PBC and PSC: Diagnostic Criteria and Treatment

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Outline

- Discuss diagnostic challenges in PBC and PSC
- Current and novel therapies in PBC
- Management strategies in PSC

Primary Biliary Cholangitis (PBC)

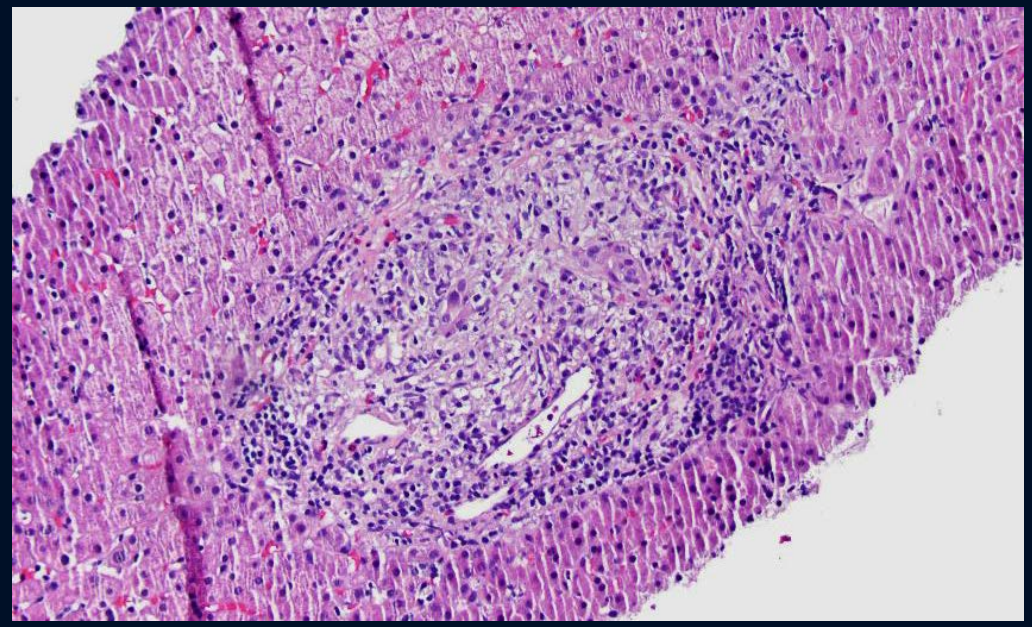
- Chronic cholestatic liver disease
- Autoimmune in nature
- Inflammation and destruction of small interlobular bile ducts

- Affects predominantly middle-aged females
- Rising incidence and prevalence

Carey E et al. Lancet 2015

PBC Diagnosis

- Unexplained Elevation of ALP ≥ 1.5x ULN
- Positive anti-mitochondrial antibody
- Non-suppurative destructive cholangitis on histology



Two out of these 3 criteria are required for the diagnosis of PBC

Variant Syndromes

AMA-negative PBC

- 50% will have antinuclear antibodies (ANA)
  - PBC-specific ANA – anti gp210, anti sp100
  - Same clinical presentation; May have reduced survival

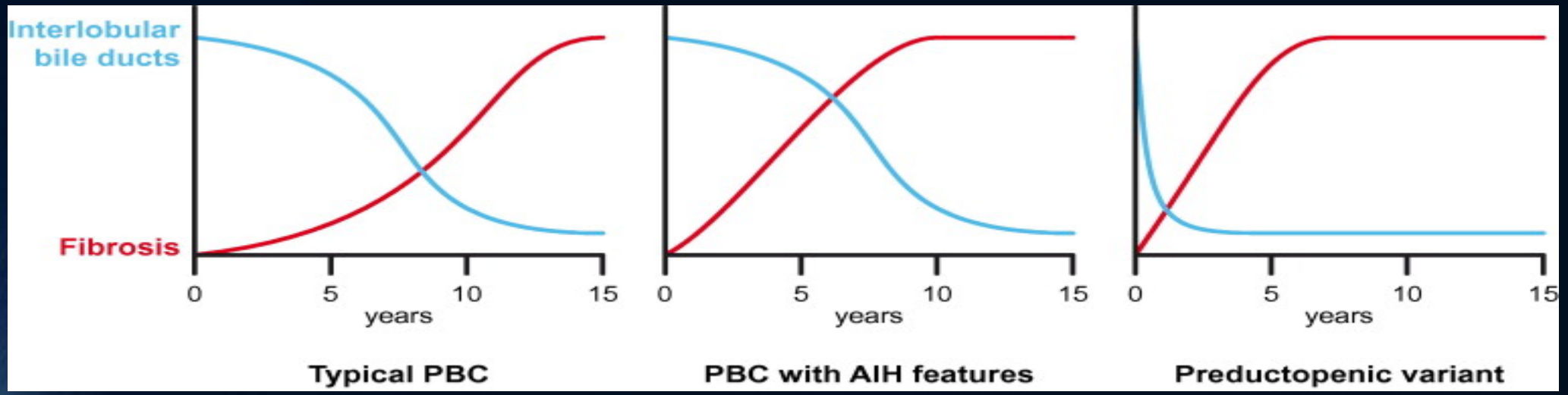
Overlap syndrome with autoimmune hepatitis

- Consider when ALP : transaminase ratio <1.5, IgG is elevated and smooth muscle antibodies are present with titer >1:80

Premature Ductopenic Variant

- 5-10%
- Very rapid onset of ductopenia, severe icteric cholestasis and fast progression towards cirrhosis

Patterns of development of ductopenia and fibrosis in PBC



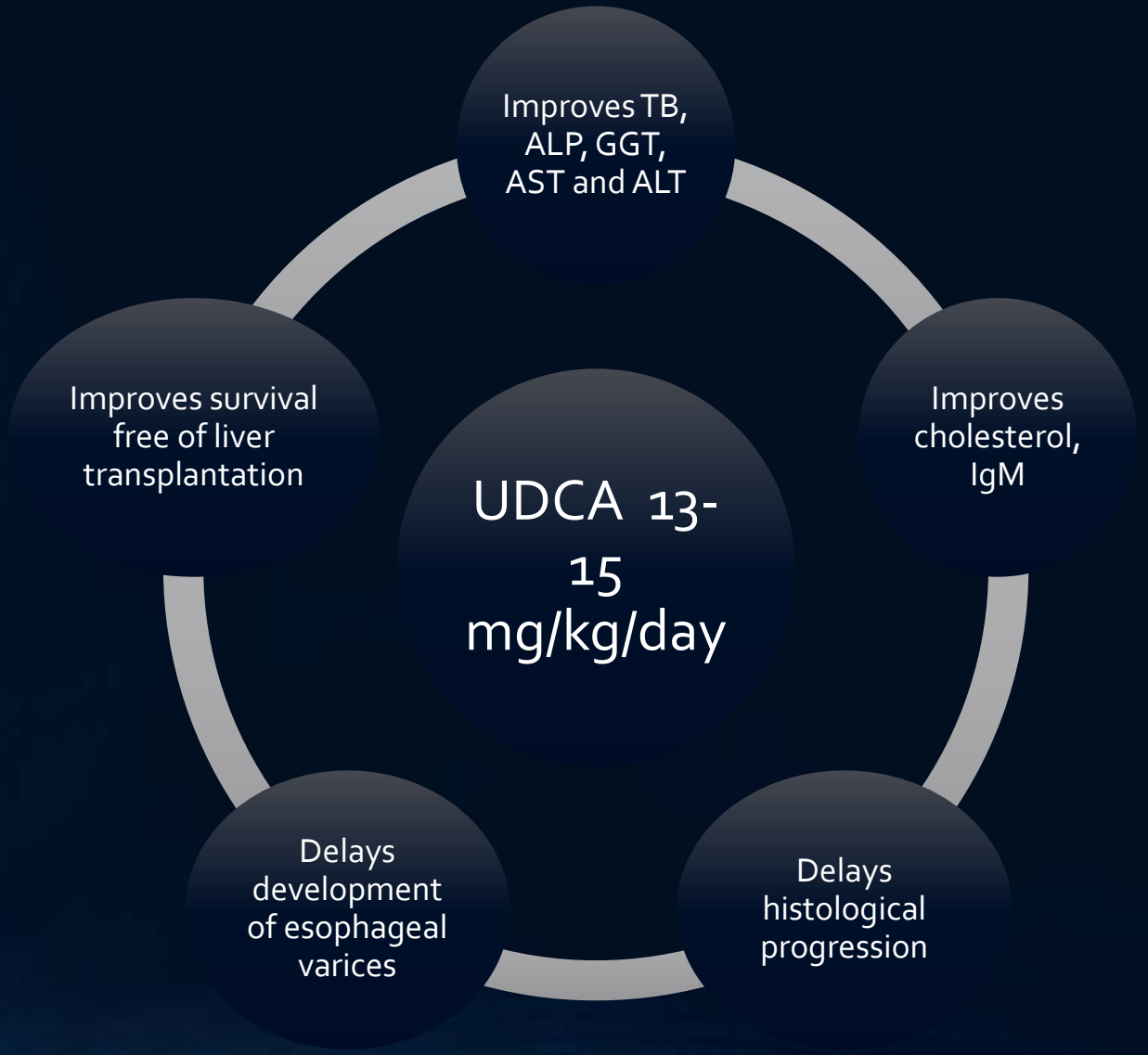
Poupon et al. J Hepatol 2010

First Line Therapy: Ursodeoxycholic Acid

- Orally administered, naturally occurring, hydrophilic secondary bile acid
- Dose: 13-15 mg/kg/day
- Improvement in liver tests may be seen within a few weeks and 90% of the improvement usually occurs within 6-9 months

Lindor K et al. *Hepatology* 2009;50:291-308.

Therapeutic Effects UDCA



Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IgM, immunoglobulin M; TB, total bilirubin; UDCA, ursodeoxycholic acid.

Levy C and Lindor KD. In: *Zakim and Boyer's Hepatology: A Textbook of Liver Disease.* Elsevier Inc;2011:738-753. Graphic courtesy of Dr. Cynthia Levy.

