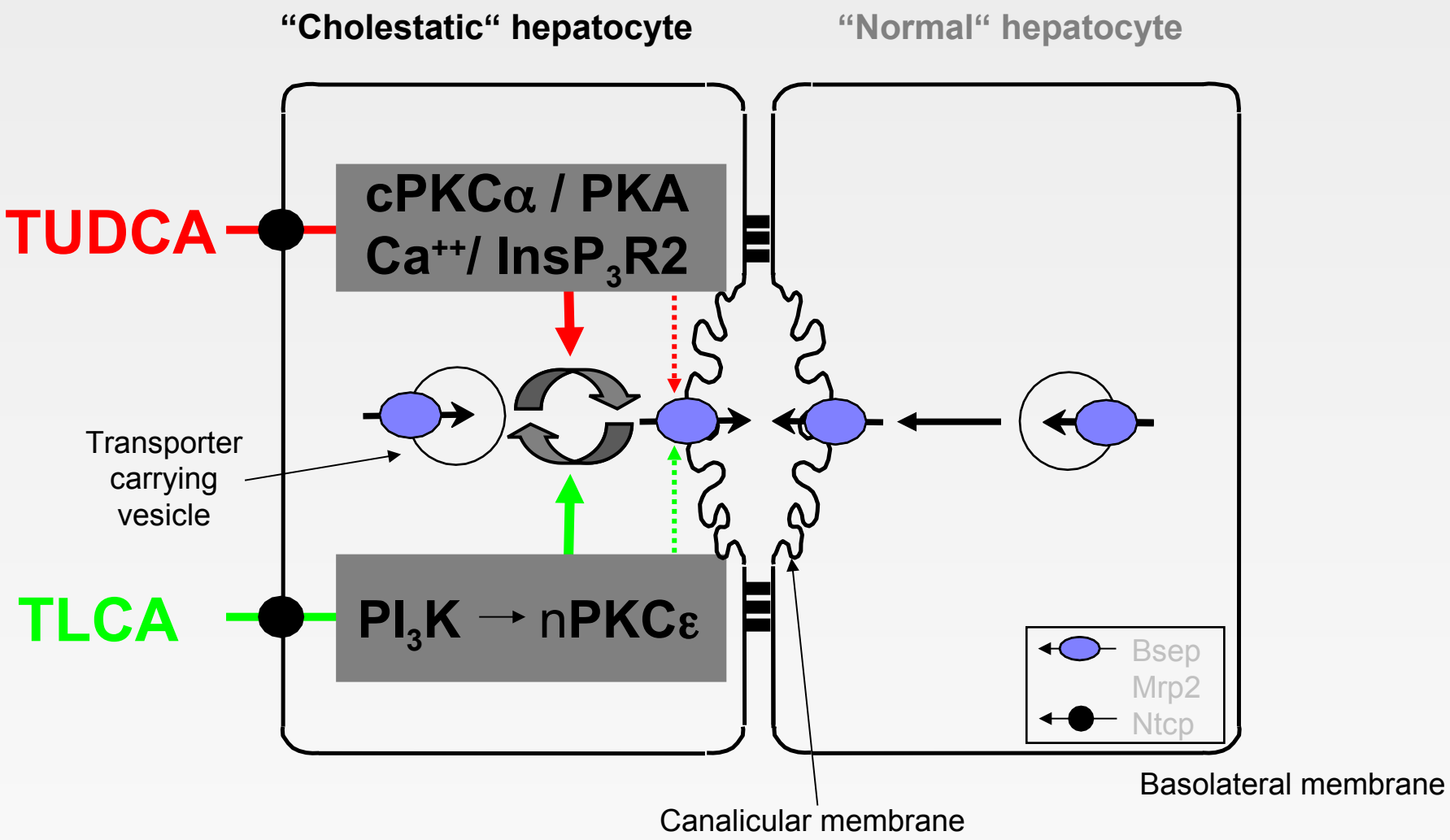
Putative mechanisms and sites of action of UDCA in cholestatic liver diseases



Courtesy of G. Paumgartner

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

UDCA conjugates act as posttranscriptional secretagogues in experimental cholestasis

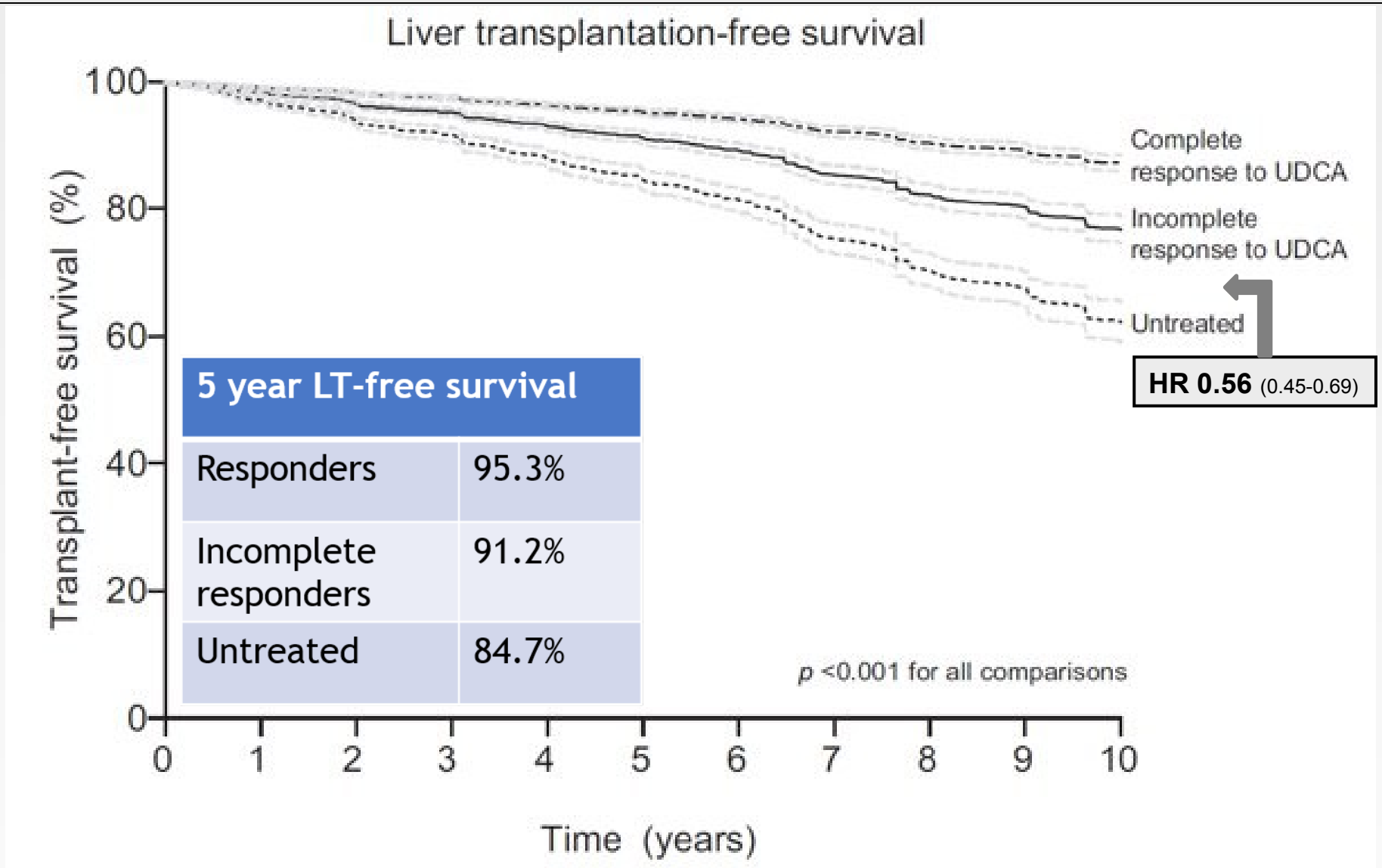


Beuers. Nature CP Gastroenterol Hepatol 2006;3:318 (references 1990-2006)

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

Cruz et al., Hepatology 2010; 52: 327

UDCA improves transplant-free survival of patients with PBC in complete *and* 'incomplete' responders



5 year LT-free survival	
Responders	95.3%
Incomplete responders	91.2%
Untreated	84.7%

Harms et al., J Hepatol 2019, epub

n = 3902

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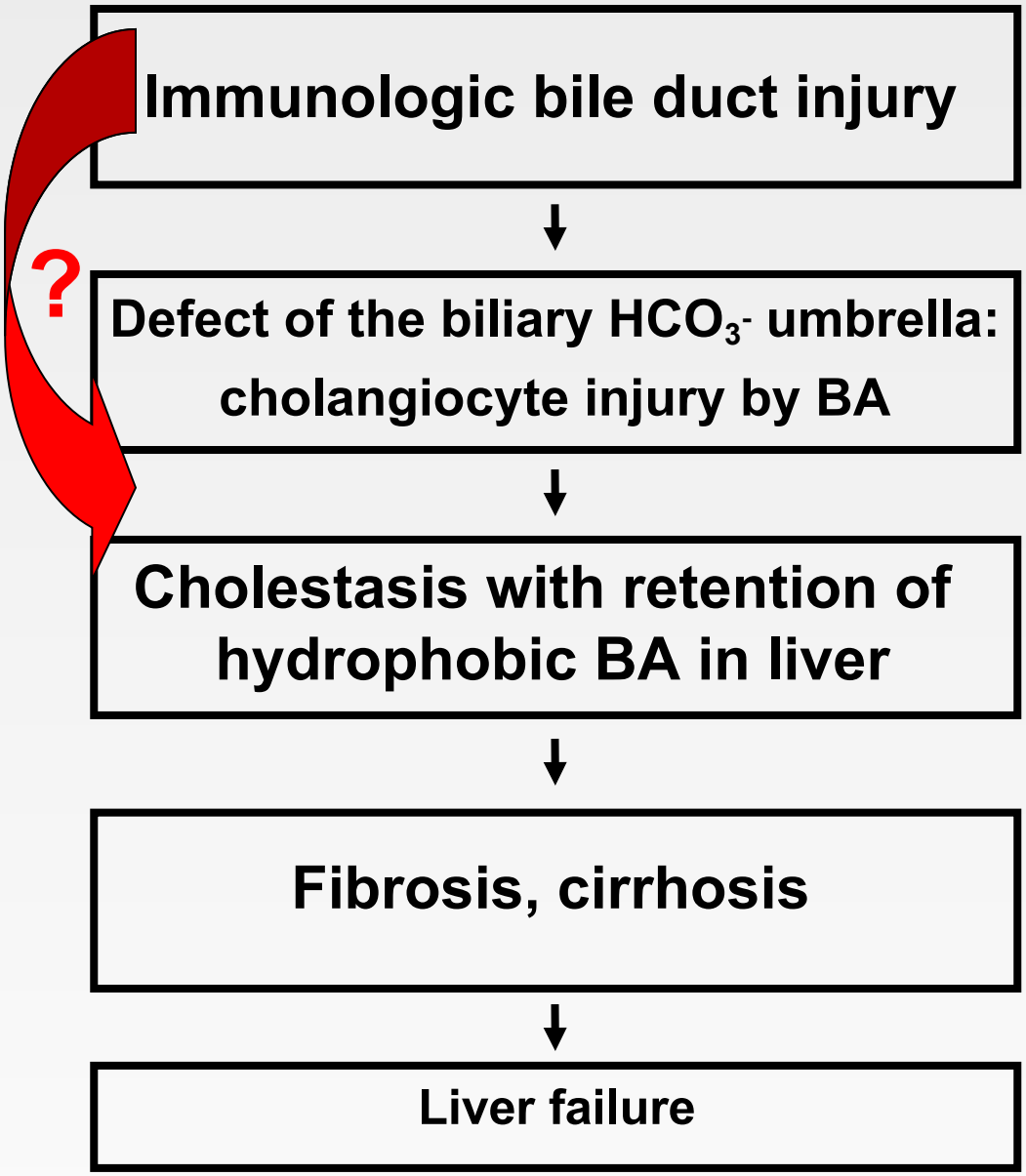
Primary biliary cholangitis: *Potentially new* Therapy

