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MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

Valdecilla Hospital Universitario Marqués de Valdecilla

ASIGNATURA 4:

ENFERMEDADES AUTOINMUNES DEL HÍGADO.

Colangitis esclerosante primaria

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1. Algunos aspectos epidemiología y patogenia

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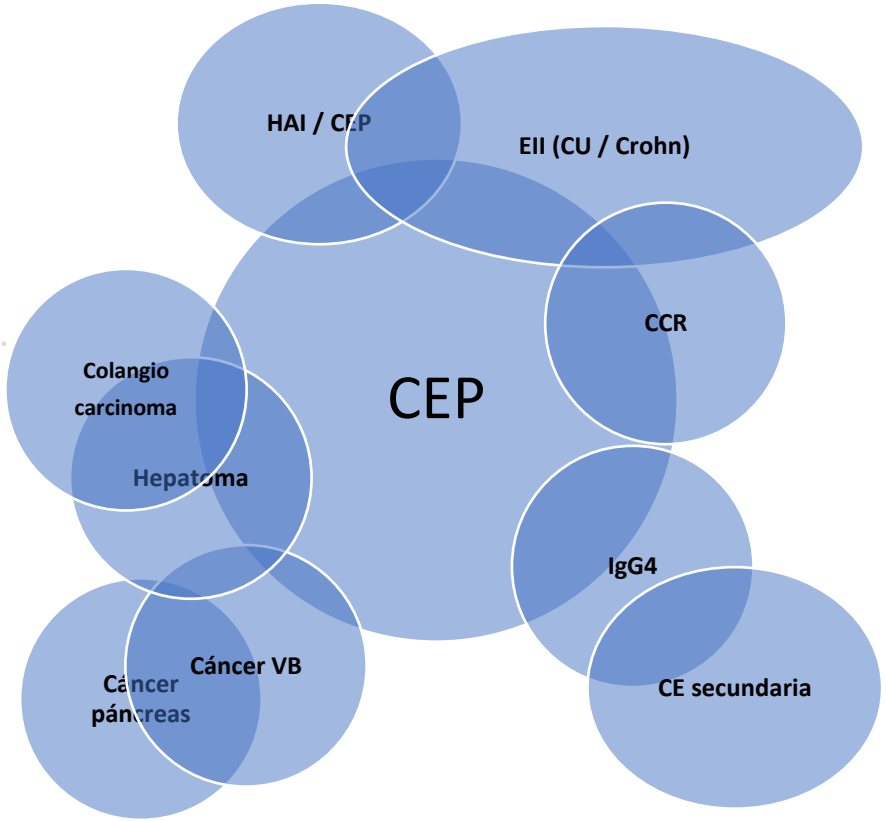
   - Diagnóstico inicial.
   - Descartar CE secundaria.
   - Categorizar adecuadamente la CEP.
   - CEP como enfermedad preneoplásica.
   - Historia natural.

3. Tratamiento de la CEP:

   - Médico.
   - Estenosis dominante.
   - Tx hepático.



Concepto

Sclerosing cholangitis spans several different aetiologies converging on final common pathways leading to a clinicopathologic presentation of fibrosis and strictures of the intraand extrahepatic bile ducts, often with concomitant colestasis and other complications related to bile duct obstruction. When no specific cause of sclerosing cholangitis can be identified, the entity is termed primary.

Table 1. Causes of secondary sclerosing cholangitis.