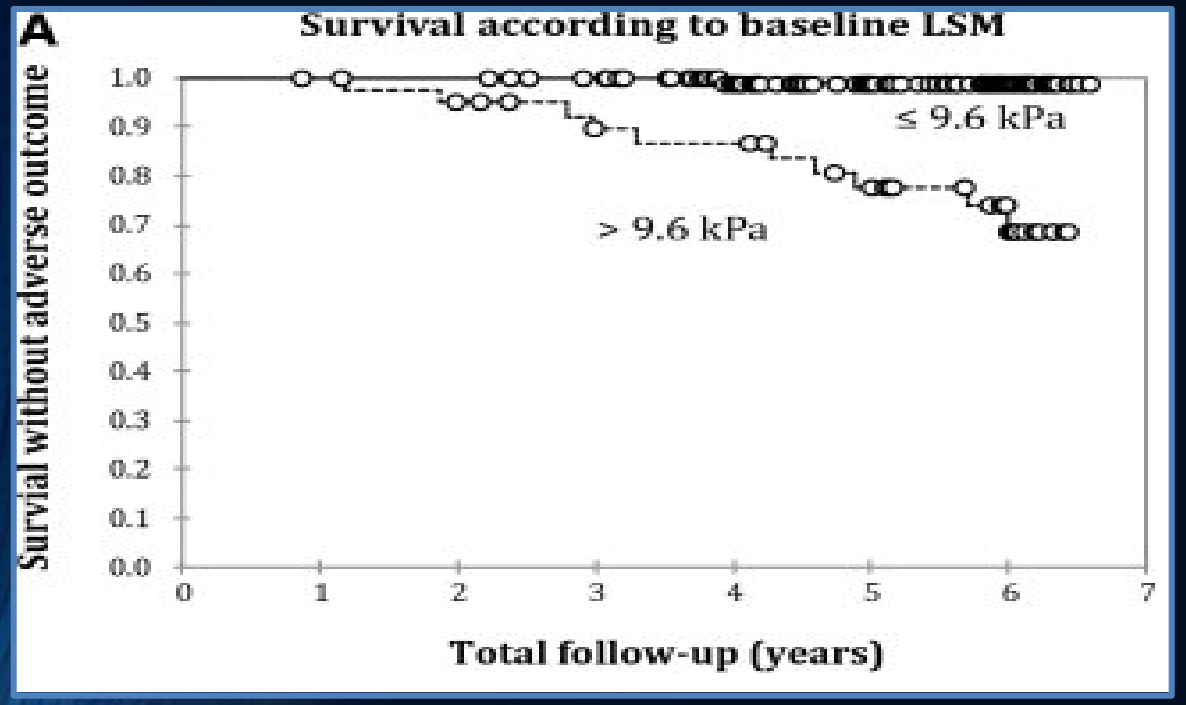
Risk Stratification in PBC

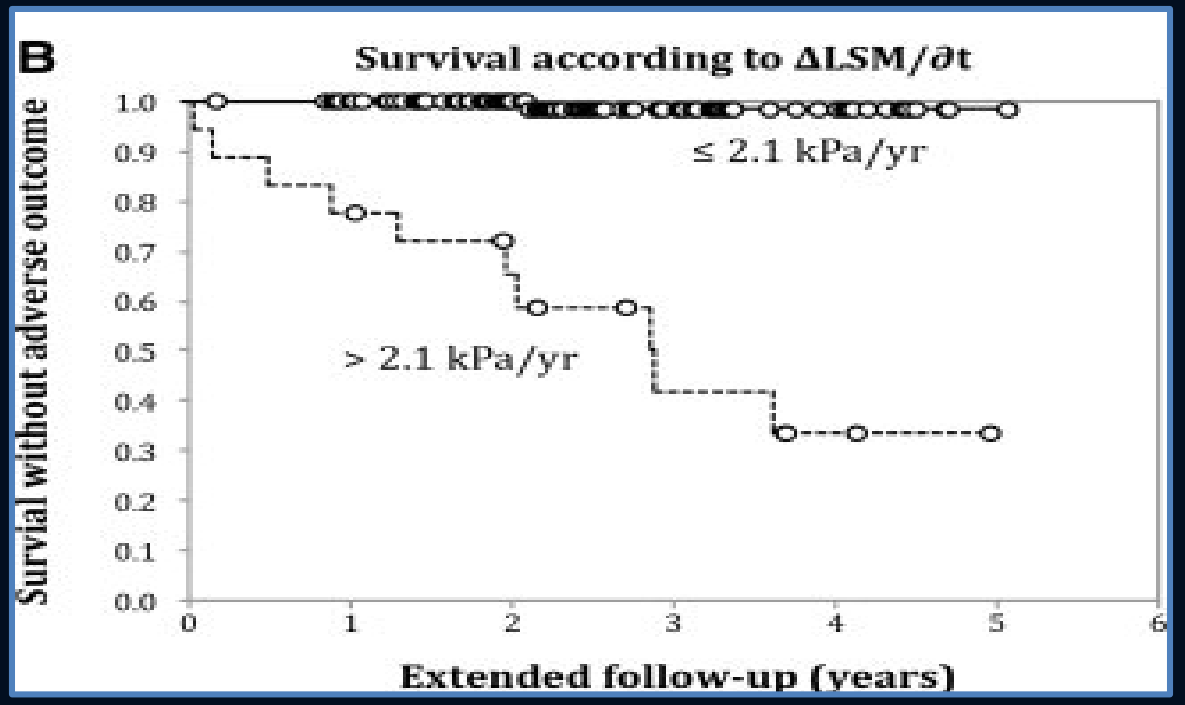
- Various response criteria
  - Barcelona, Paris, Rotterdam, Toronto, Mayo ➔ up to 40% of patients have incomplete response
    - Based on dichotomization of a continuous variable (ALP, AST, TB, albumin)
- APRI, Fibroscan
- Mathematical models
  - More sophisticated modeling of several variables
    - Mayo Risk Score
    - Globe PBC score
    - UK-PBC score

} After 1 year of treatment

1. Parés A, et al. *Gastroenterology.* 2006;130:715-720. 2. Corpechot C, et al. *Hepatology.* 2008;48:871-877. 3. Kuiper EM, et al. *Gastroenterology.* 2009;136:1281-1287. 4. Kumagi T, et al. *Am J Gastroenterol.* 2010;105:2186-2194. 5. Corpechot C. *J Hepatol.* 2011;55:1361-1367; 6. Trivedi PJ, et al. *J Hepatol.* 2014;60:1249-1258. 7. Carbone M, et al. *Hepatology.* 2016;63:930-950. 8. Lammers WJ, et al. *Gastroenterology.* 2015;149:1804-1812.

Value of Liver Stiffness in PBC



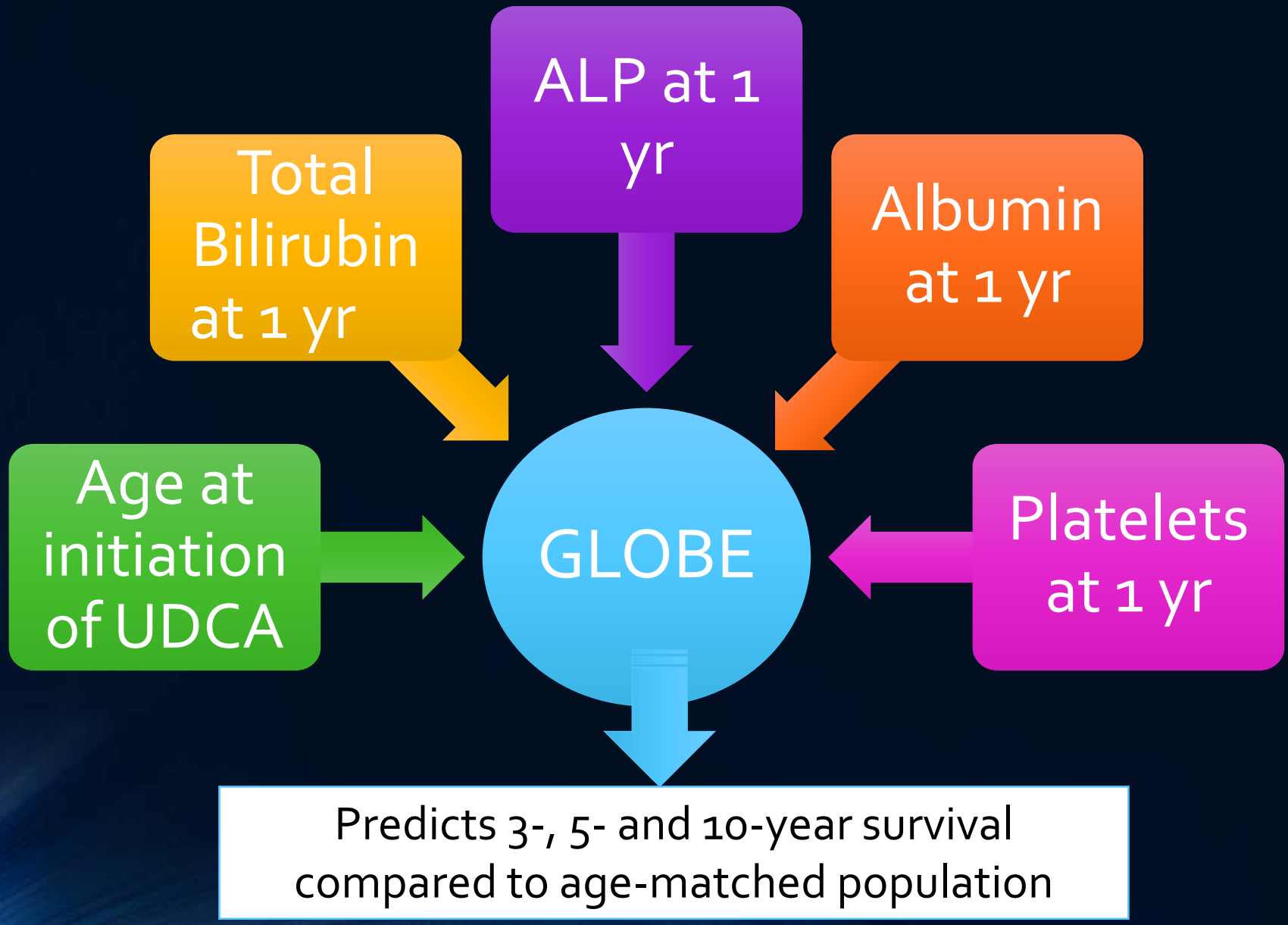


-**LS > 9.6 at baseline** associated with 5x increase in risk of adverse outcomes

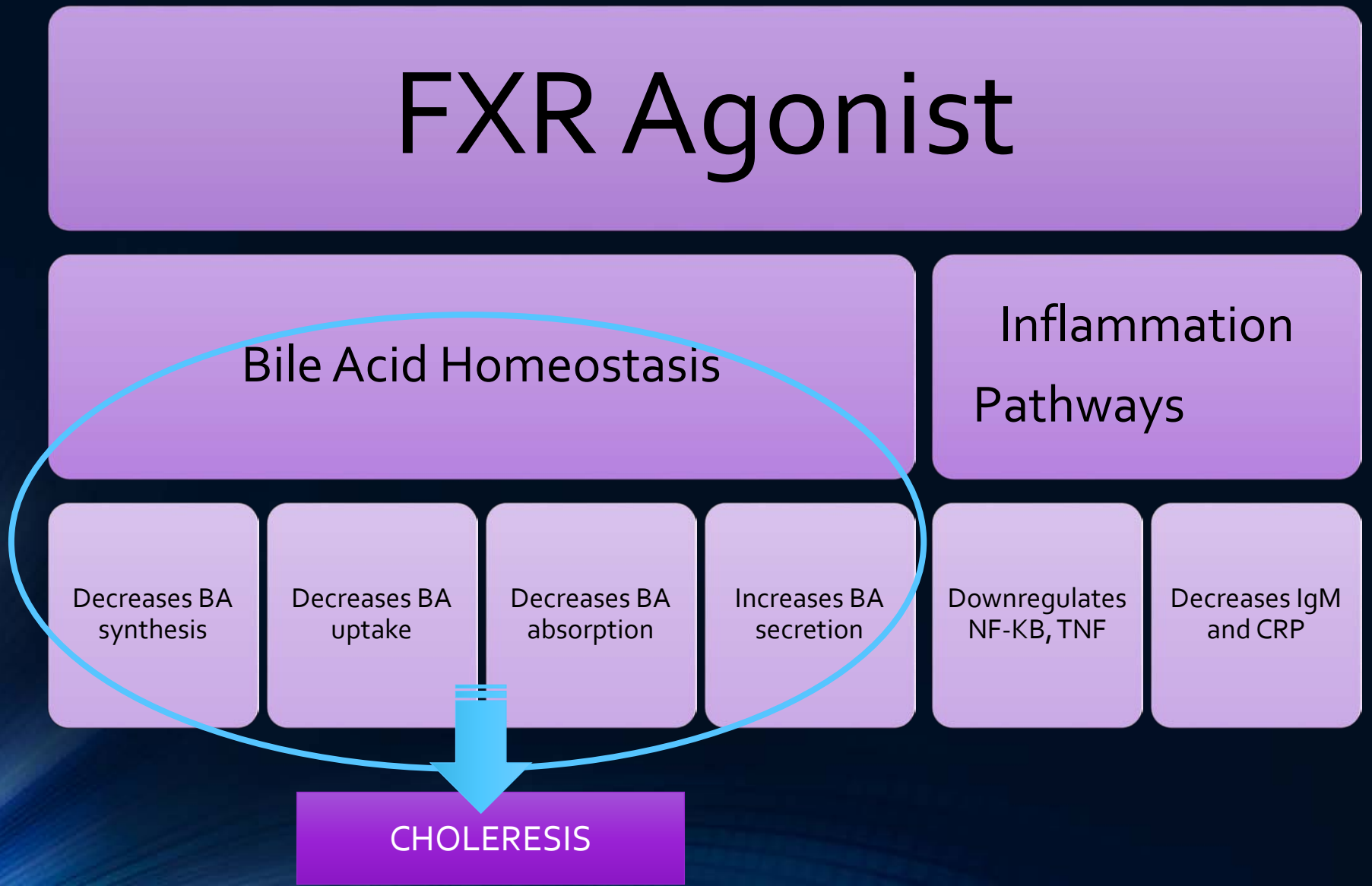
-**LS increase >2.1 kPa/year** associated with 8x increase in risk of adverse outcomes