Potential pathogenetic mechanisms



FXR agonist: Obeticholic acid

Nevens et al., New Engl J Med 2016; 375: 631

Ursodeoxycholic acid (13-15 mg/kg/d)

Liver transplantation

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

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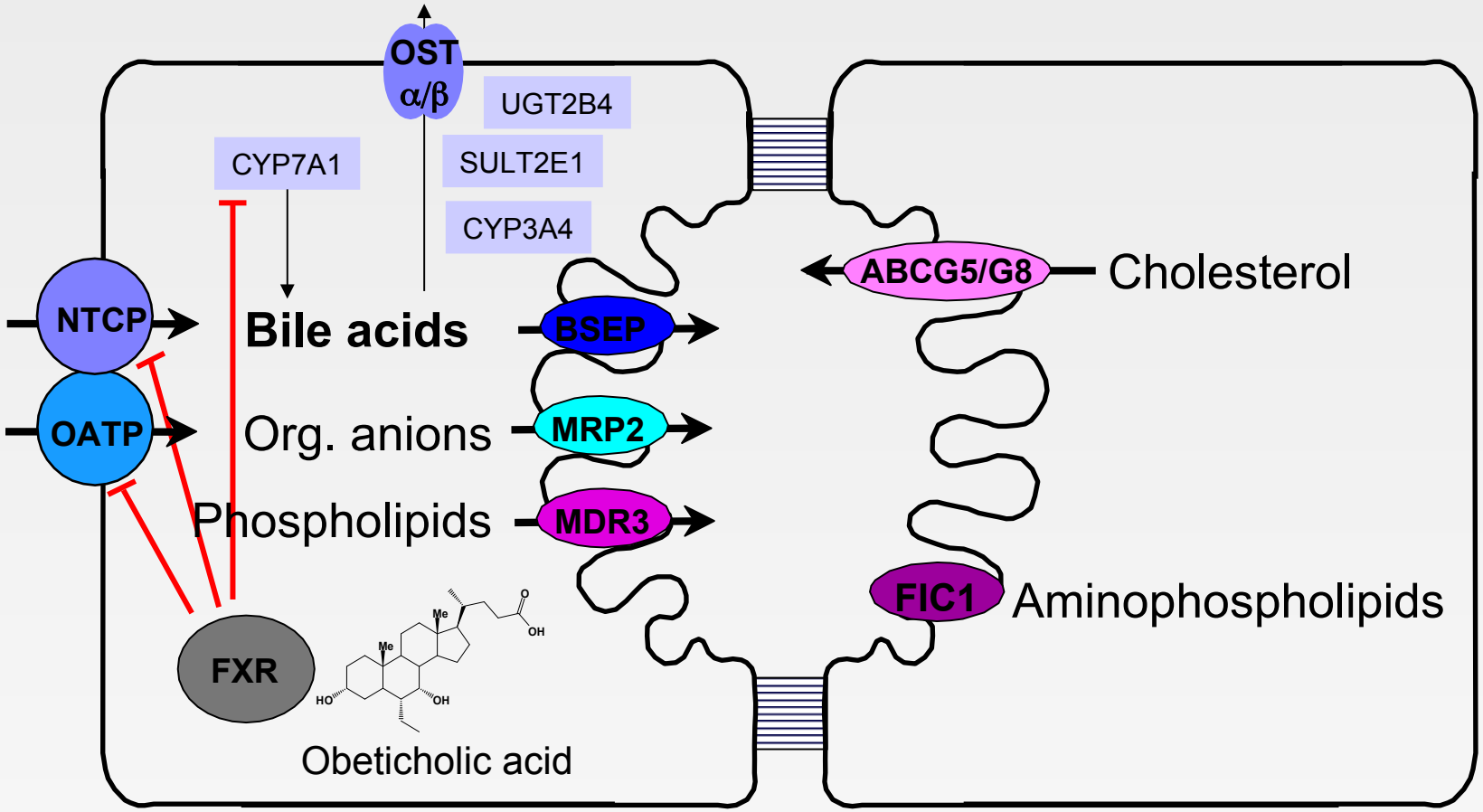
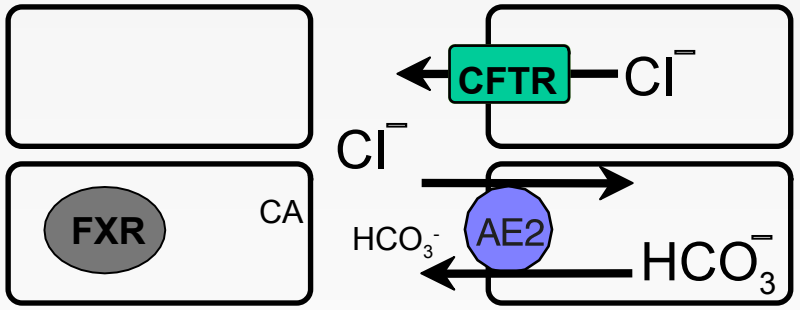
The Farnesoid X receptor (FXR) protects against toxic effects of hydrophobic bile acids





BSEP: ABCB11
MRP2: ABCC2
MDR3: ABCB4
FIC1: ATP8B1

CA, Carboanhydrase

For details, see:
Trauner et al., Hepatology 2017;65:1393

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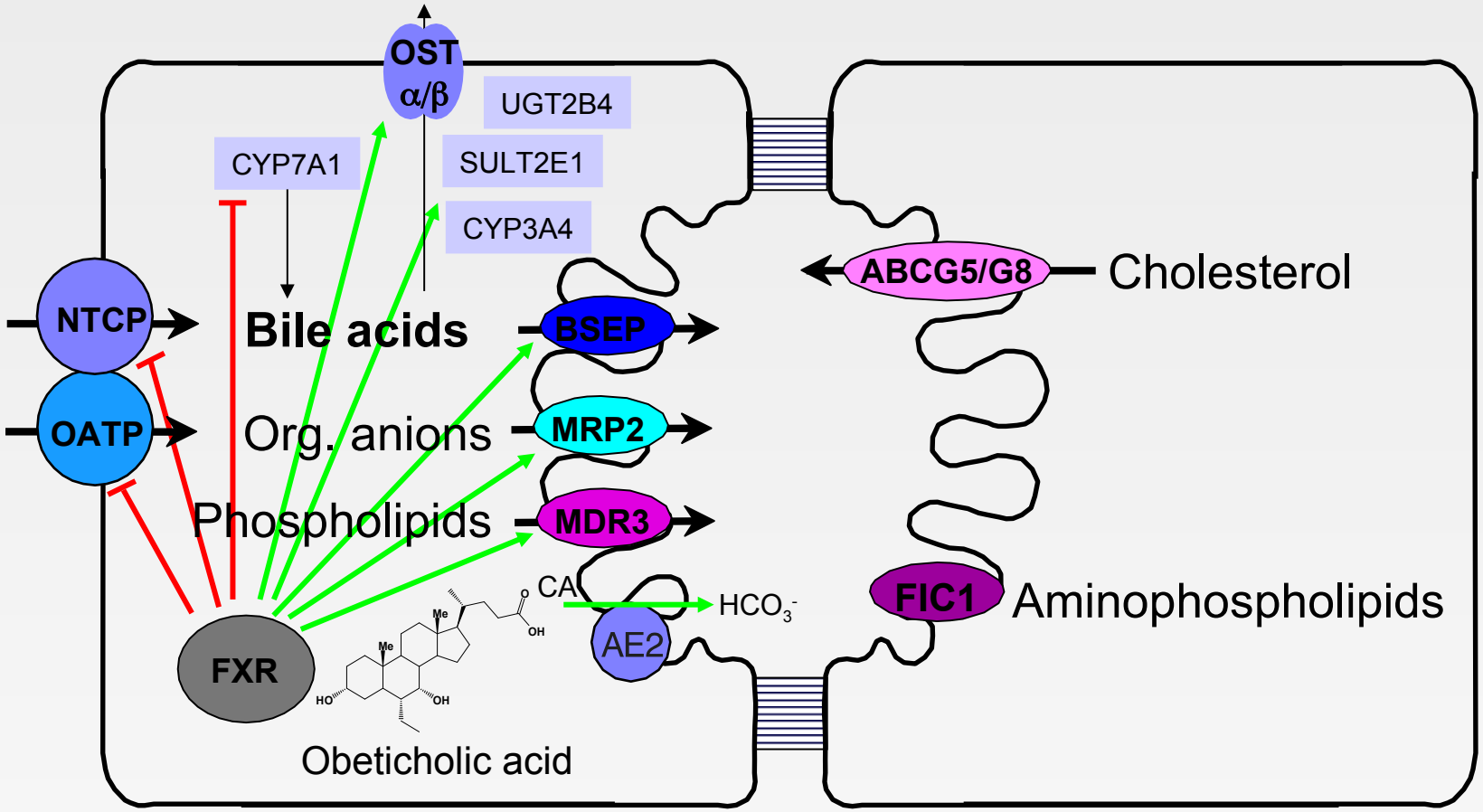