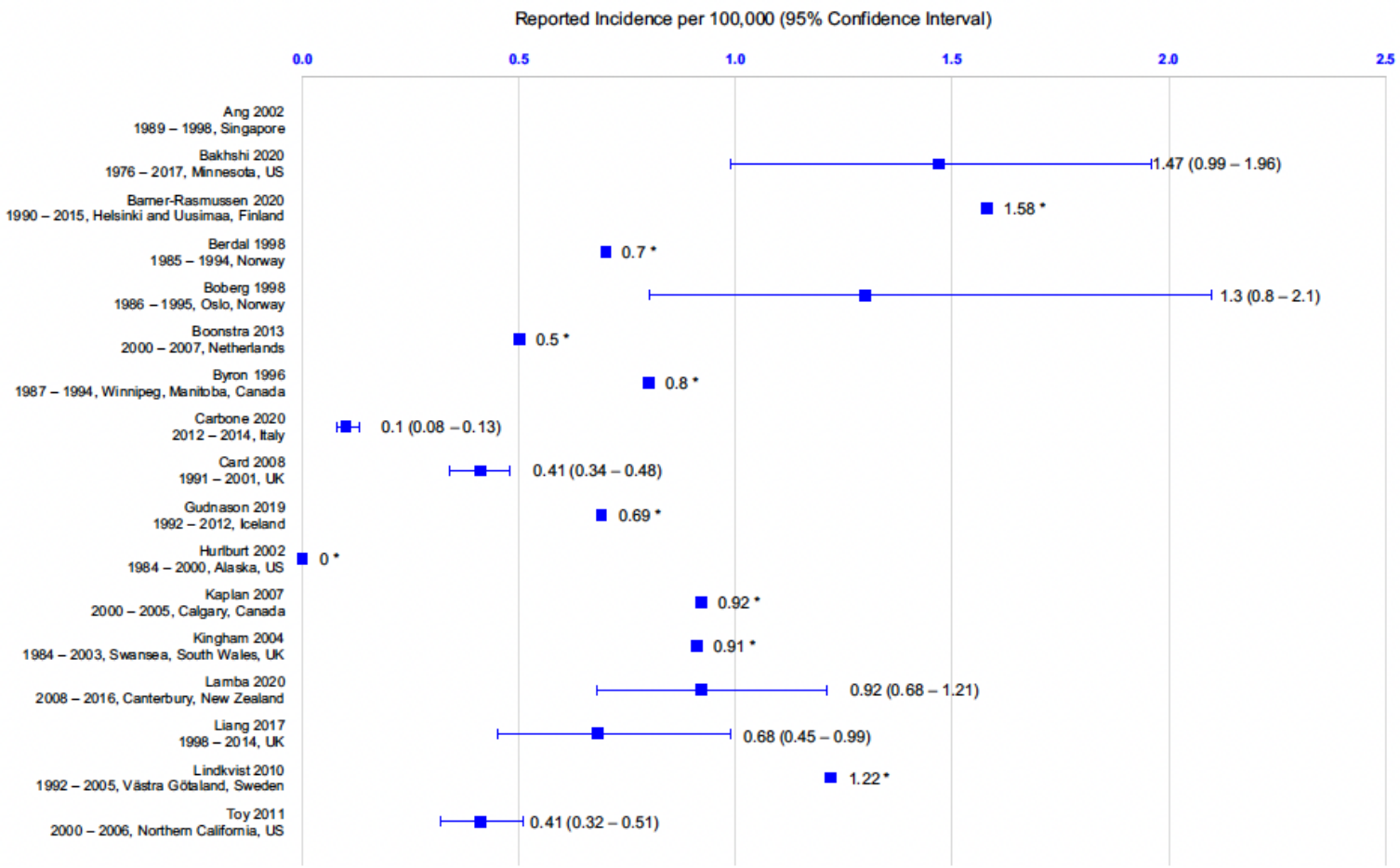
Predominant aetiology of secondary sclerosing cholangitis	Disease
Chronic obstructive	Choledocholithiasis
	Cholangiocarcinoma, other benign and malignant neoplasms
	Portal hypertensive biliopathy
	Surgical trauma (*e.g.*, during cholecystectomy)
	Anastomotic stricture after surgery (*e.g.*, liver transplantation, hepaticojejunostomy)
	Chronic pancreatitis
Immune-mediated	IgG4-related cholangitis
	Hepatic sarcoidosis
	Eosinophilic cholangitis
	Mast cell cholangiopathy
	Hepatic allograft rejection
Infectious	Recurrent pyogenic cholangitis
	Chronic biliary infestation (liver fluke, ascaris)
	Histiocytosis X
	Cryptosporidiosis, microsporidiosis
	Cytomegalovirus
	AIDS-related cholangiopathy
Ischaemic	Non-anastomotic strictures after liver transplantation
	Hepatic artery thrombosis (*e.g.*, after liver transplantation)
	Transarterial chemotherapy / embolisation therapy
	Sclerosing cholangitis of the critically ill patient including COVID-19-related cholangiopathy
	Systemic vasculitis
Hereditary	Cystic fibrosis-associated cholangiopathy
	ABCB4 deficiency (histological)
Toxic	Ketamine