Corpechot et al Hepatology 2012

GLOBE Score: Online Calculation



Second Line Therapy: Obeticholic Acid



Effects of OCA during POISE trial

- 46% achieved primary endpoint (ALP < 1.67x ULN, greater than 15% drop in ALP and normal TB)
- Significant drop in ALP, AST, ALT, GGT, TB
- Significant reduction in inflammatory markers
- Reduction in HDL-cholesterol (20% in 10mg/day, 9% in 5-10 mg/day)
- No change in liver stiffness scores (50% had LS measured)
- Significant reduction in serum bile acid levels and increase in FGF 19 levels

Nevens F et al. NEJM 2016

Adverse Events in POISE and Open-Label Extension

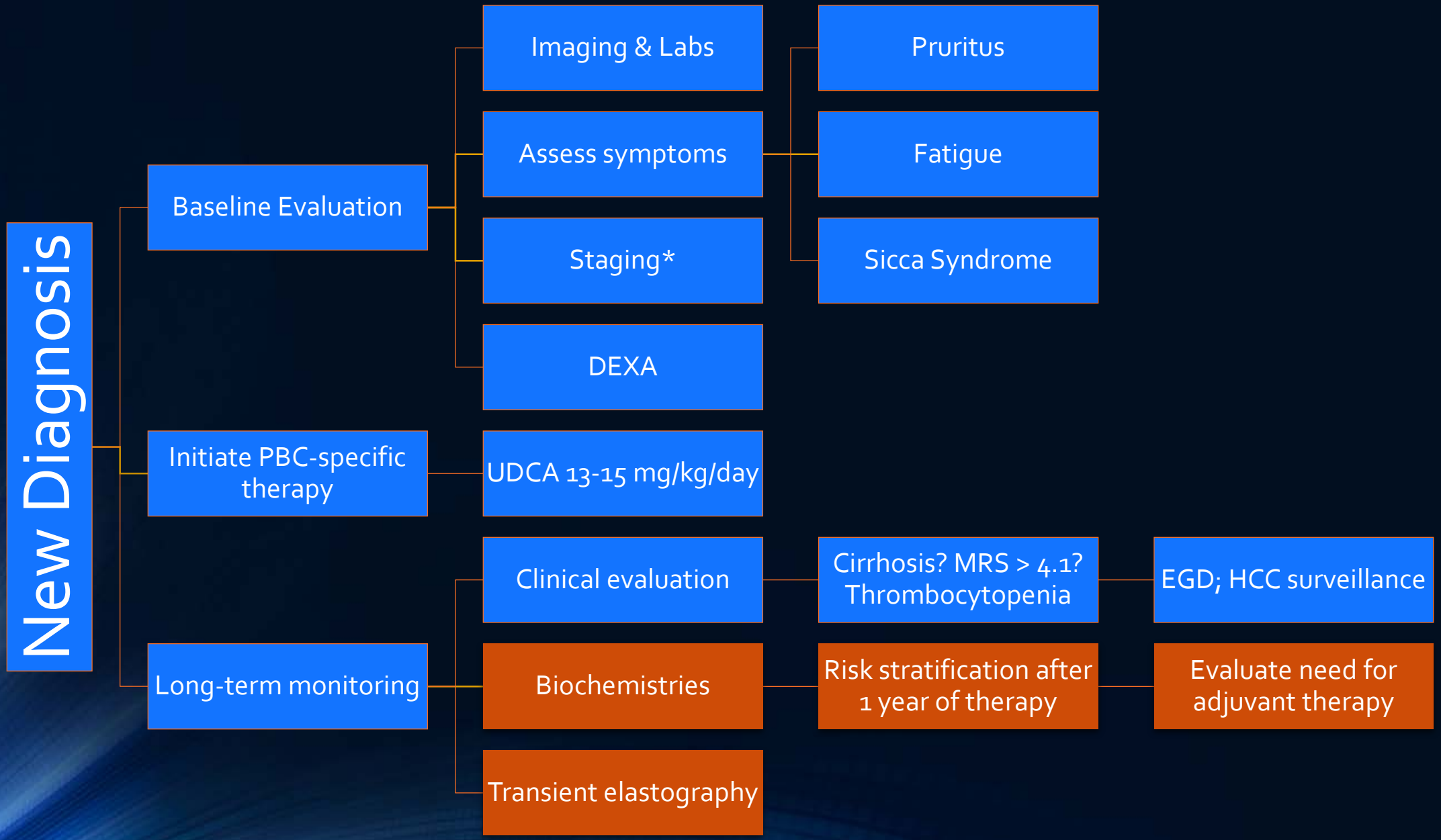
Event	Placebo (N=73)	OCA 5 -10 mg (N=70)	OCA 10 mg (N=73)	Open Label (N=193)
Pruritus	28 (38)	39 (56)	50 (68)	138 (72)
Nasopharingitis	13 (18)	17 (24)	13 (18)	45 (23)
Headache	13 (18)	12 (17)	6 (8)	36 (19)
Fatigue	10 (14)	11 (16)	17 (23)	50 (26)
Nausea	9 (12)	4 (6)	8 (11)	28 (15)
SAE	3 (4)	11 (16)	8 (11)	27 (14)

Modified from Nevens F et al. N Engl J Med 2016;375:631-643.

Overall Findings

- The effect of OCA was consistent independent of age at diagnosis, duration of PBC and baseline ALP.
- Titration from 5 to 10 mg based on clinical response improved tolerance, minimized dropouts due to pruritus, and showed comparable efficacy to 10 mg OCA after 1 year.
- *OCA given to individuals with PBC with an inadequate response to or unable to tolerate UDCA produced a significant clinically meaningful improvement in liver biochemistry, which has been shown to correlate strongly with clinical benefit.*

Summary: Updated Management Strategy



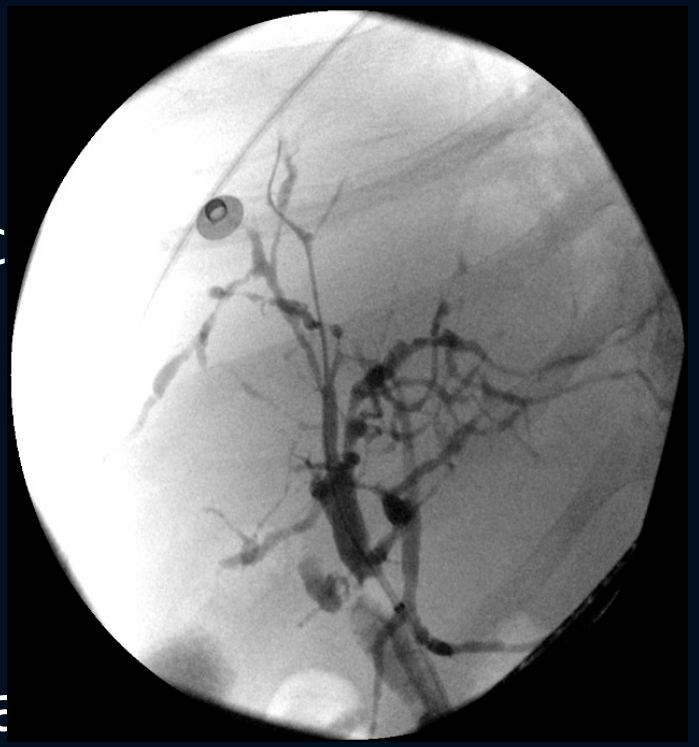
Novel Therapies

Compound	NCT	Mechanism of Action	Status
Bezafibrate Fenofibrate	NCT01654731 NCT02823353	PPAR alpha agonist	Phase 3, Europe Phase 2, China
NGM 282	NCT02026401	FGF 19 analog	Phase 2, has results
LJN452	NCT02516605	FXR agonist	Phase 2, recruiting
MBX-8025	NCT02955602	PPAR delta agonist	Phase 2, recruiting
FFP104	NCT02193360	CD40 Inhibitor	Phase 1/2 - Europe
Abatacept	NCT02078882	Inhibits T cell activation	Phase 4, ongoing
LUM001	NCT01904058	ASBT inhibitor	Phase 2, complete; primary endpoint: itching
GS9674	NCT02943447	FXR agonist	Phase 2, recruiting
GSK 672	NCT02966834	IBAT inhibitor	Phase 2, recruiting; primary endpoint: itching

Primary Sclerosing Cholangitis

Primary Sclerosing Cholangitis

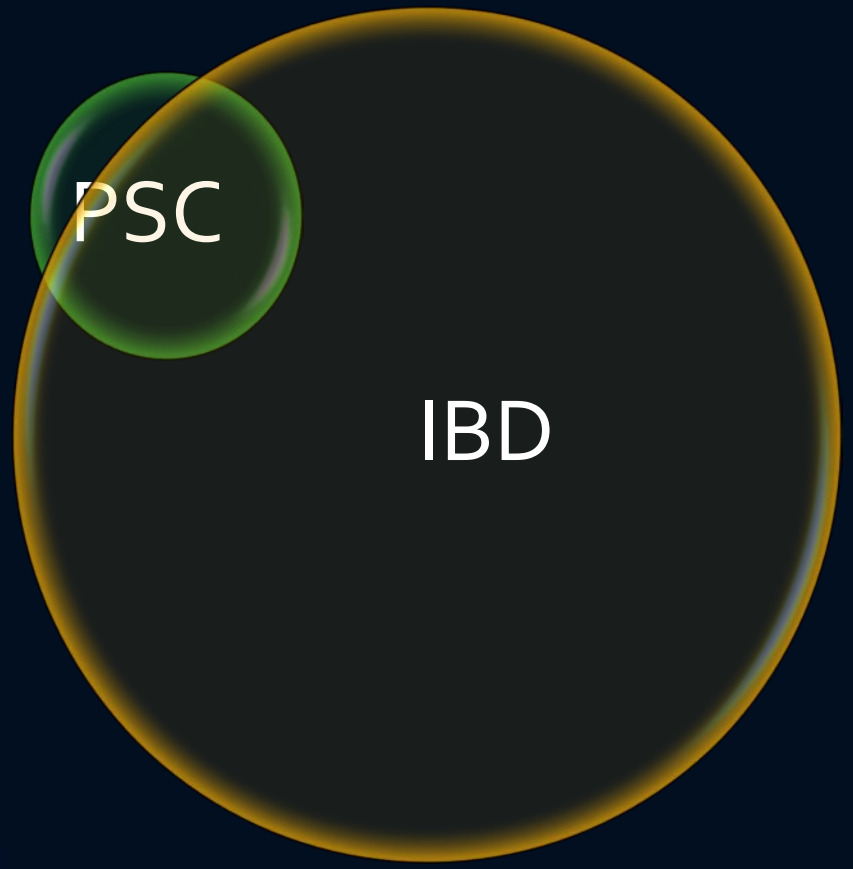
- ✓Chronic cholestatic liver disease
- ✓Characterized by stricturing of intra/extra-hepatic biliary tree
- ✓Variable rate of progression
- ✓Diagnosis of exclusion
- ✓Unclear pathogenesis – genetic and environmenta