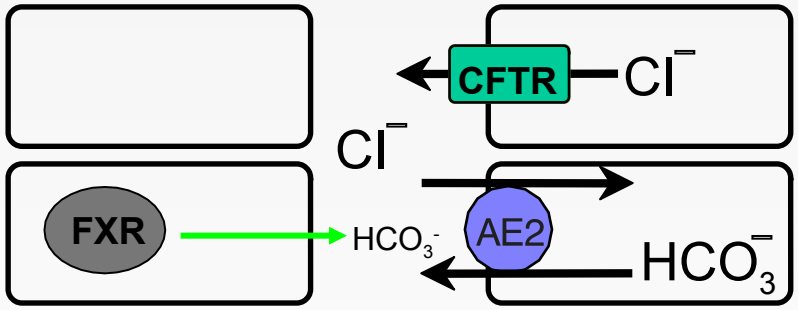

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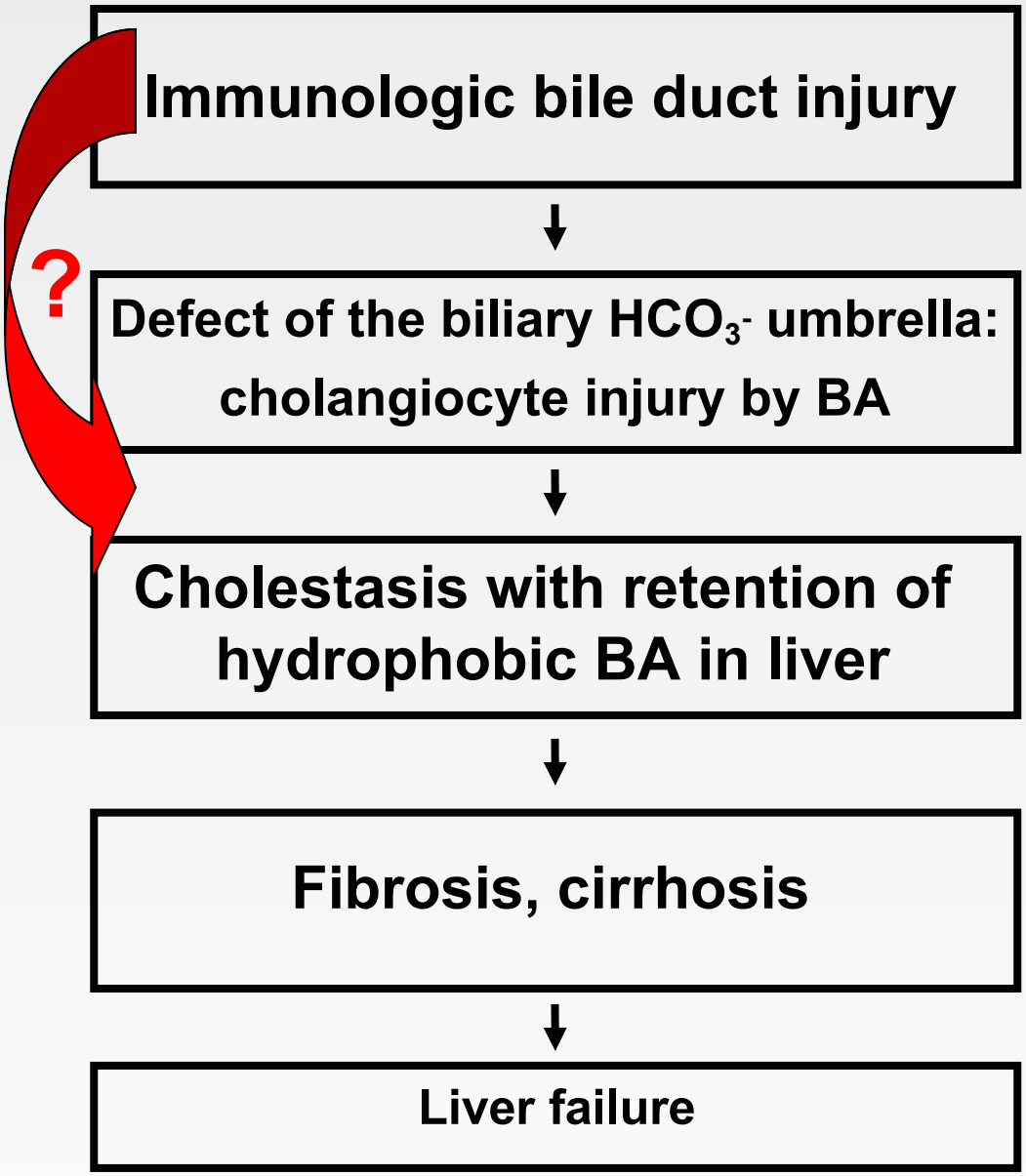
Primary biliary cholangitis: *Potentially new* Therapy

Potential pathogenetic mechanisms



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Nevens et al., New Engl J Med 2016; 375: 631

PPAR agonist: Bezafibrate

Corpechot et al., New Engl J Med 2018;378:217

Ursodeoxycholic acid (13-15 mg/kg/d)

Liver transplantation

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

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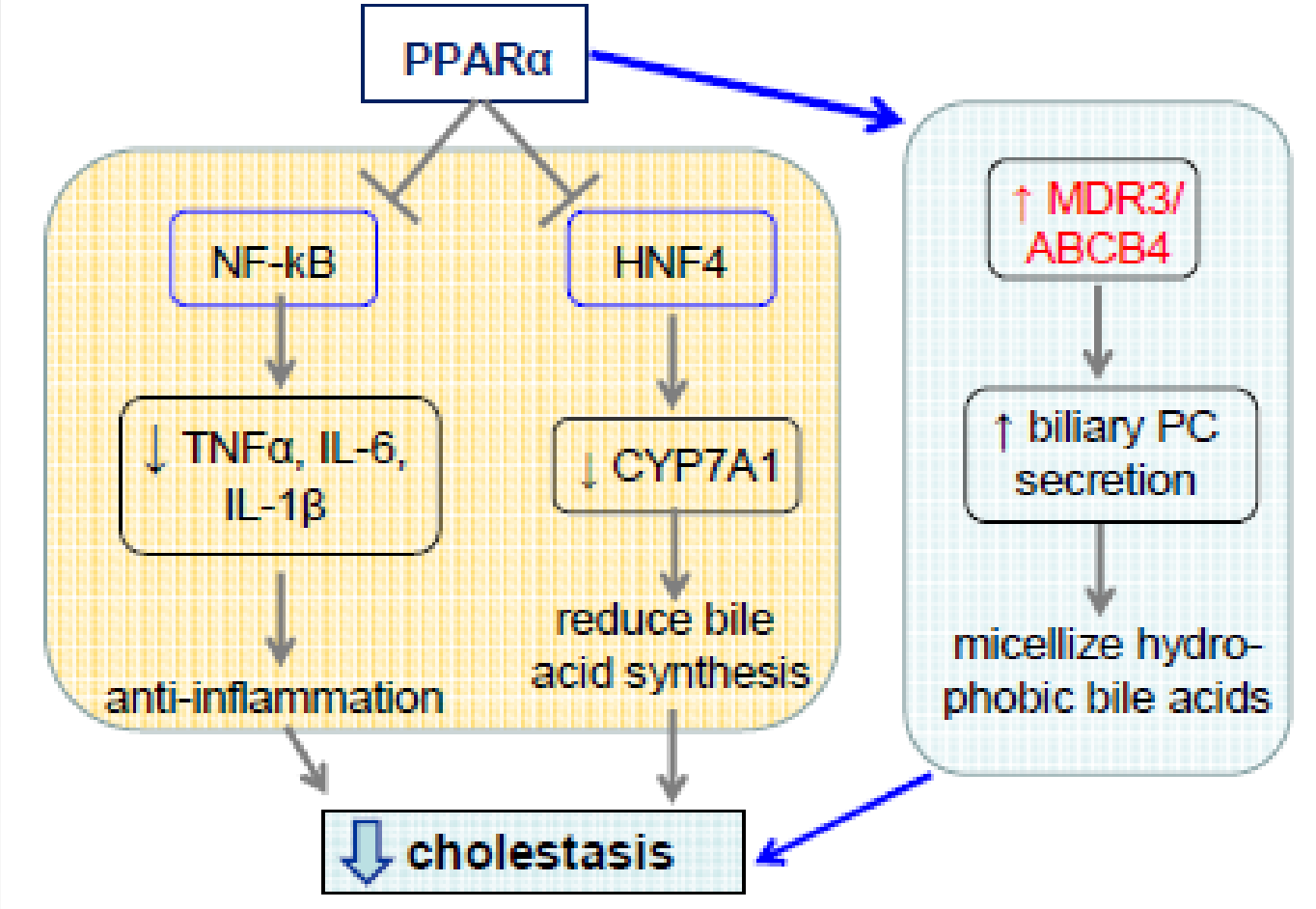
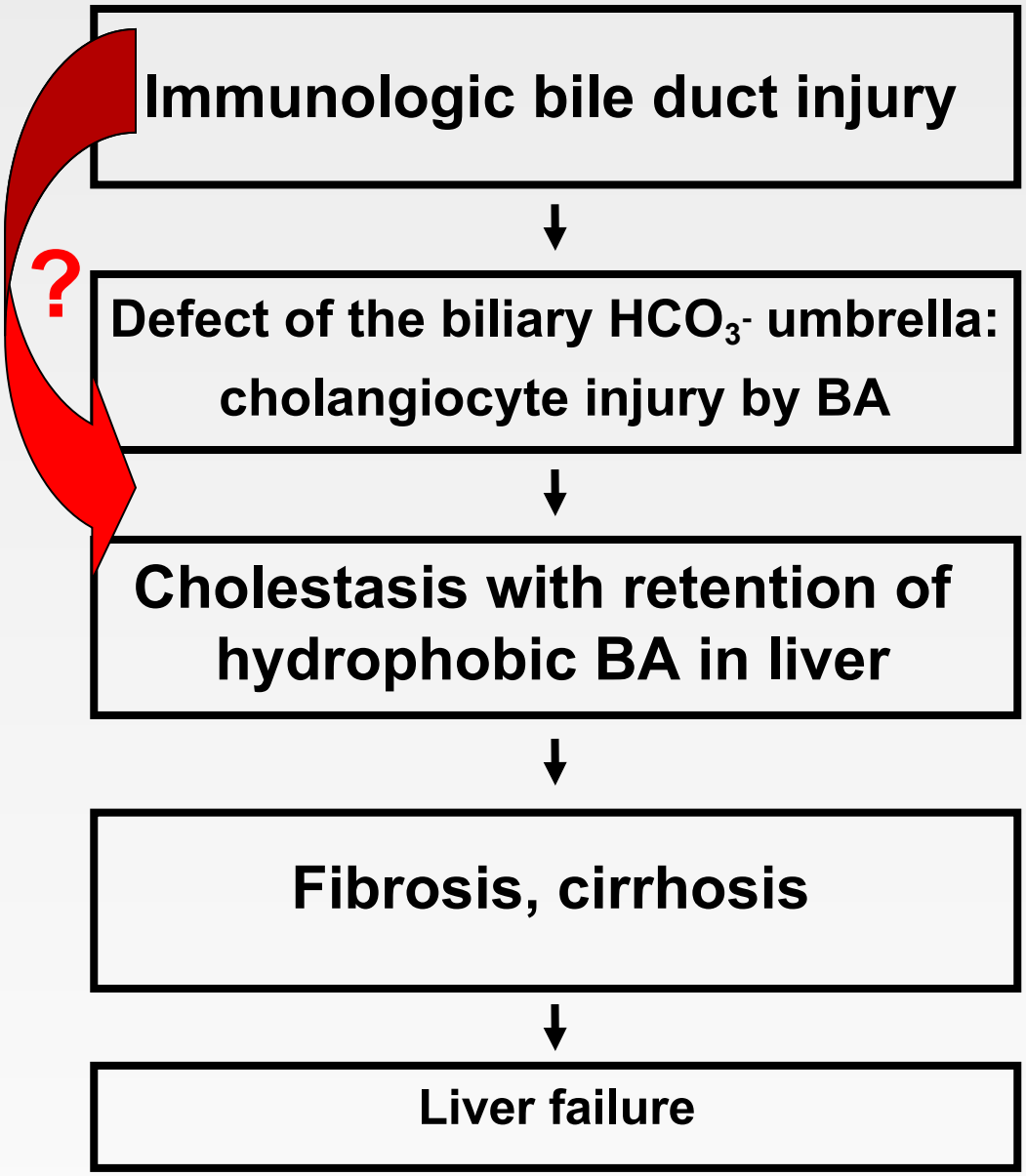
Putative mechanisms of fibrate-induced reduction of cholestasis in the liver



Ghonem, Assis, Boyer. Hepatology 2015;62:635

Primary biliary cholangitis: *Potentially new* Therapy

Potential pathogenetic mechanisms



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GR/PXR-Agonists: e.g., Budesonide?
Hirschfield et al, in preparation

Ursodeoxycholic acid
(13-15 mg/kg/d)