TABLE 2 Etiologies of secondary sclerosing cholangitis

Infectious	HIV-related cholangiopathy Recurrent pyogenic cholangitis Cholangitis lenta or subacute nonsuppurative cholangitis Parasitic cholangiopathy • Hydatid cyst • Echinococcosis • Clonorchiasis and opisthorchiasis • Ascariasis • Fascioliasis • Schistosomiasis
Ischemic	Critically ill patients Hereditary hemorrhagic telangiectasis Intra-arterial chemotherapy Hepatic artery thrombosis
Malignant	Cholangiocarcinoma Diffuse intrahepatic metastasis Langerhans cell histiocytosis Lymphoma
Autoimmune	Eosinophilic cholangitis Hepatic inflammatory pseudotumor IgG4-associated cholangitis Mast cell cholangiopathy Sarcoidosis
Anatomic	Choledocholithiasis Intrahepatic lithiasis Cystic fibrosis liver disease Surgical biliary trauma Anastomotic stricture Portal hypertensive biliopathy Recurrent pancreatitis Sickle cell cholangiopathy Choledochal cyst
Drug-induced	Immunotherapy with checkpoint inhibitors • Pembrolizumab • Nivolumab • Atezolizumab

EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.
Bowlus CL et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023; 77: 659-702.

Incidencia CEP



Trivedi PJ, Bowlus CL, Yimam KK, Razavi H, Estes C. Epidemiology, Natural History, and Outcomes of Primary Sclerosing Cholangitis: A Systematic Review of Population-based Studies. Clin Gastroenterol Hepatol. 2021: S1542-3565(21)00919-8. doi: 10.1016/j.cgh.2021.08.039. Epub ahead of print. PMID: 34474162.