Hirschfield GM et al. Lancet 2013

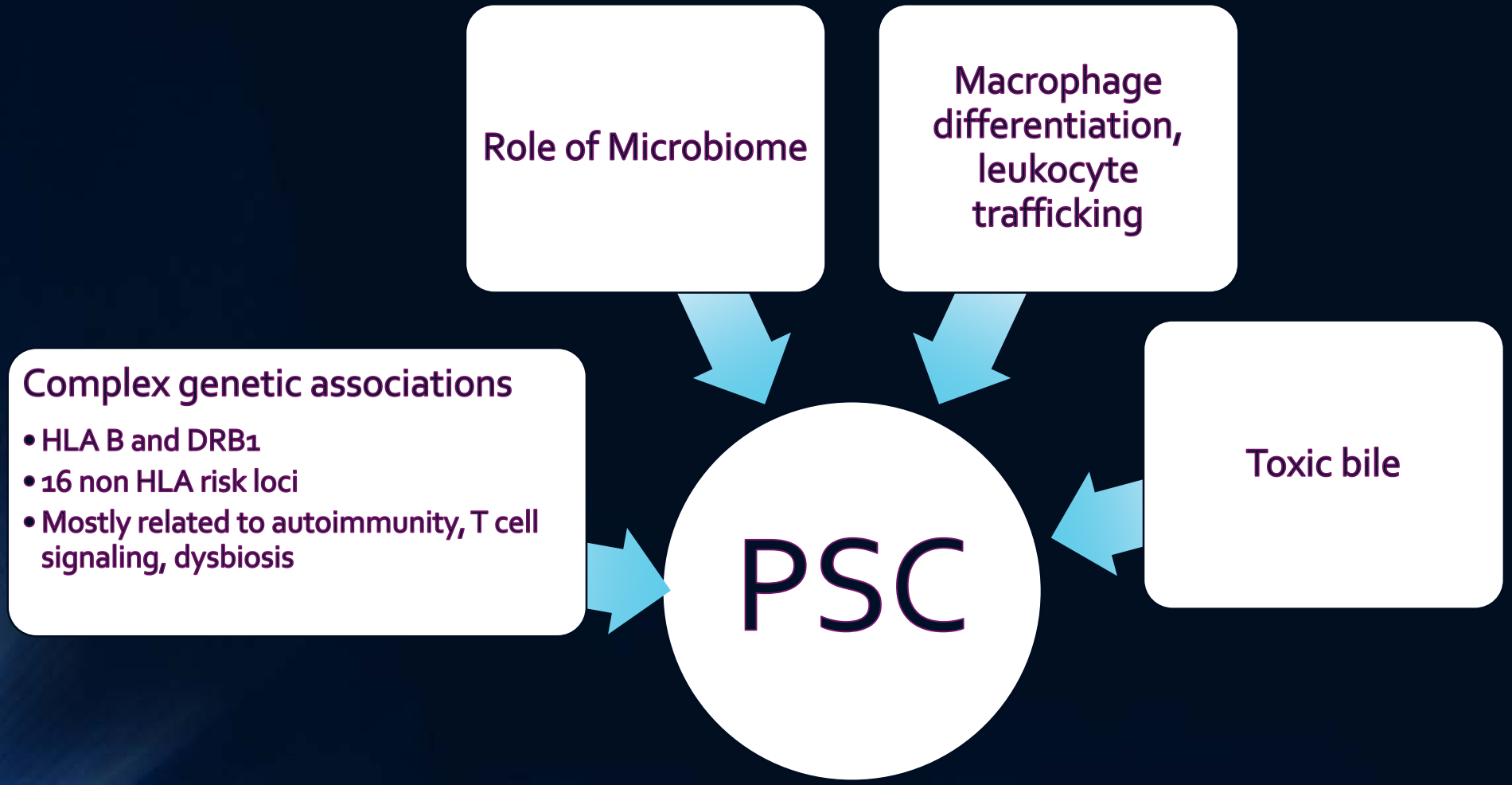
Epidemiology

- ✓Incidence 1-3/100,000
- ✓Prevalence 16/100,000
- ✓60-70% males; Mean age 30-40 yo
- ✓Strong association with inflammatory bowel disease
  - ✓Must refer for colonoscopy with bx at time of dx
- ✓Accounts for roughly 10% of LT/year



Hirschfield et al. Lancet 2013; Olsson R et al. Gastroenterology 1991

Pathogenesis



Polheimer et al. Best Pract Res Clin Gastroent 2011;
Tabibbian et al. Scand J Gastro 2014

Diagnosis

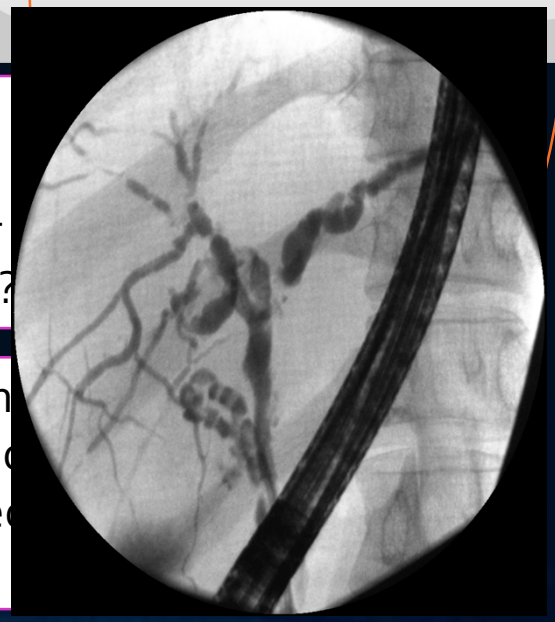
Chronic cholestasis

Multifocal strictures on cholangiogram

Liver biopsy seldom required*

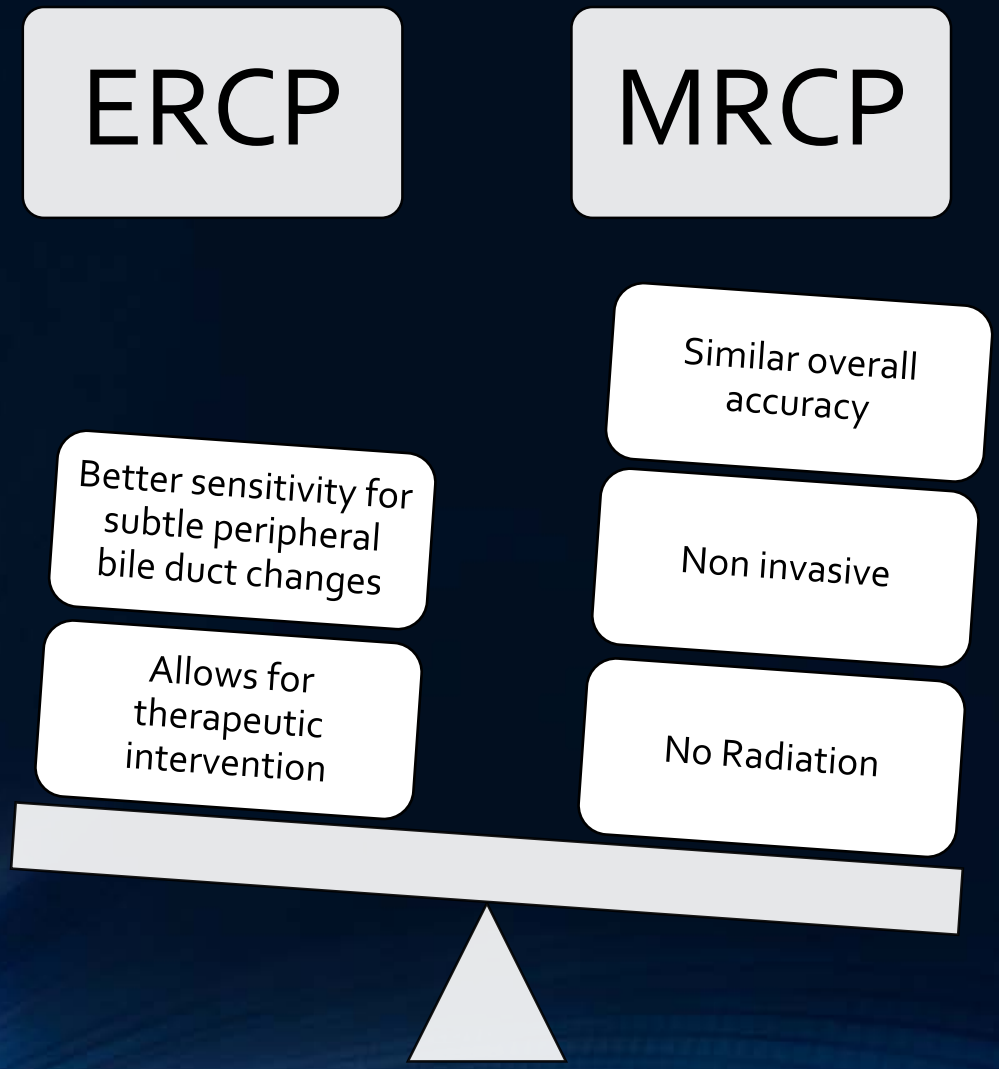
- Asymptomatic
- Pruritus
- Symptoms of advanced liver
- Inflammatory bowel disease?

- Labs: ALP, autoantibodies, h
  high IgM (50%); 10% elevate
- High IgG4 possibly associate
  faster progression



- Small duct PSC
- Overlap cases

MRCP IS THE PREFERRED IMAGING MODALITY



False-Positives
MRCP: cirrhosis

ERCP:
Incomplete biliary distension

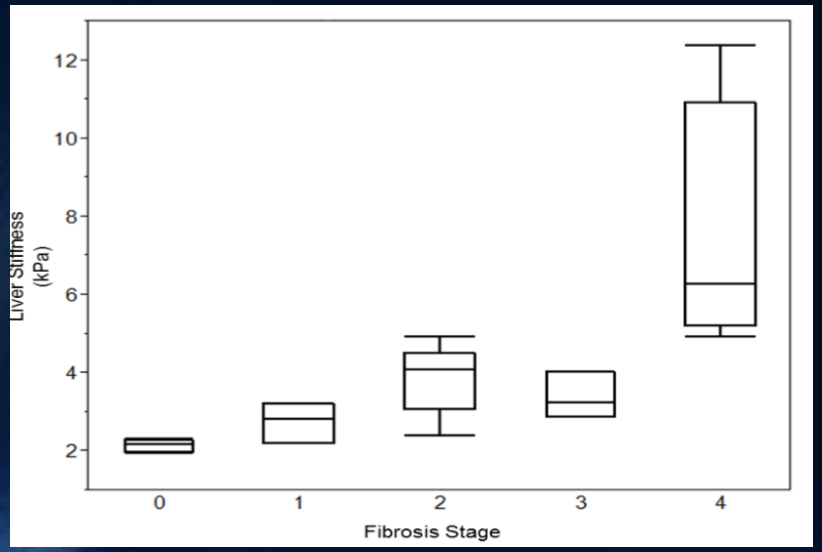
False-Negatives
MRCP: Very mild/early changes

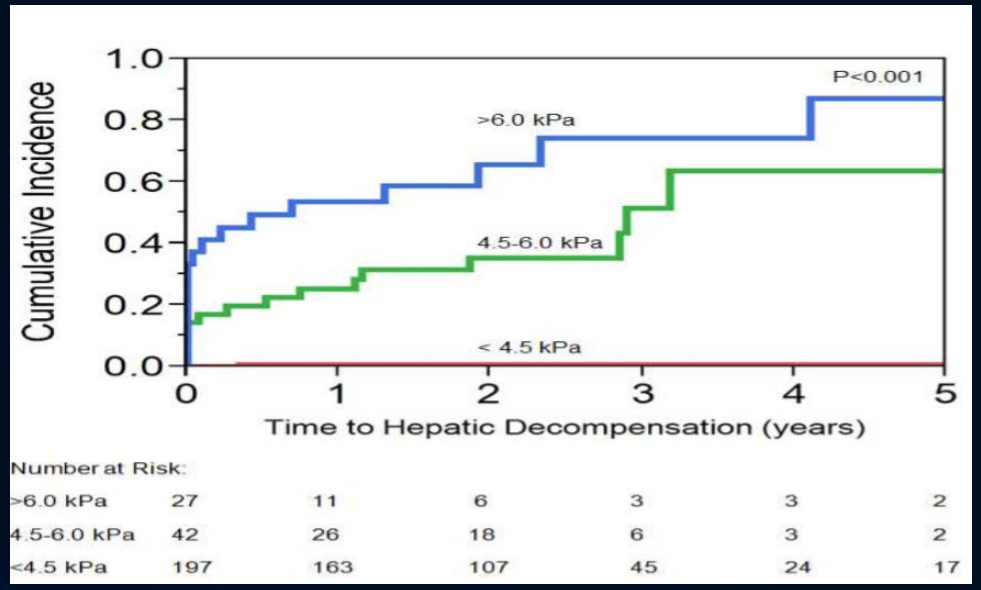
ERCP: High grade strictures

Berstad et al CGH 2006; Talwalkar et al Hepatology 2004

Role of MR Elastography

- Liver Stiffness cut-off 4.93 kPa optimal to detect F4
- Serum ALP < 1.5 x ULN excluded presence of advanced LS
- LS was associated with development of decompensated liver disease (HR 1.55)