Liver transplantation

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

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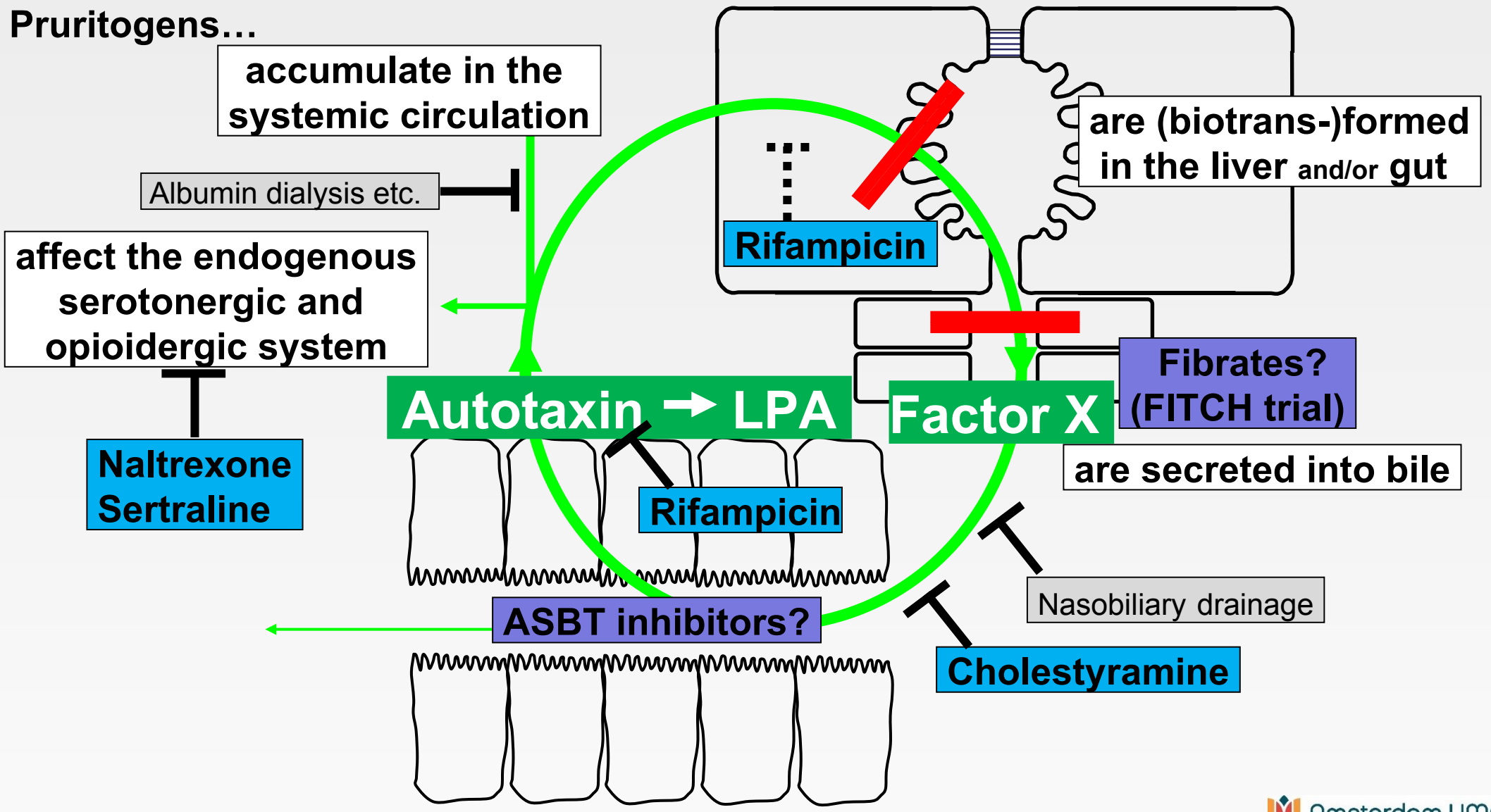
Therapeutic Targets in Pruritus of Cholestasis

Present and future



Beuers, Kremer, Bolier, Oude-Elferink, Hepatology 2014;60:399

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

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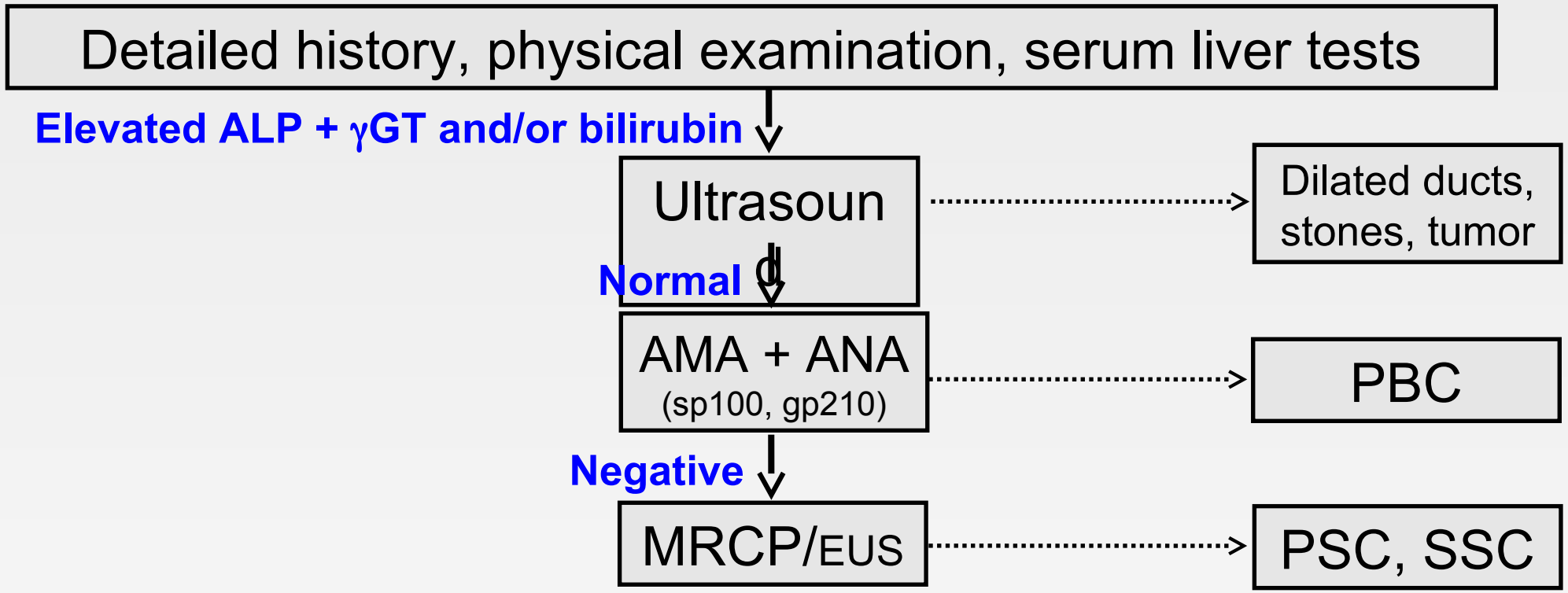
Diagnostic approach to cholestasis



EASL CP Guidelines Cholestasis, J Hepatol 2009;51:237
EASL CP Guidelines PBC. J Hepatol 2017; 67:145-172

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Abdominal Imaging II

♀ 80 yrs

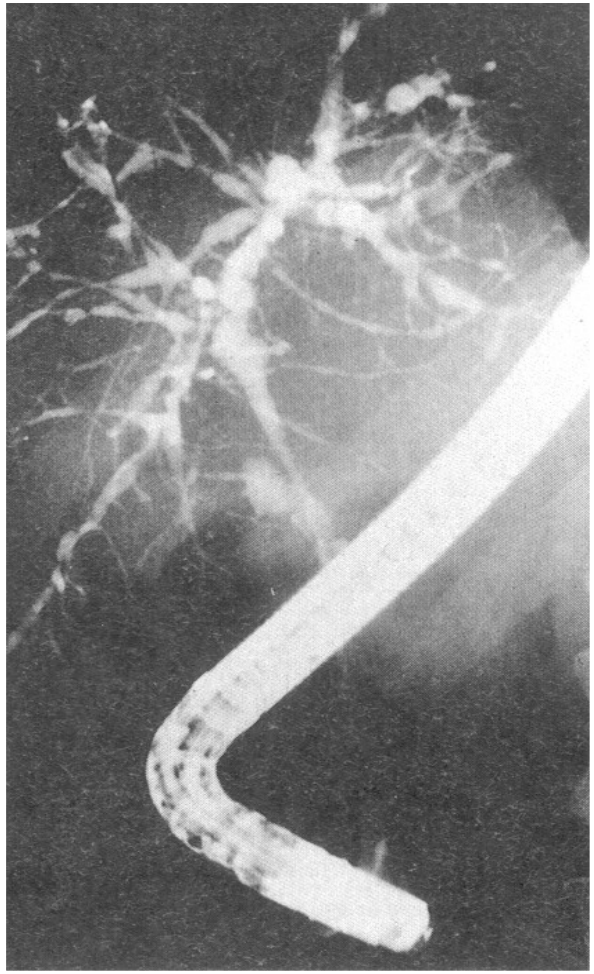
CT abdomen:

- Normal aspect pancreas
- Normal aspect liver
- Perihilar bile ducts slightly thickened, otherwise no abnormalilies

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)

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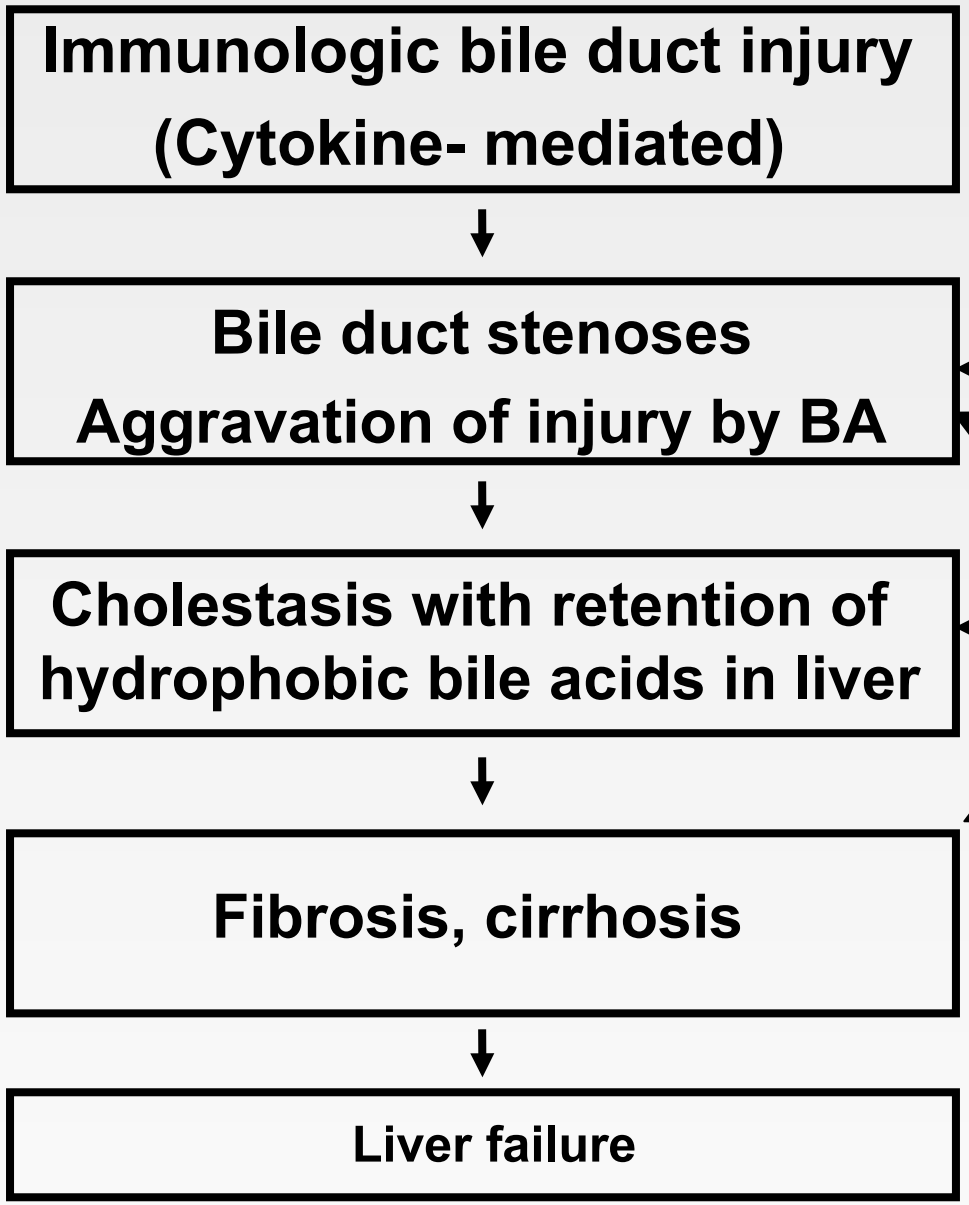
PSC : Therapy

Pathogenetic model



Endoscopic balloon dilatation

Ponsioen et al., Gastroenterology 2018;155:752

Ursodeoxycholic acid

(15-20 mg/kg/d)

?