Prevalencia CEP

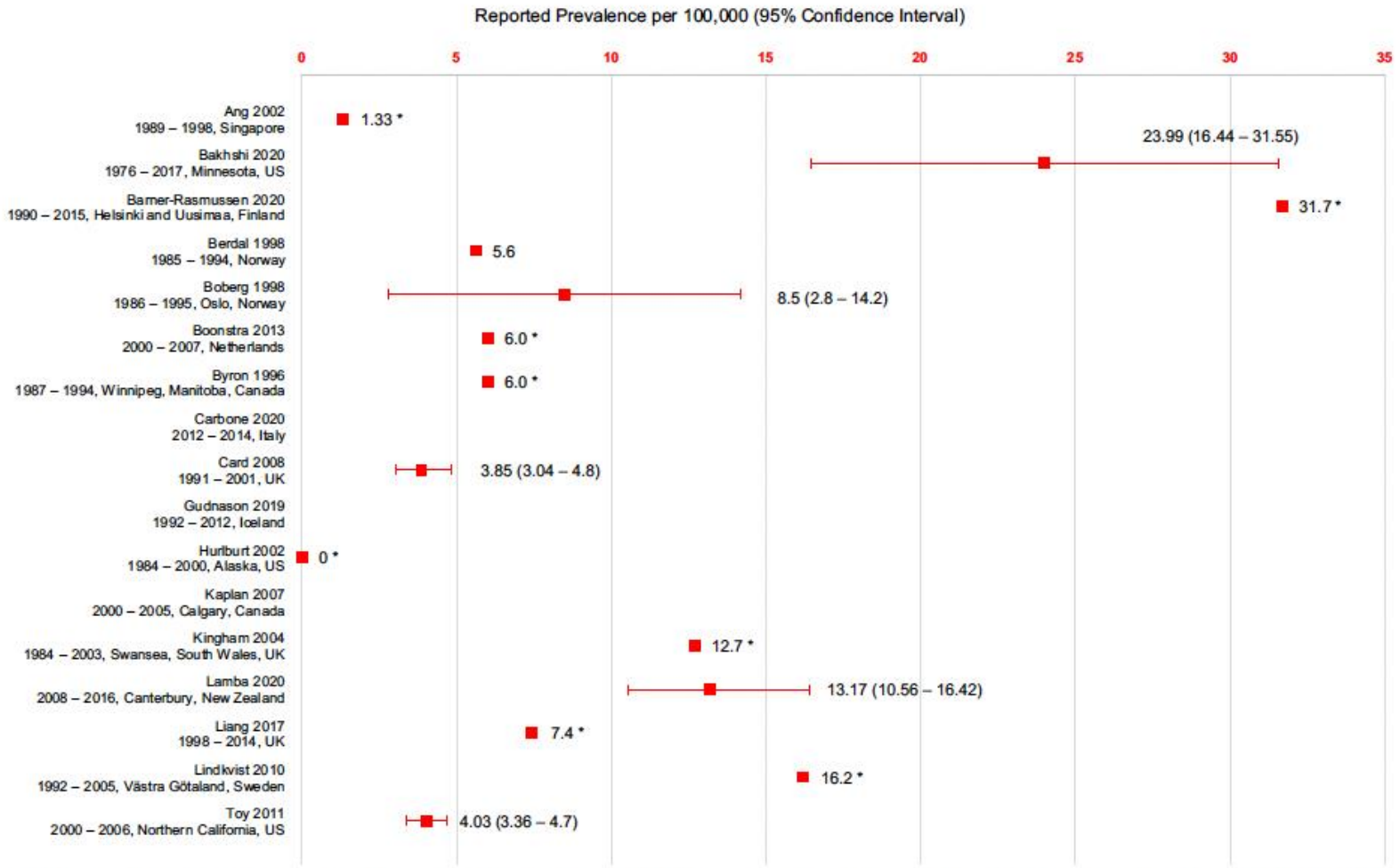
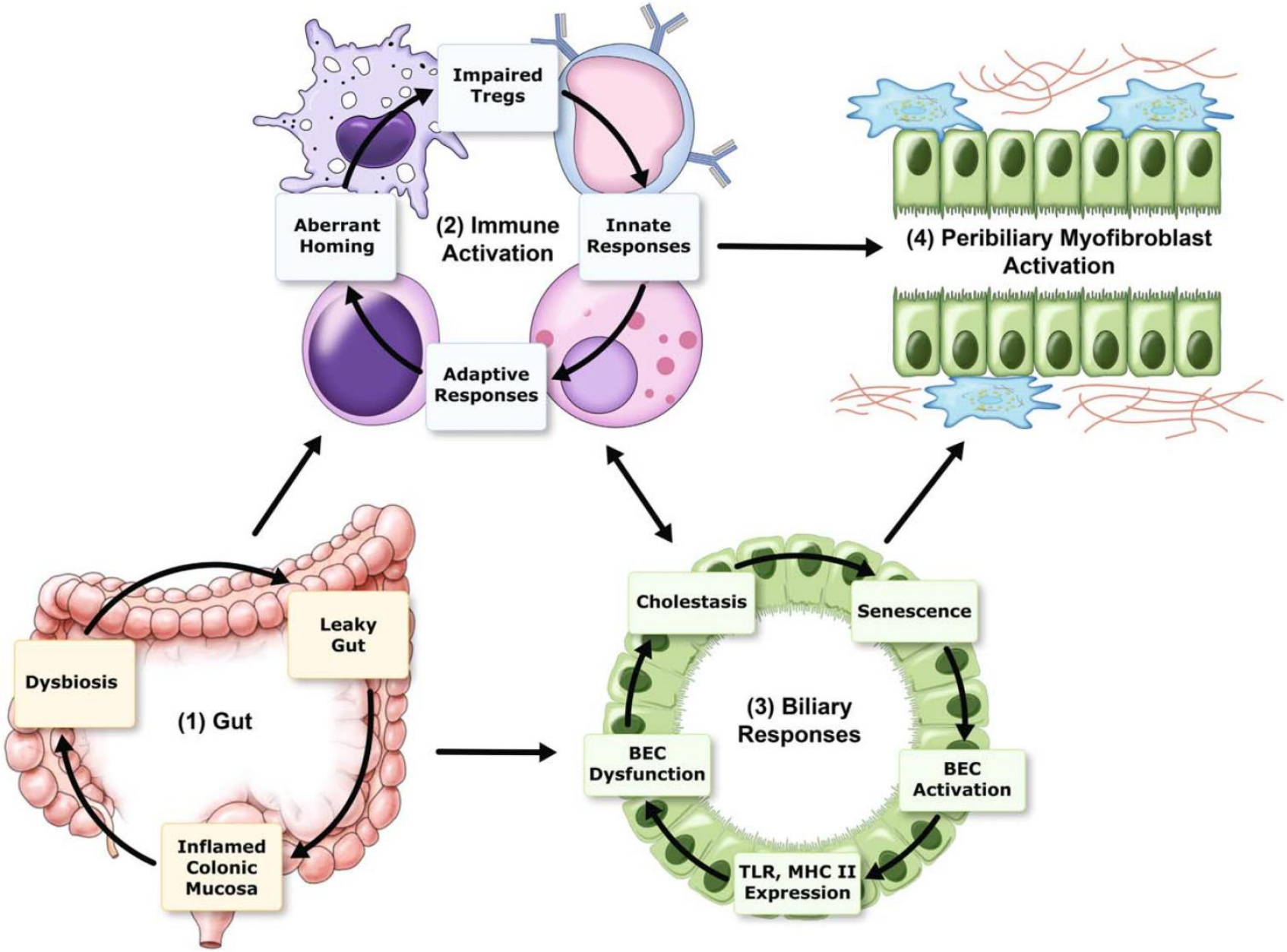