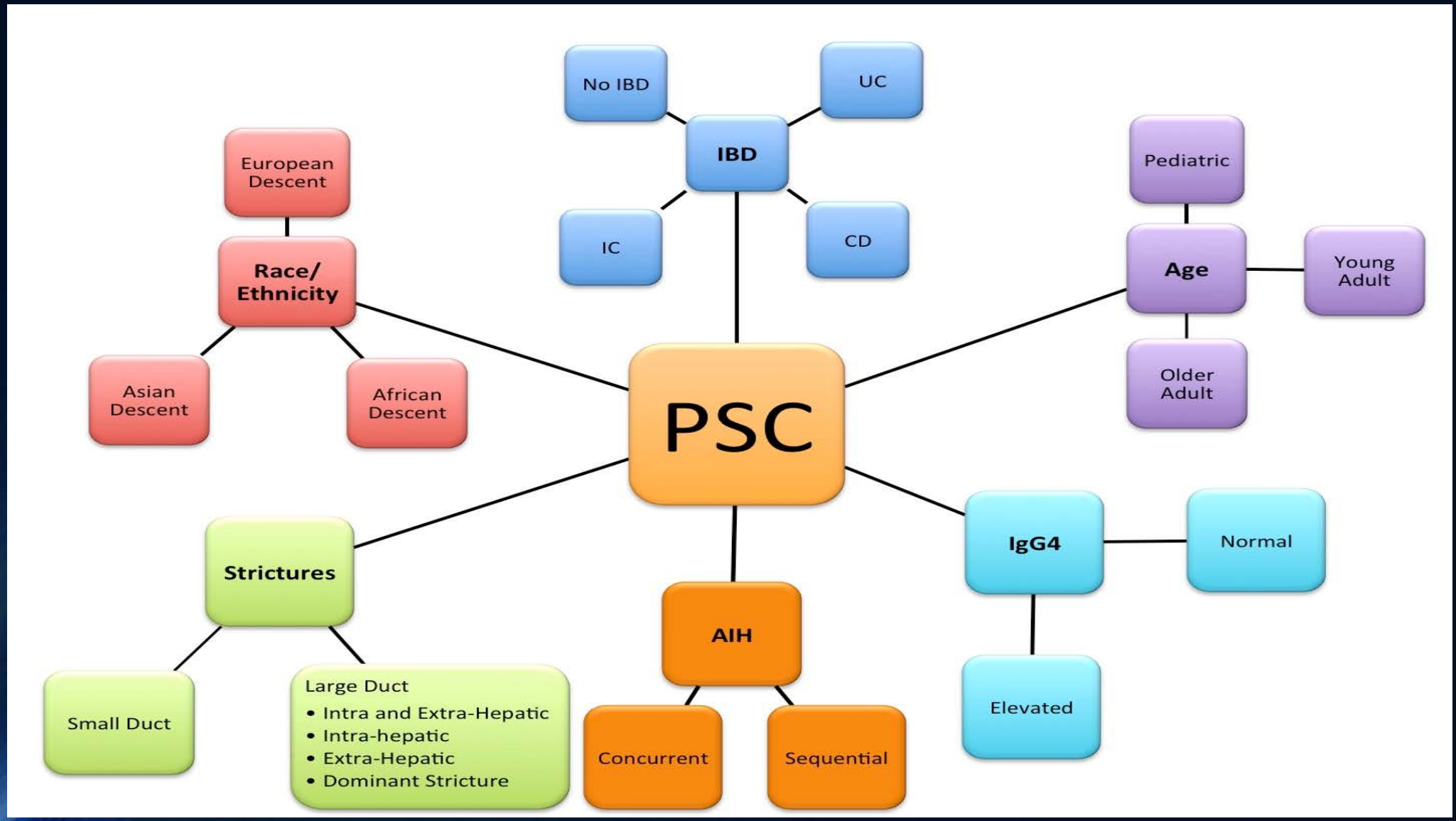


Eaton et al. J Gastroenterol Hepatol Dec 2015 [epub ahead of print]

Differential Diagnosis

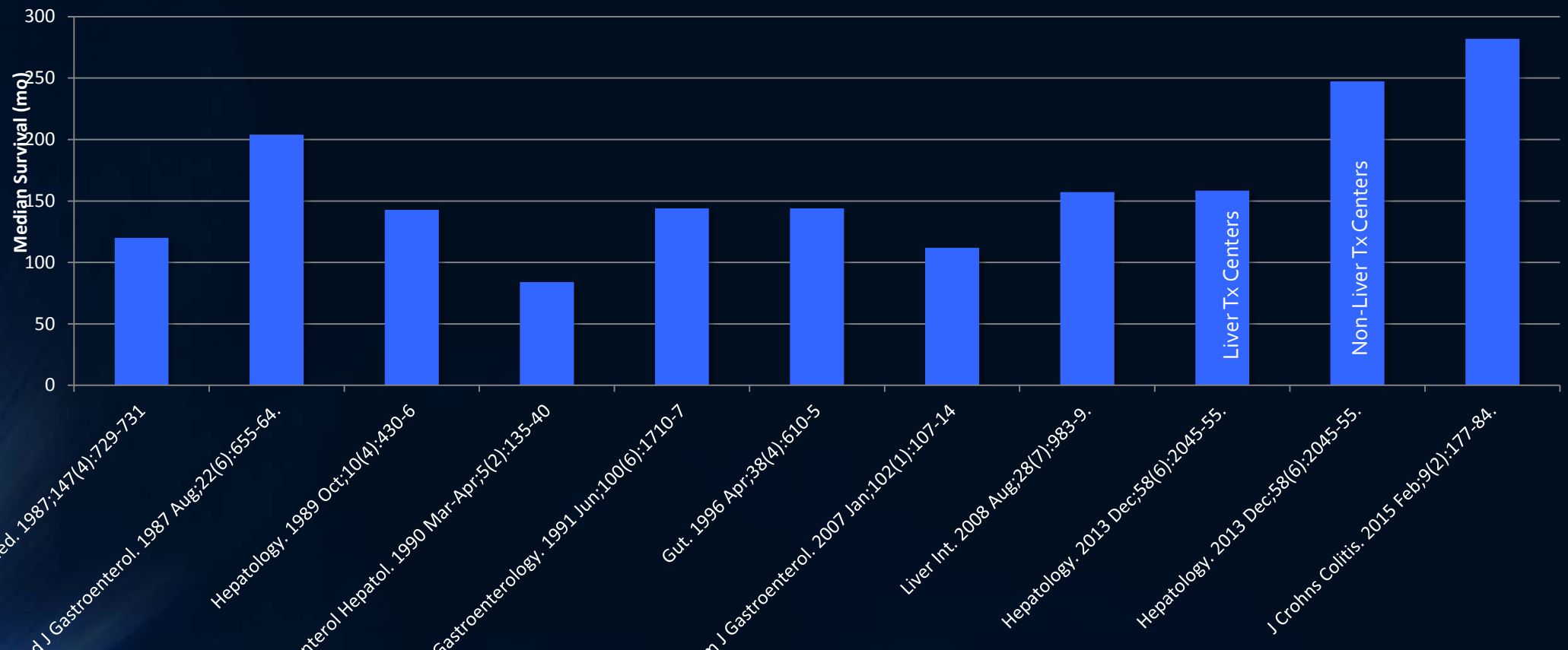
Cholangiocarcinoma
Choledocholithiasis
IgG 4 –related sclerosing cholangitis
AIDS cholangiopathy
Ischemic cholangitis
Portal hypertensive biliopathy
Diffuse intrahepatic metastasis
Surgical biliary trauma
Recurrent pyogenic cholangitis
Recurrent pancreatitis
Sclerosing cholangitis in critically ill
Intra-arterial chemotherapy