Liver transplantation

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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 ?

Endoscopic balloon dilatation

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

Nuclear receptor agonists ?
-PPAR
-FXR
FGF19 homologues ?

Liver transplantation

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The Patient with Sclerosing Cholangitis

Diagnostic Algorithm

Sclerosing Cholangitis

↓

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

↓ no

Primary sclerosing cholangitis

yes ↓

- Bile duct surgery
- Abdominal trauma
- Choledocholithiasis *
- **Cholangiocarcinoma** *
- Recurrent pancreatitis
- Ischemic cholangitis
- Eosinophilic cholangitis
- Mastcell cholangiopathy
- AIDS cholangiopathy
- Recurrent pyogenic cholangitis
- Portal hypertensive biliopathy
- **IgG4-related cholangitis**
- *ABCB4* deficiency
- others

Secondary sclerosing cholangitis

*** may be consequence of PSC**

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

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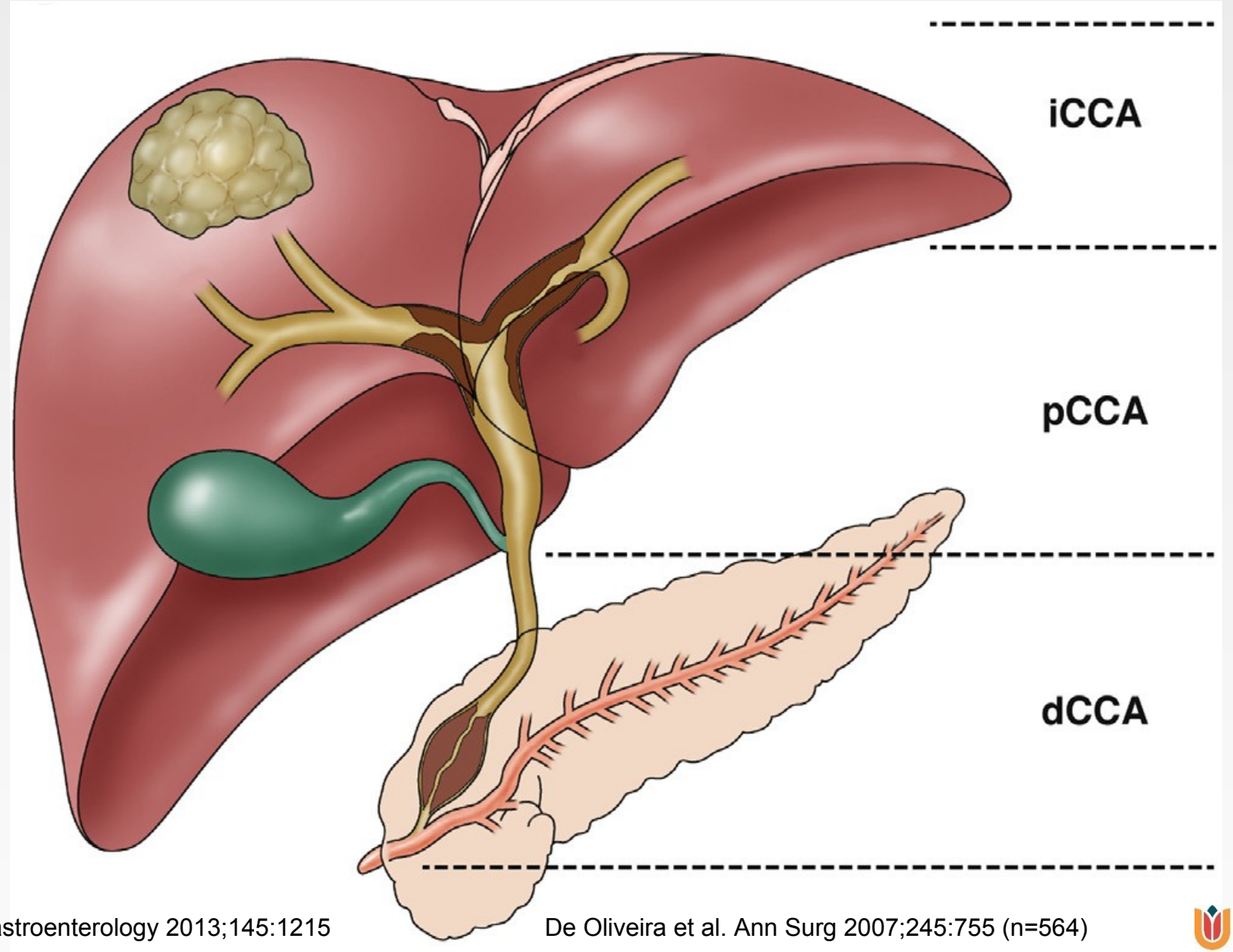
Localization of cholangiocarcinoma (CCA)



Rizvi & Gores, Gastroenterology 2013;145:1215

De Oliveira et al. Ann Surg 2007;245:755 (n=564)

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Association of medical conditions with cholangiocarcinoma

	pCCA, dCCA (n=549) [OR]	iCCA (n=535)
Choledochal cyst	47	37
Cholangitis	46	64
Biliary cirrhosis	12	20
Cholelithiasis	11	14
Choledocholithiasis	34	23
Cholecystitis	6	9
Alcoholic liver disease	5	3
Cirrhosis	5	10
HCV		4
IBD	2	4
Duodenal ulcer	2	3
Diabetes mellitus	2	2
Smoking		2
Obesity		2

Welzel et al., Clin Gastroenterol Hepatol 2007;5:1221

n=102.782 cancer-free controls

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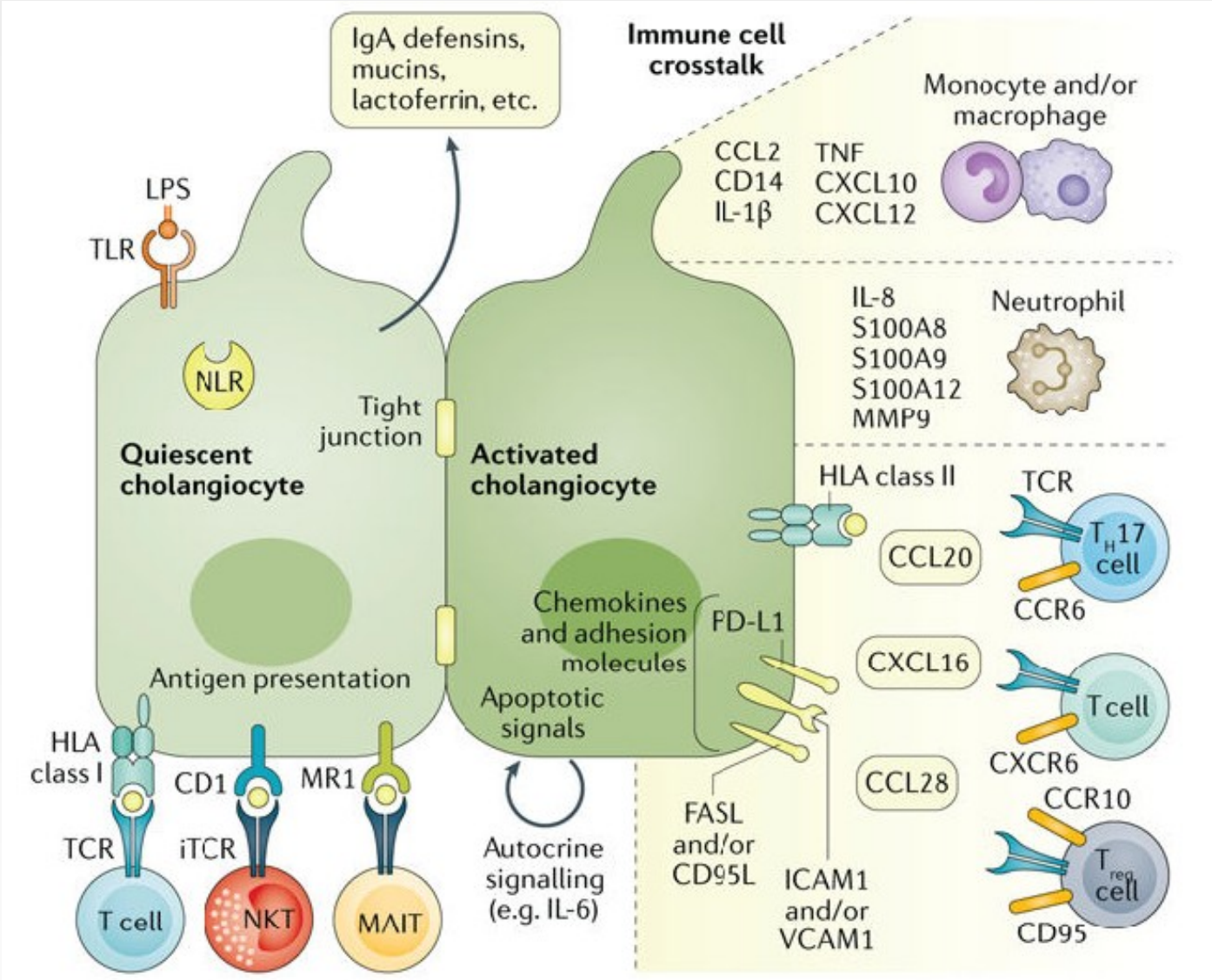
Key aspects of cholangiocyte immunobiology



Banales, …Gores. Nat Rev Gastroenterol Hepatol 2019;16:269

The Patient with Sclerosing Cholangitis

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Secondary sclerosing cholangitis

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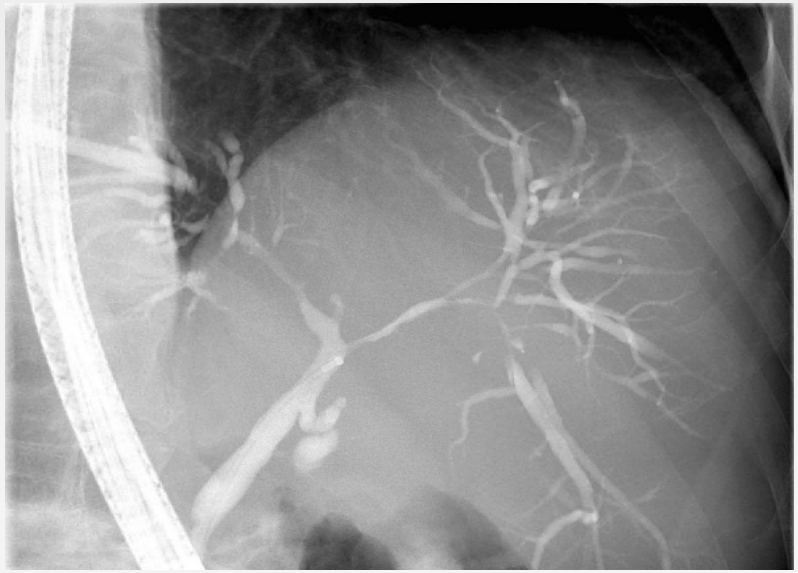
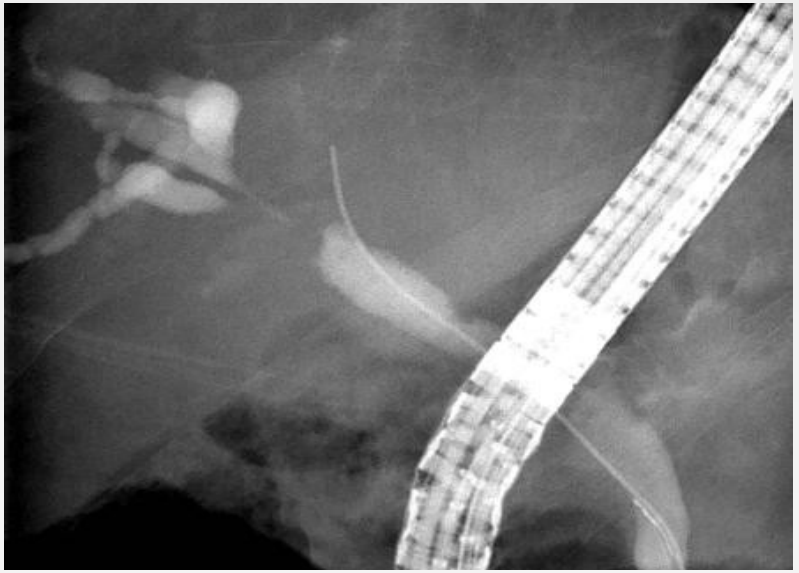
IgG4-related cholangitis mimics PSC and CCA



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



Cholangiographic appearance mimicking cholangiocarcinoma (**CCA**)

Misdiagnosis is common!

Hubers & Beuers, Viszeralmedizin 2015;31:185

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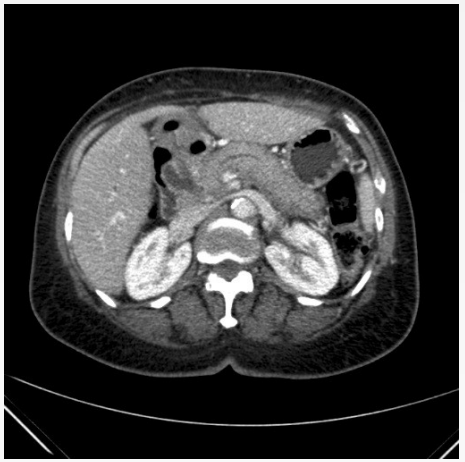
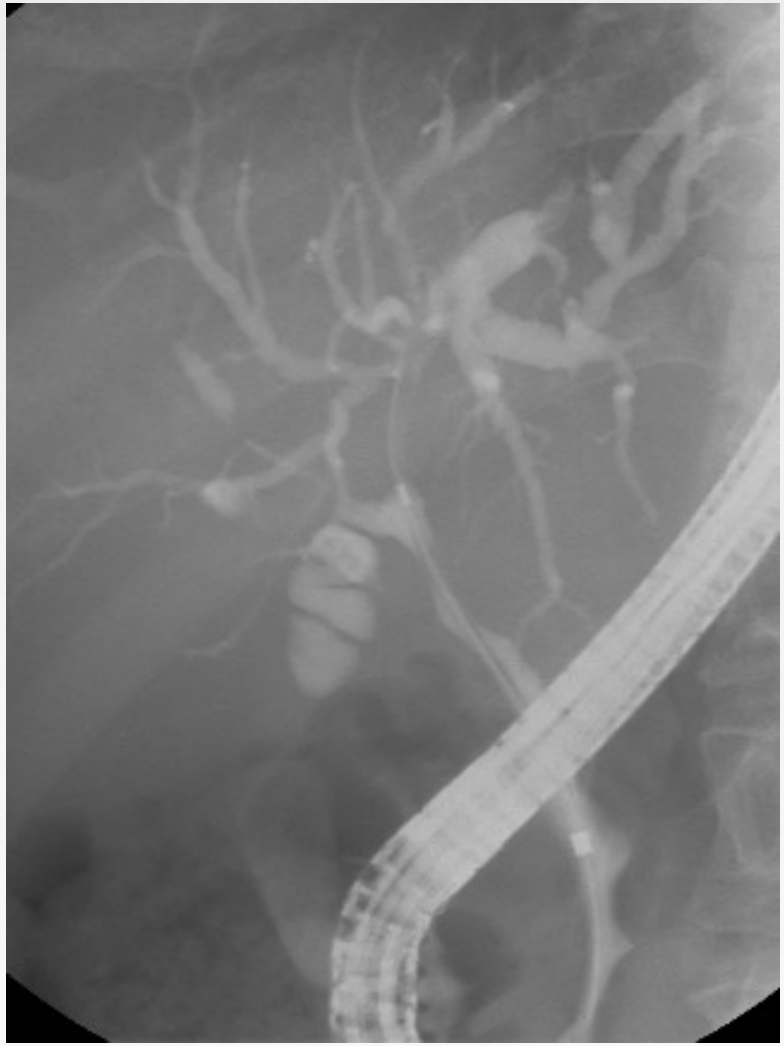
IgG4-related cholangitis

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





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

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IgG4-related cholangitis

HISORt Criteria

• **H**istology	IgG4+ plasma cells, storiform fibrosis, obliterative phlebitis
• **I**maging	Organ swelling
• **S**erology	Serum IgG4
• **O**ther organ involvement	Glands, others
• **R**esponse to **t**reatment	Corticosteroids

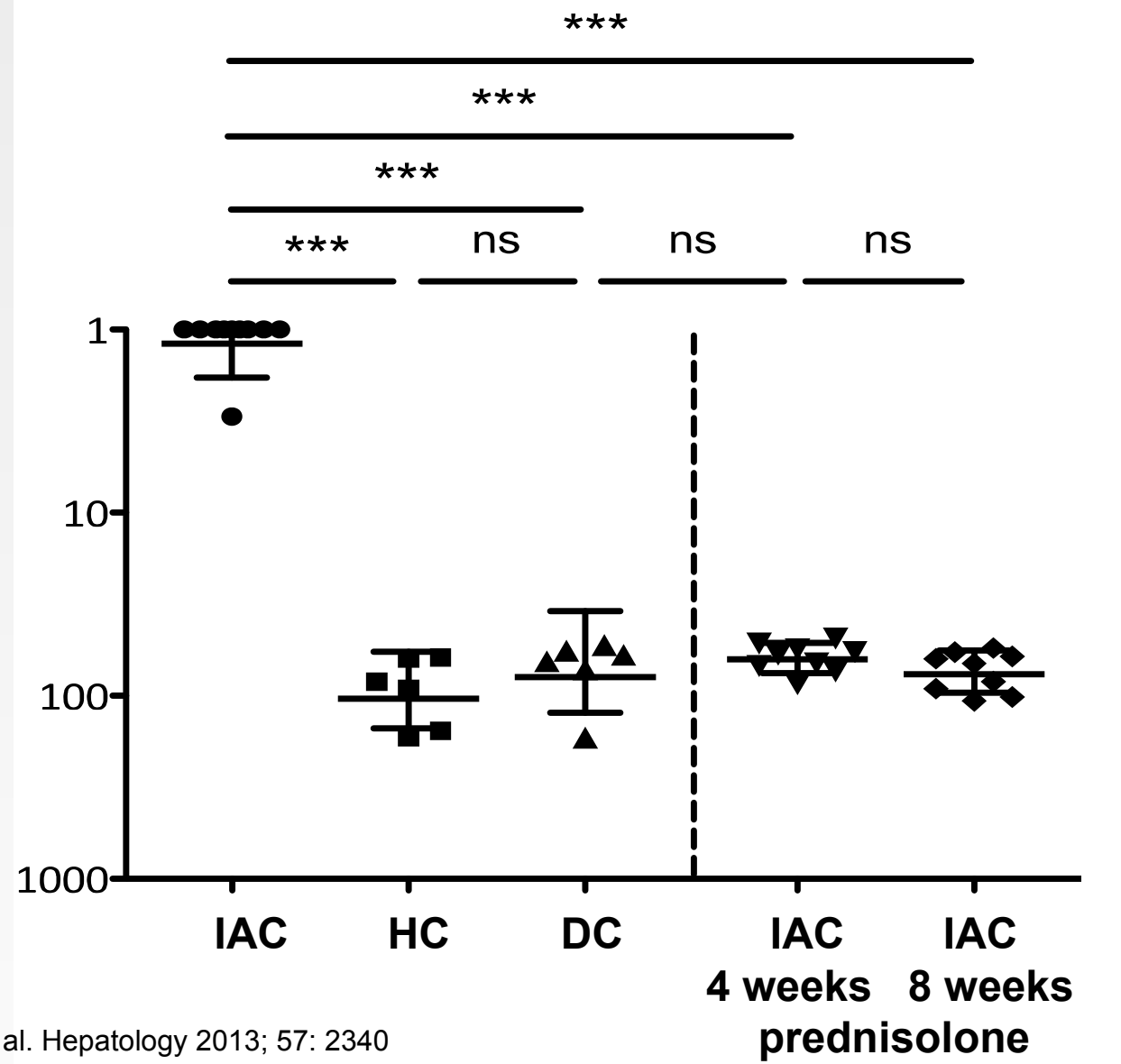
Ghazale et al., Gastroenterology 2008;134:706

IgG4-related cholangitis: B cell receptor sequencing

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

Ranking of the most prominent IgG4+ BCR clone

among all IgG clones



IAC: IgG4-related cholangitis

HC: Healthy control

DC: Disease control

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

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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

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Treatment of IgG4-related 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; Tacrolimus