PSC Phenotypes



Slide courtesy of Dr Chris Bowlus

TRANSPLANT-FREE SURVIVAL IN PSC



Slides courtesy of Dr Chris Bowlus

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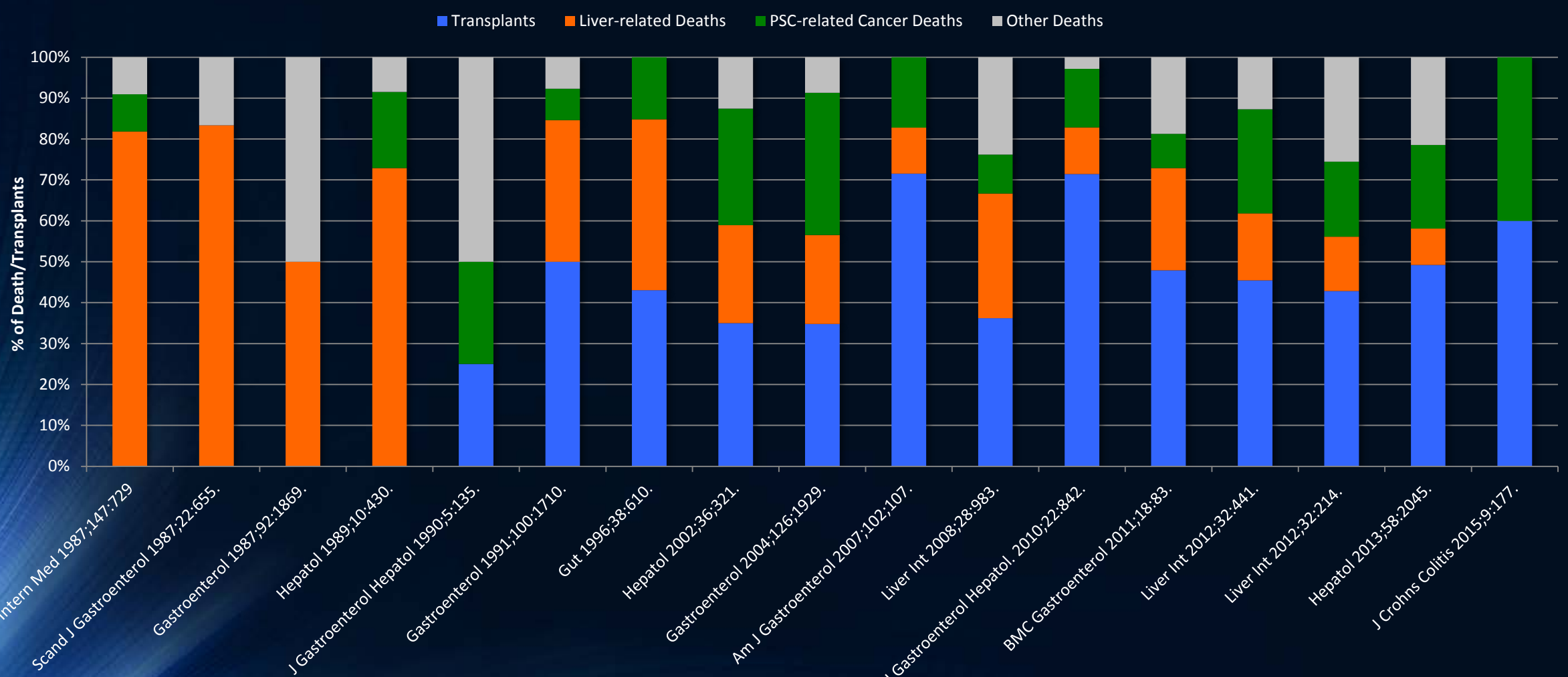
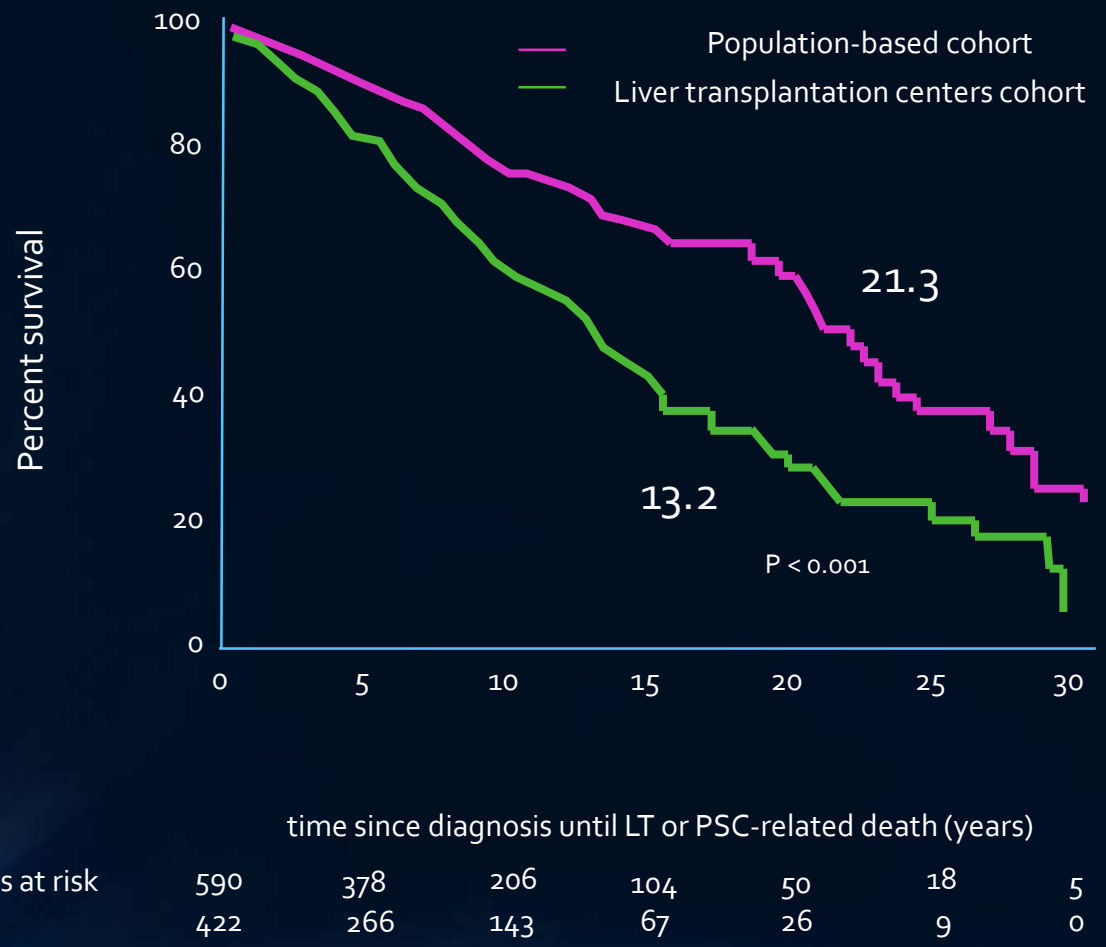


Slide courtesy of Dr Chris Bowlus

Natural History: Survival Without Liver Transplant



Causes of death:

-CCA (32%)
-Liver failure (18%)
-LT-related complications (9%)
-CRC (8%)

Boonstra et al. Hepatology 2013

Medical Therapy

- ✓No established medical therapy

Role of UDCA in PSC

Low dose 13-15 mg/kg/d

- Improves biochemistries
- No change in survival

Median dose 17-23 mg/kg/d

- Improves biochemistries
- Trend towards improved survival
- Study underpowered (n=219)

High dose 25-30 mg/kg/d

- Increased rates of treatment failure compared to placebo

Lindor KD. NEJM 1997; Mitchell SA et al. Gastroenterology 2001; Harnois et al. Am J Gastroenterol 2001; Olsson R et al. Gastroenterology 2005; Lindor KD et al. Hepatology 2009

High Dose UDCA: Endpoints

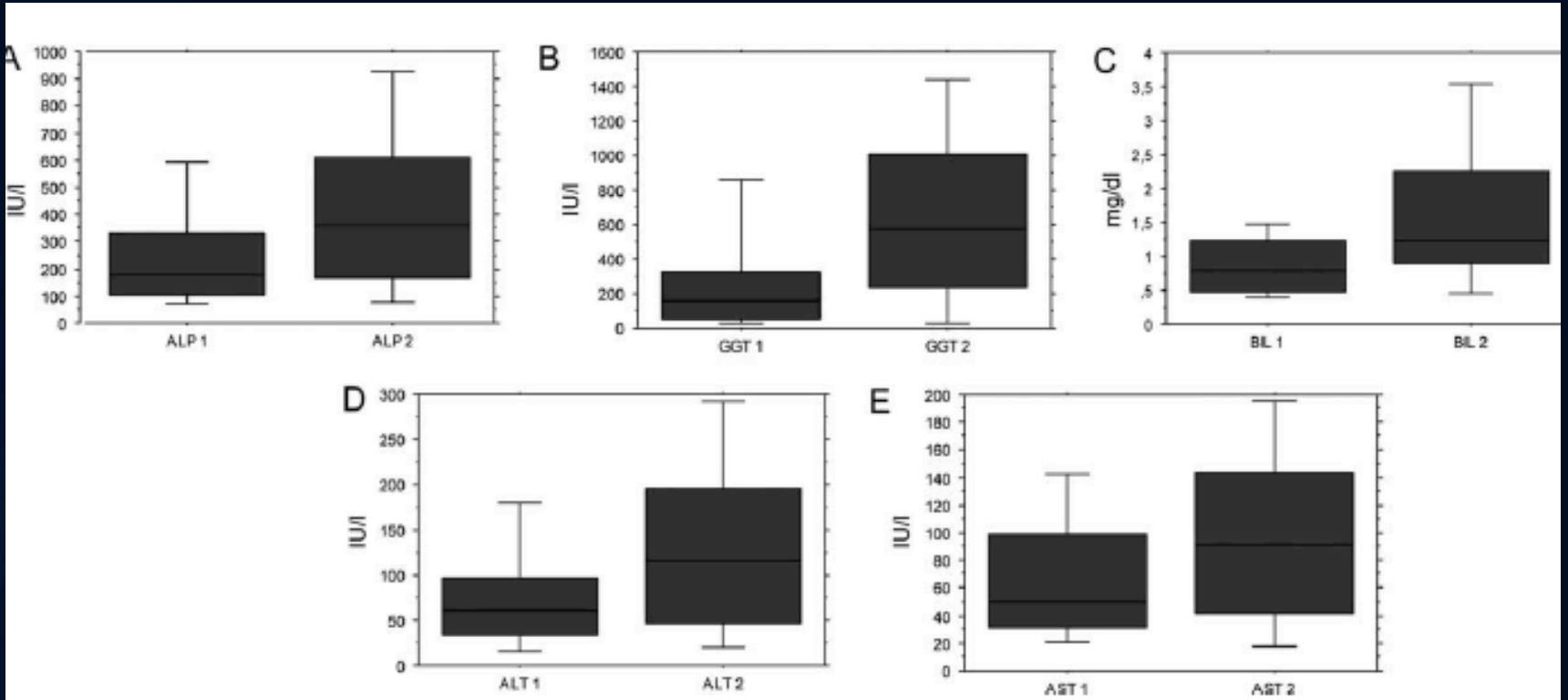
Primary Endpoints	UDCA	Placebo
Death	5	3
Liver transplantation	11	5
Minimal listing criteria	13	10
Development of cirrhosis	6	4
Esophageal /gastric varices	15	5
cholangiocarcinoma	2	2
Total endpoints	52	29
N reaching primary endpoint	30	19
N reaching death, LT, minimal listing criteria	22	15

- Hazard Ratio:
  - Primary endpoint
    - 2.27 (1.24-4.16)
  - Death, LT, minimal listing
    - 2.11 (1.04-4.28)

High dose UDCA was associated with increased risk for colorectal neoplasia in the setting of PSC/IBD

Lindor et al. Hepatology 2009;
Eaton JE et al. Am J Gastro 2011

UDCA discontinuation led to worsening liver chemistries



. 1. Changes in liver biochemistry tests after UDCA withdrawal with respect to (A) ALP, (B) GGT, (C) total bilirubin, (D) ALT, and (E) A
s of individual tests before UDCA withdrawal. 2, Results of individual tests 3 months after UDCA withdrawal.

Wunsch et al. Hepatology 2014;60:931

Prognostic Value of ALP in PSC

Author	Site	ALP measure	% meeting ALP reduction	Outcome
Al Mamari	UK	ALP < 1.5x ULN	40%	6% vs. 48% clinical decompensation or death
Lindstrom	Scandinavia	>40% drop	41%	Improved survival
Stanich	USA	Normalization	40%	14% vs. 33% reached clinical endpoint
Rupp	Germany	ALP < 1.5x ULN (+ all above)	57%	Survival free of LT: 22.6 yrs vs. 16.2 yrs
De Vries	Netherlands	Normalization or reduction of ALP to < 1.5xULN		PSC related death Liver transplantation Cholangiocarcinoma

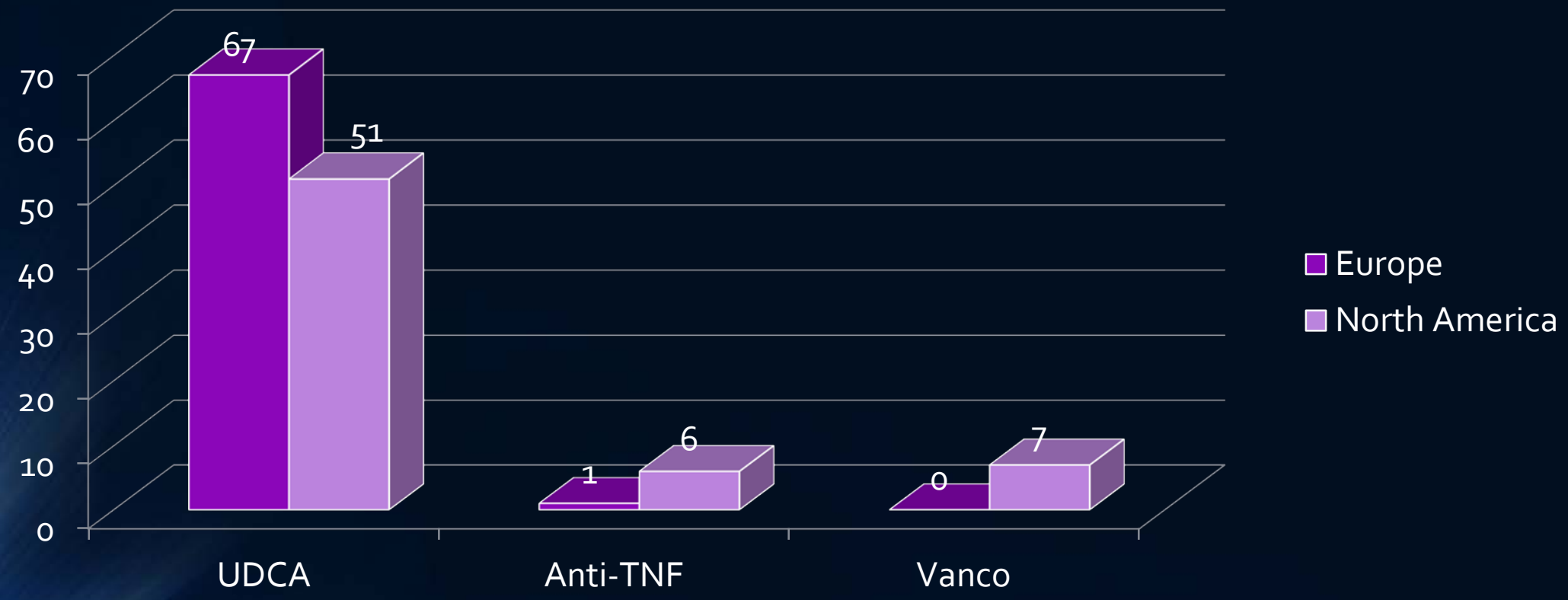
ACG Guidelines PSC

Recommendation for Medical Treatment
UDCA in doses >28 mg/kg/day should not be used for management of PSC

" (…) patients who normalize liver biochemistries (…) have a better prognosis. This has led some to revisit the issue of UDCA treatment for PSC; many practicioners are using a dose of ≈ 20 mg/kg/day although data from well controlled clinical trials are lacking."