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

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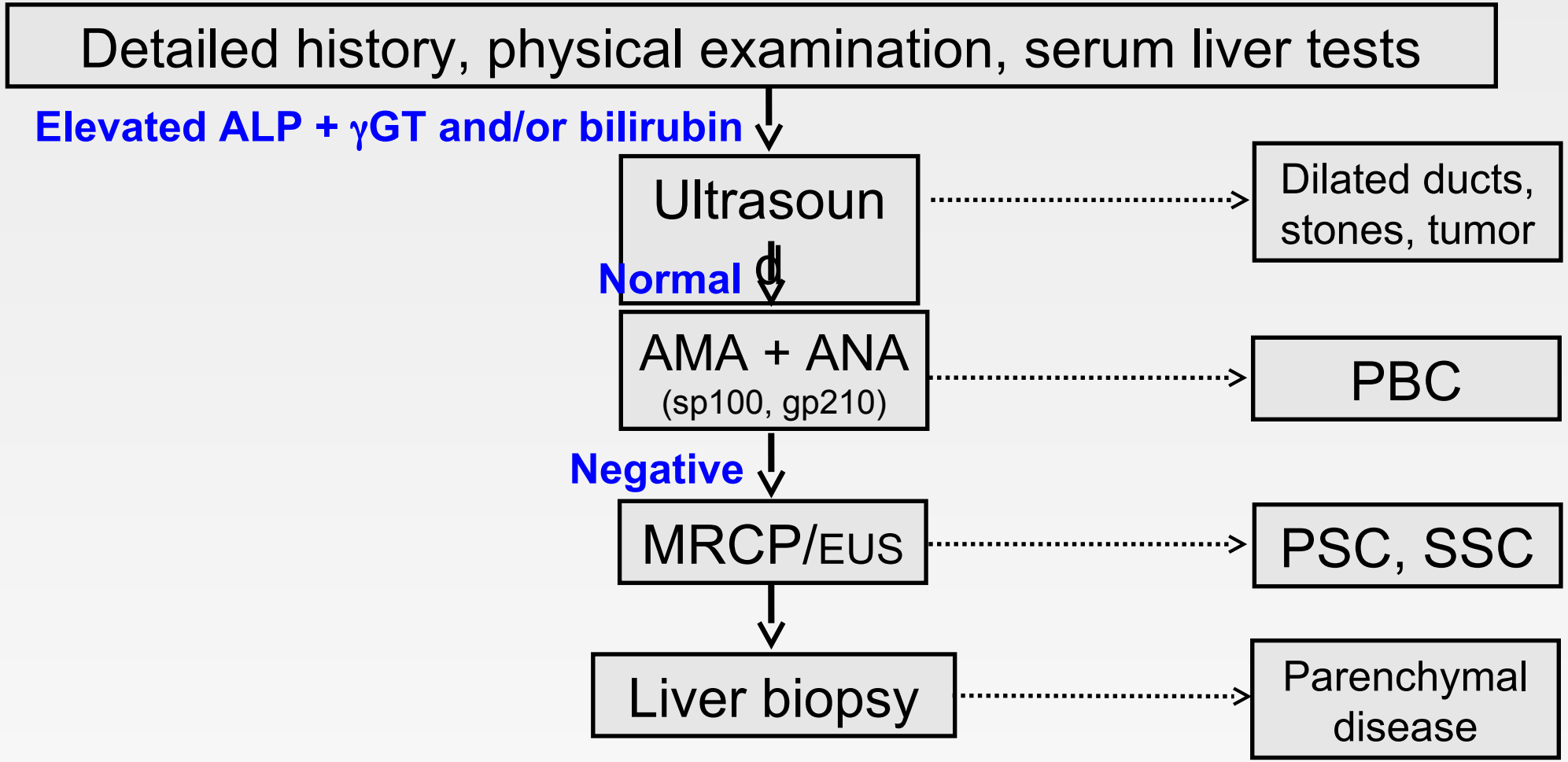
Diagnostic approach to cholestasis

♀ 80 yrs



EASL CP Guidelines Cholestasis, J Hepatol 2009;51:237
EASL CP Guidelines PBC. J Hepatol 2017; 67:145-172

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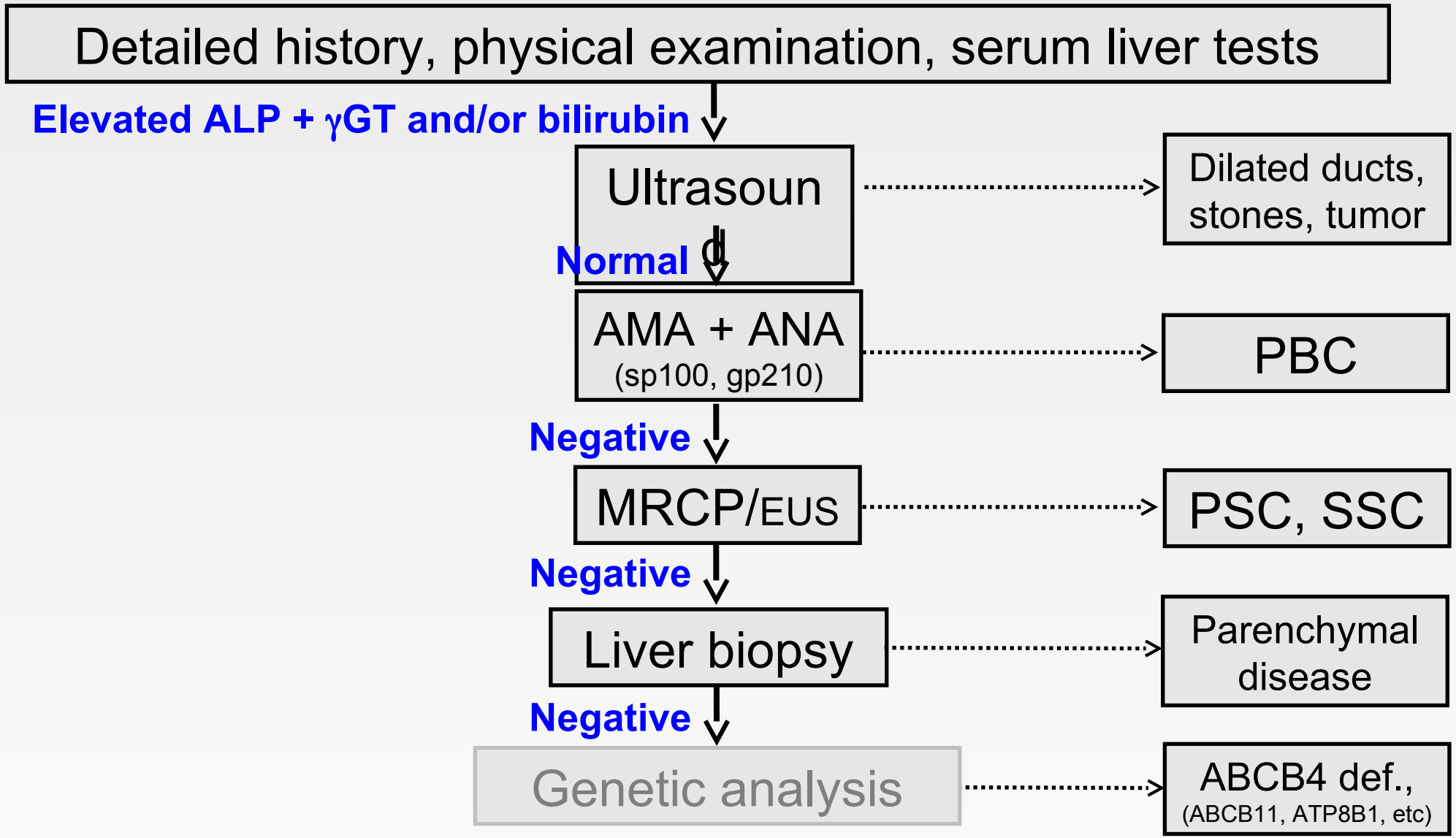
Diagnostic approach to cholestasis



EASL CP Guidelines Cholestasis, J Hepatol 2009;51:237
EASL CP Guidelines PBC. J Hepatol 2017; 67:145-172

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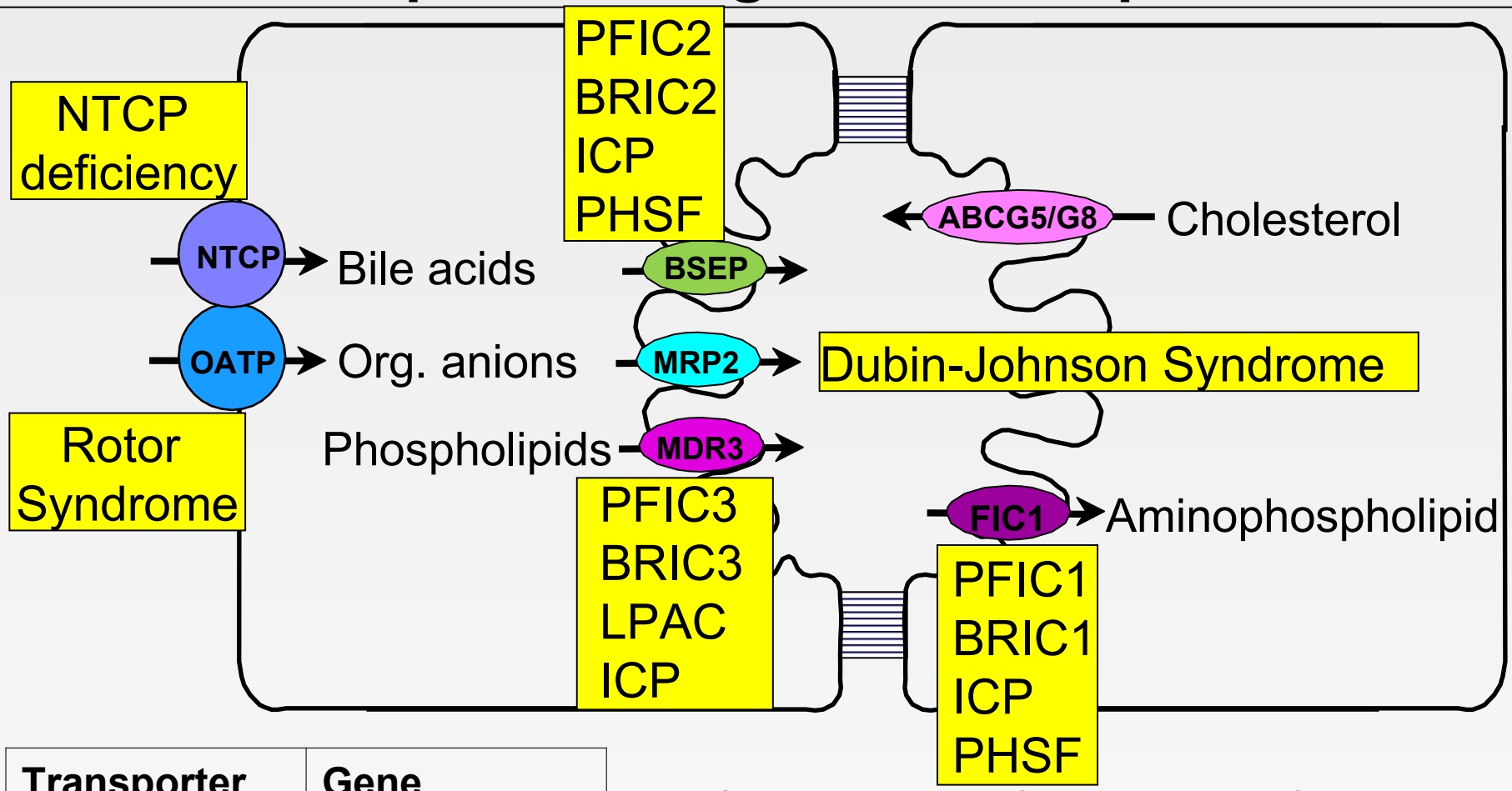
Consequences of genetic transporter defects



Transporter	Gene
FIC1	*ATP8B1*
BSEP	*ABCB11*
MDR3	*ABCB4*

PFIC: Progressive familial intrahepatic cholestasis

BRIC: Benign recurrent intrahepatic cholestasis

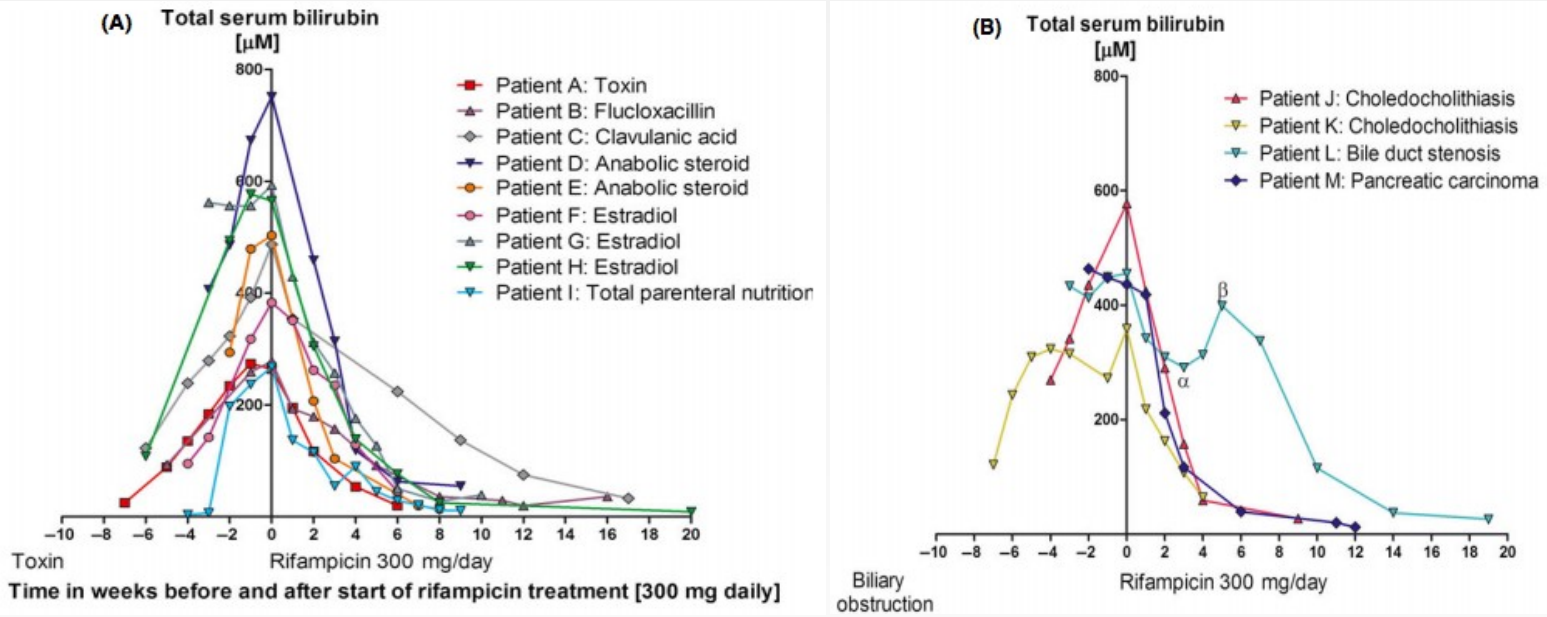
PHSF: Persistent hepatocellular secretory failure

LPAC: Low phospholipid associated cholelithiasis

ICP: Intrahepatic cholestasis of pregnancy

Persistent hepatocellular secretory failure (PHSF)

- Serum bilirubin >255 μmol/L (>15 mg/dL)
- Persistently elevated bilirubin (>1 week) after removal of the underlying cause (medication, toxin, transient mechanical obstruction)
- Exclusion of bile duct obstruction by imaging
- No underlying liver disease
- Rapid response to rifampicine



van Dijk,…Beuers. Liver Int 2015; 35:1478, modified

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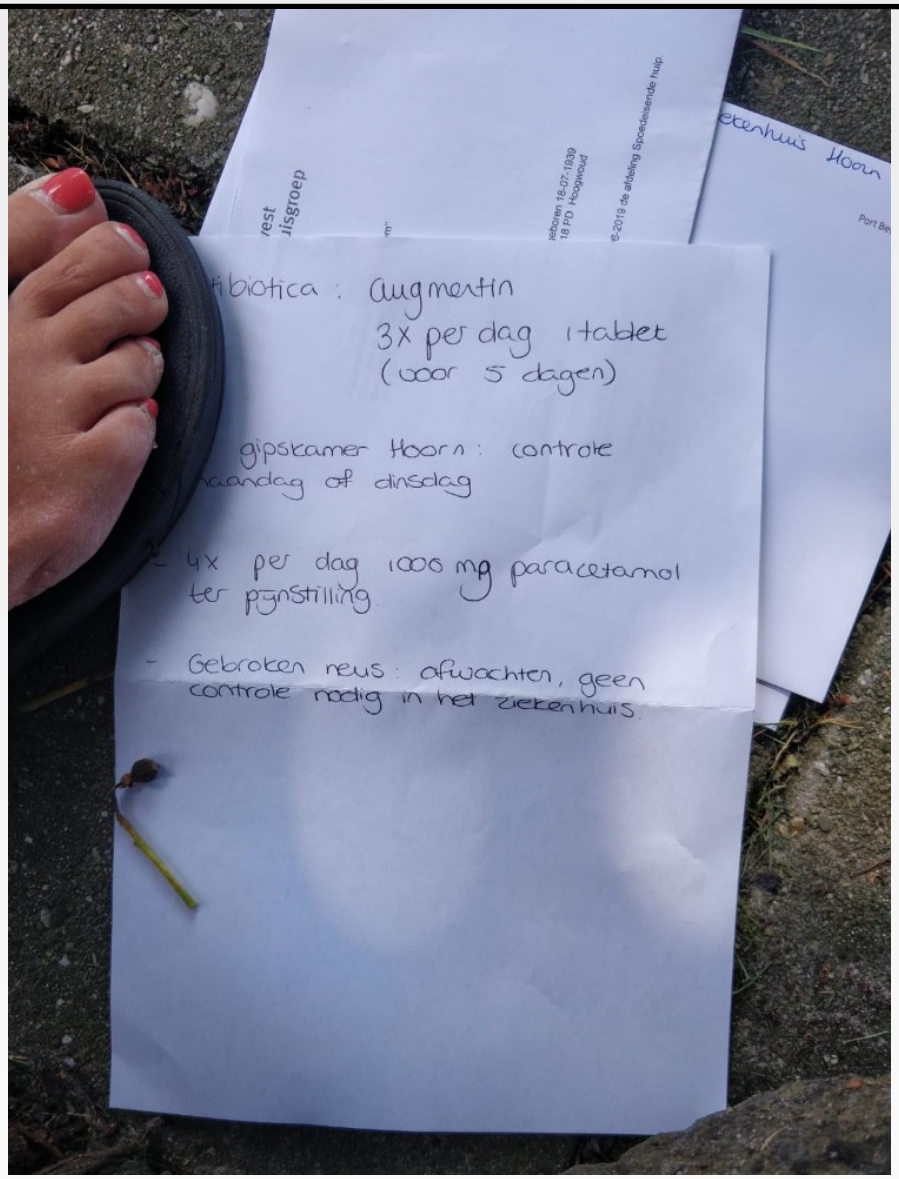
Diagnosis

♀ 80 yrs

?

…via WhatsApp sent to outpatient clinic by 2nd daughter…



♀ **80 yrs**

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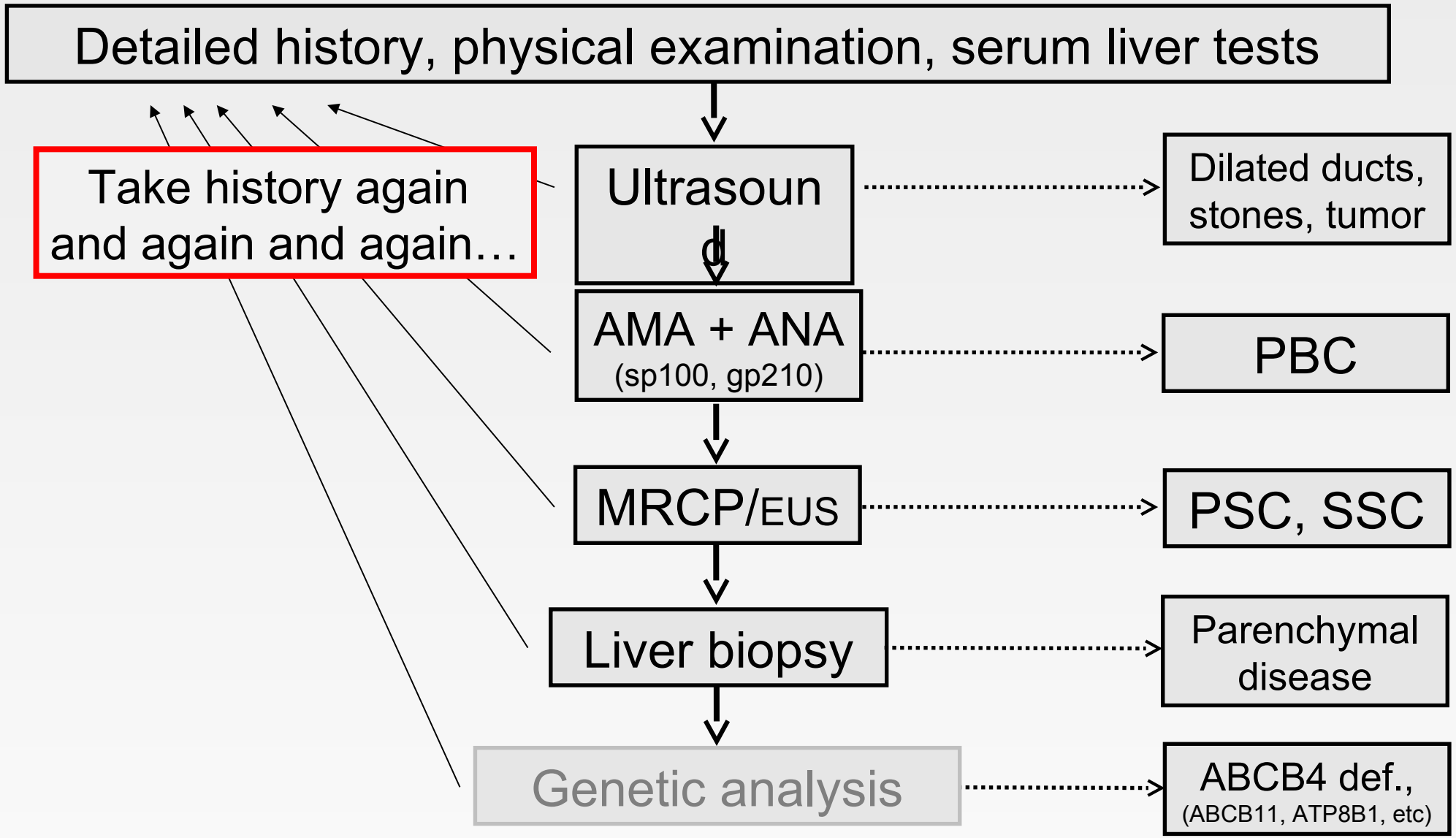
Diagnosis

♀ 80 yrs

Claculanic acid-induced liver injury

(DILI)

Management of cholestatic liver diseases 2020



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