Lindor KD et al. AJG 2015

Treatment Practices in PSC

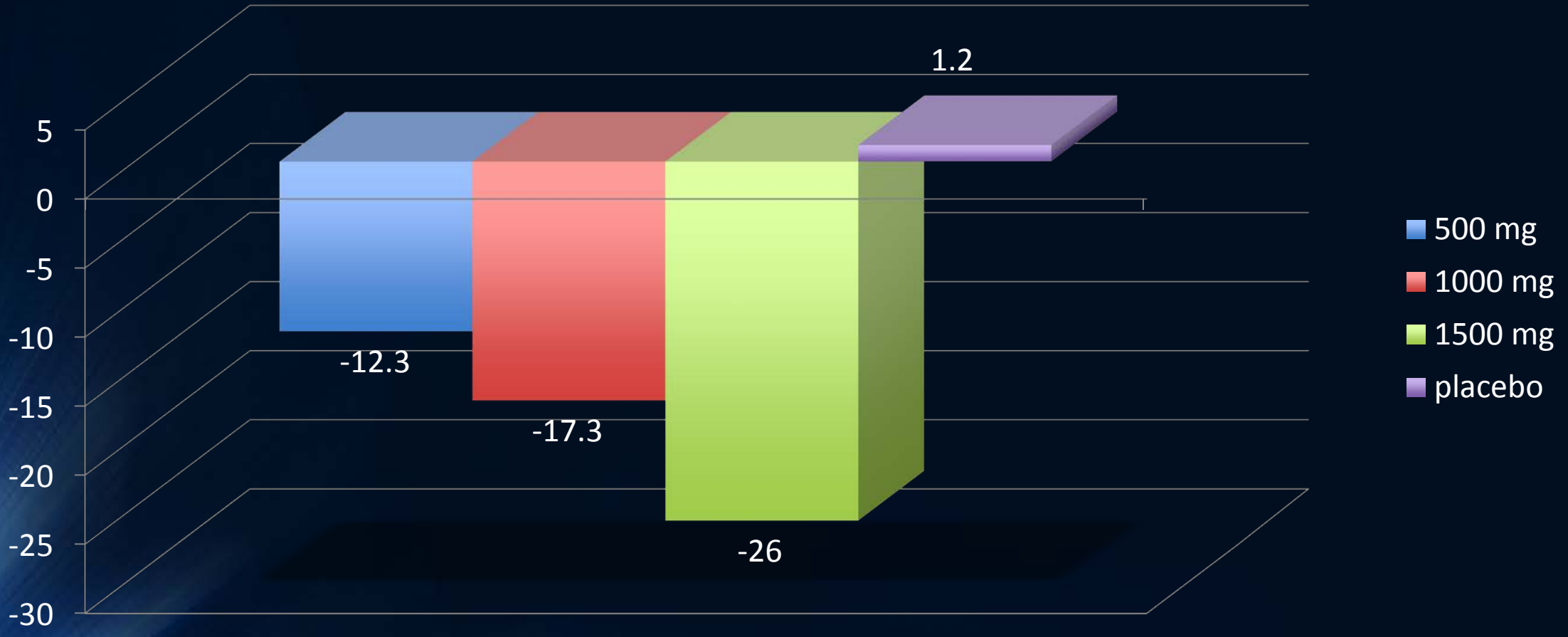


EASL 2016

Drug Development in PSC

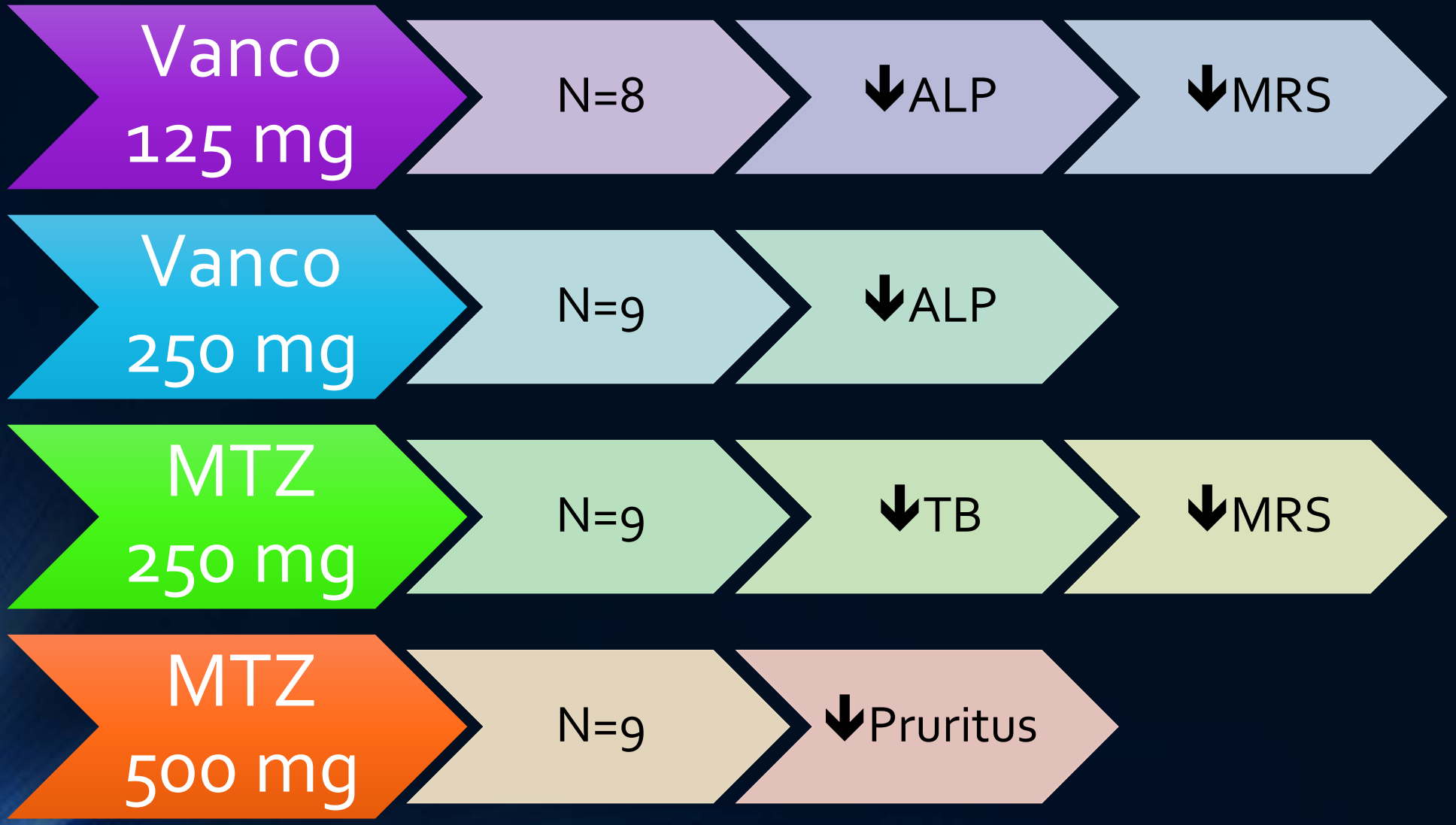
- **Simtuzumab** (Gilead) - LOXL-2 Antibody
- **LUM001** (Shire) – Apical sodium Bile Acid Transporter Inhibitor
- **Obeticholic Acid** (Intercept) – FXR agonist
- **NGM 282** (NGM) – FGF19 Agonist
- **Cenicriviroc** (Tobira) – inhibitor of ligand binding to CCR2- and CCR5-expressing cells
- **Vedolizumab** (Takeda) – Selective anti integrin
- **Nor UDCA** – Bile Acid
- **Vancomycin** – antibiotic, immunomodulatory activity
- **Retinoic Acid**

Nor UDCA: % Change in ALP after 12 weeks (n=159)



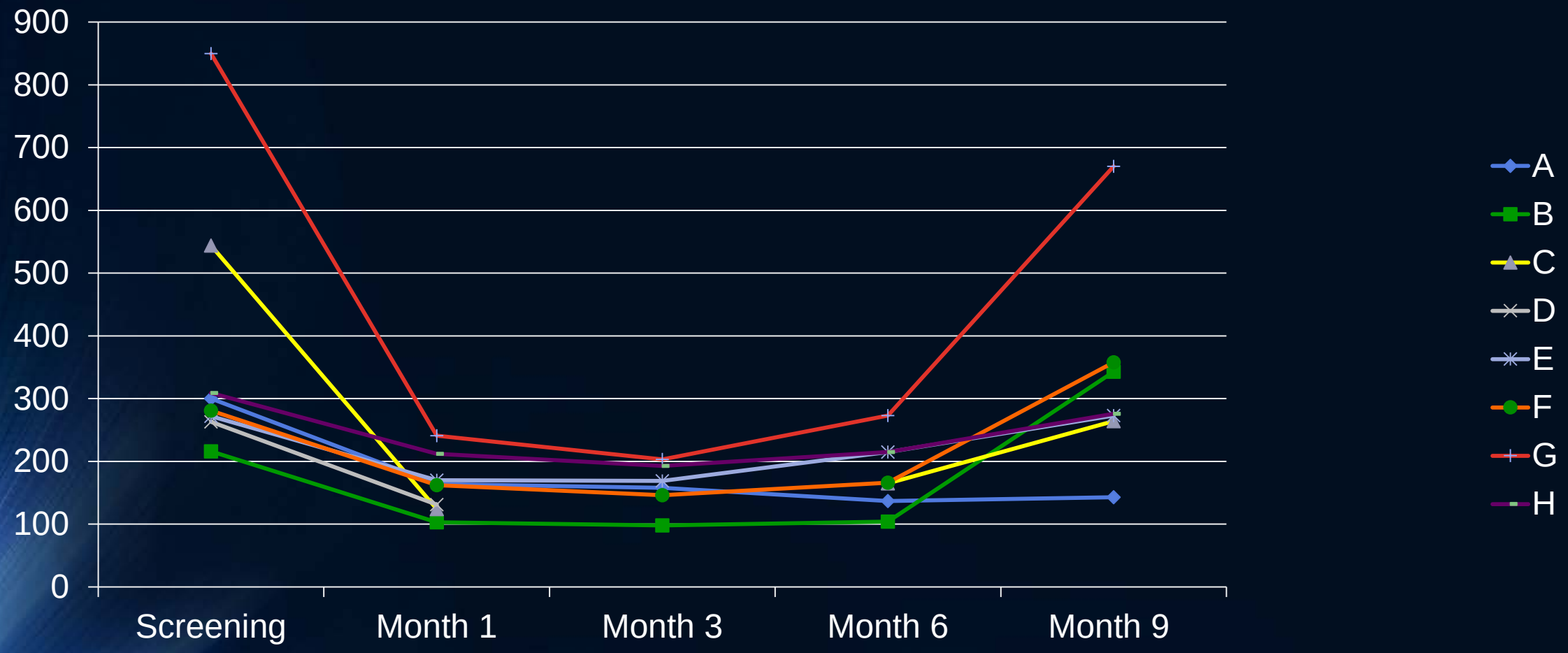
Trauner et al. J Hepatol 2016

Antibiotics



Tabibian et al. AP&T 2013

Fenofibrate – Pilot US data



8 Patients treated with fenofibrate 160 mg/day for 6 months

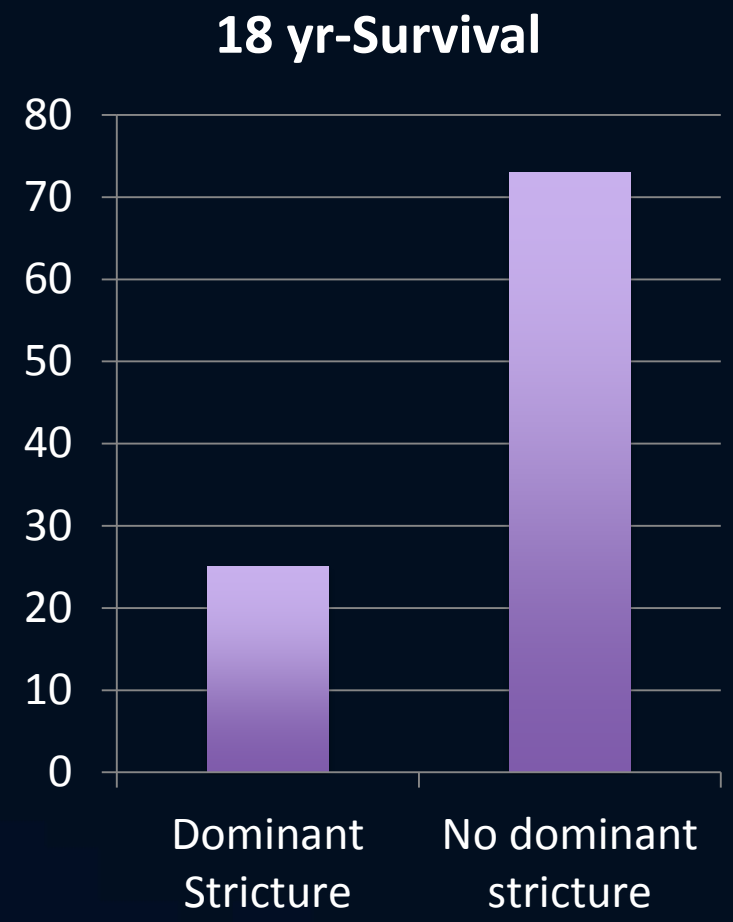
Levy C et al. DDW 2013

Biliary Complications

- Dominant Strictures
- Bacterial cholangitis
- Malignancy _ CCA and GB cancer

Dominant Strictures

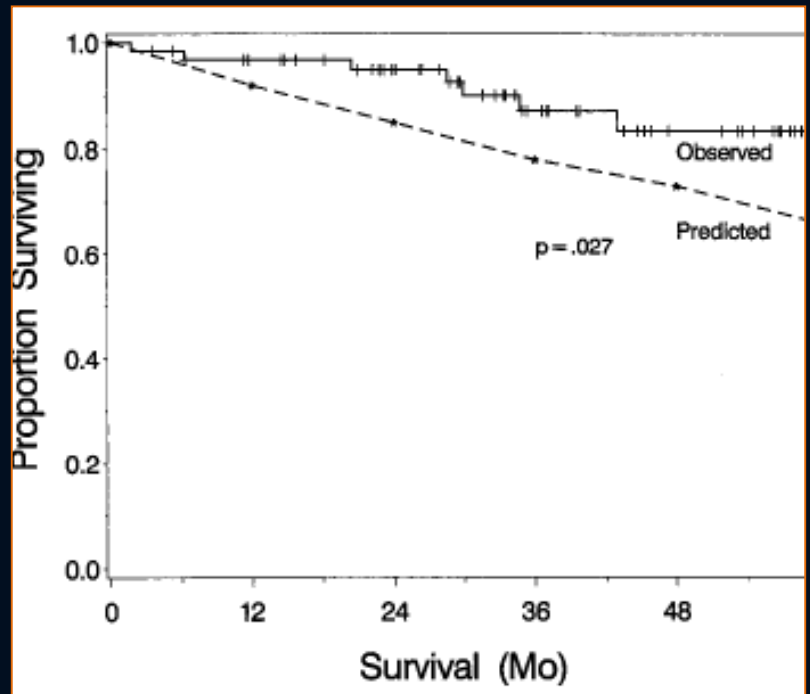
- Stenosis < 1.5 mm in the CBD or < 1mm in he hepatic ducts within 2 cm from bifurcation
- Occur in ≈ 50%
- May cause sudden worsening with jaundice and cholangitis
- More frequently benign, but 22-26% are malignant
- Need to rule out CCA



Culver EL and Chapman R. AP&T 2011; Chapman MH et al. Eur J Gastro & Hepatol 2012; Rudolph et al. J Hepatology 2009; Tischendorf et al. Endoscopy 2006; Lindor KD AJG 2015

Dominant Strictures: Role of endoscopic therapy

- Improvement in jaundice
- Reduced rates of hospitalization
- Radiological improvement of strictures
- Retrospective studies show reduced mortality compared to predicted survival per Mayo Risk Score
  - Dilatation +/- short term stenting preferred



igure 1. Observed and predicted survival of the stu
roup. The 1-, 3-, and 5-year observed survival rates we
7%, 87%, and 83% and the corresponding predicted s
ival rates were 92%, 77%, and 65%, respectively.

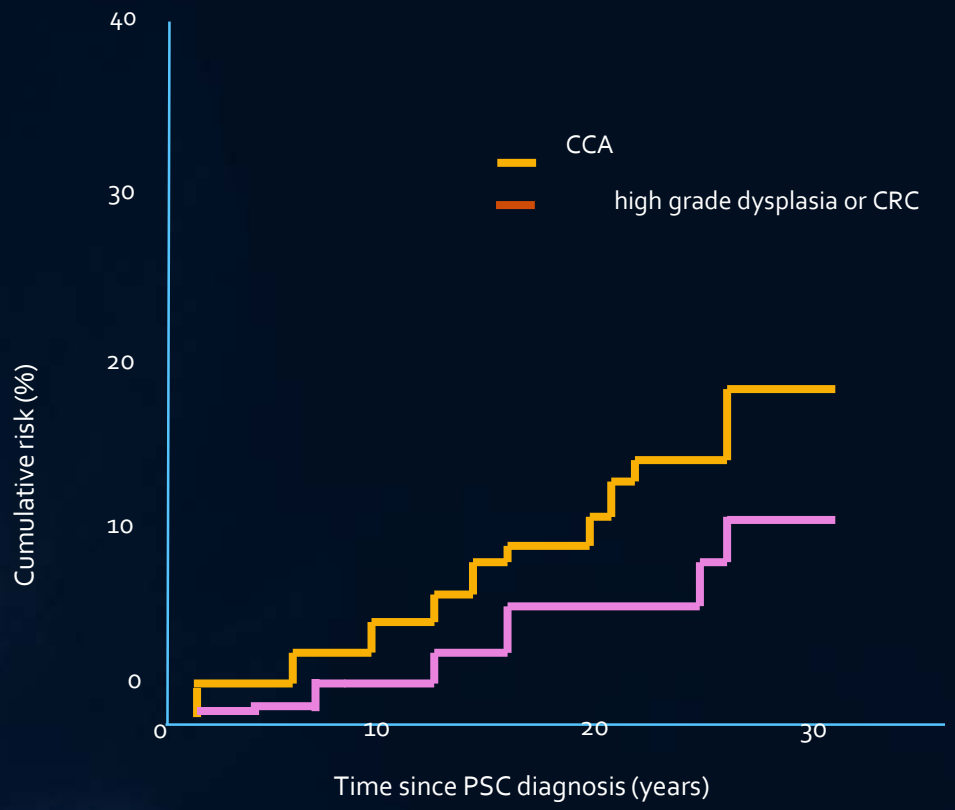
Stiehl A. Semin Liver Dis 2006; Johnson GK et al. GIE 1991; Lee JG et al. Hepatology 1995; Kaya M et al AJG 2001; Balayut et al. GIE 2001; Gluck et al J Clin Gastroent

Bacterial Cholangitis

- ✓ May be the initial presentation of PSC
- ✓ Associated with bacterial colonization of the biliary tree
- ✓ Risk Factors:
  - ✓ dominant strictures
  - ✓ intraductal stones
  - ✓ endoscopic/percutaneous intervention
  - ✓ surgical exploration
- ✓ Often require therapeutic drainage in addition to antibiotics

Culver EL and Chapman R. AP&T 2011

Malignancy Risk



398-fold increased risk of developing CCA

Cumulative risk of CCA and high-grade colon dysplasia or CRC in PSC patients.

Boonstra et al. Hepatology 2013

Cholangiocarcinoma & PSC

- Half of cases are diagnosed in the first year after initial diagnosis of PSC
- Yield of diagnosis can be increased by FISH technique → sensitivity of cytology increases from 30 to 64%
- Serial polysomy associated with 70% PPV
- Value of CA 19-9 is limited
- Other techniques:
  - Cholangioscopy
  - Confocal laser microscopy
  - Intraductal ultrasound
  - Pet CT

Burak K et al. AJG 2004

ACG Guidelines PSC

Endoscopic Management
-ERCP with balloon dilatation is recommended for dominant strictures causing pruritus and/or cholangitis to relieve symptoms
-PSC with dominant stricture seen on imaging should have ERCP with cytology/bx/FISH to exclude cholangiocarcinoma
-PSC patients undergoing ERCP should always receive prophylactic antibiotics
-Routine stenting after dilatation is not required. Short term stenting may be needed for severe stricture

ACG Guidelines - Surveillance

Surveillance Strategies: Hepatobiliary and GB CA
Based on expert opinion, very low quality of evidence
Cross sectional imaging q 6-12 months
Serum CA 19-9 q 6-12 months
Cholecystectomy for polyps > 8 mm

Current guidelines do not support surveillance for cholangiocarcinoma in children

Lindor KD et al. AJG 2015

Risk of Colorectal Neoplasia

- Risk is increased 4-5X compared to IBD alone
- Possible benefit of low dose UDCA in chemoprevention- not enough data
- Annual colonoscopy with bx recommended in PSC/IBD patients

Liver Transplantation

- Definitive treatment for patients with decompensated liver disease
- Considerations for requesting MELD exemption points:
  - >2 episodes of bacterial cholangitis or >1 episode of sepsis
  - CCA < 3cm, no mets, undergoing strict IRB-approved protocol
  - Intractable itching
- 5 yr survival 80-85%
- Recurrence: 20% at 5 years
  - UC post transplant and younger age are risk factors
  - 4x increase in risk of death

Graziadei et al. Hepatology 1999; Fosby et al WJG 2012; Goldberg et al. Am J Transpl 2012; Campsen et al. Liver transplant 2008; Ravikumar et al. J Hepatol 2015

General Management

Condition	Management/Screening
Pruritus	Bile acid resin → rifampin → naltrexone → sertraline
Esophageal varices	Screen if plat <150,000
Osteoporosis	Screen with DEXA at baseline
Fat-soluble vitamin malabsorption	Screen in advanced liver disease

PSC – Key Points

- At diagnosis:
  - Measure IgG4
  - Refer for screening colonoscopy w bx
  - If platelets <150,000 or suspicion for cirrhosis ➔ EGD to r/o varices
  - Use of UDCA should be individualized
- During follow-up:
  - Monitor labs quarterly
  - If IBD: annual colonoscopy w bx
  - Every 6-12 months: Cross- sectional imaging and CA 19-9
- Dominant strictures (initial or symptomatic) ➔ ERCP with brush cytology + FISH.
  - May need dilatation
  - If stents are placed, prefer short duration (<2 wks)
- Clinical decompensation, MELD >14 or suspicion for CCA ➔ refer for Liver Transplant