Figure 2. Annual incidence and endpoint prevalence of PSC. Forrest plots indicating the reported mean annual incidence (*A*) and prevalence (*B*) of PSC according to study period and geographical location. Upper and lower bounds indicate the minimum and maximum reported rates. *95% CI not reported.

Trivedi PJ, Bowlus CL, Yimam KK, Razavi H, Estes C. Epidemiology, Natural History, and Outcomes of Primary Sclerosing Cholangitis: A Systematic Review of Population-based Studies. Clin Gastroenterol Hepatol. 2021: S1542-3565(21)00919-8. doi: 10.1016/j.cgh.2021.08.039. Epub ahead of print. PMID: 34474162.



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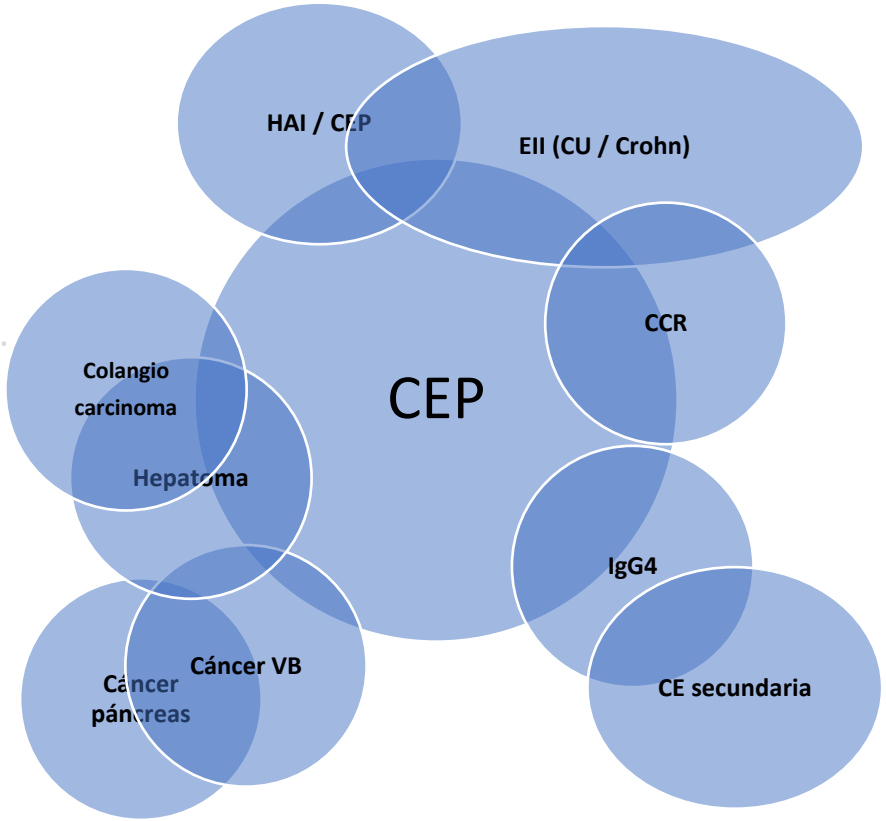
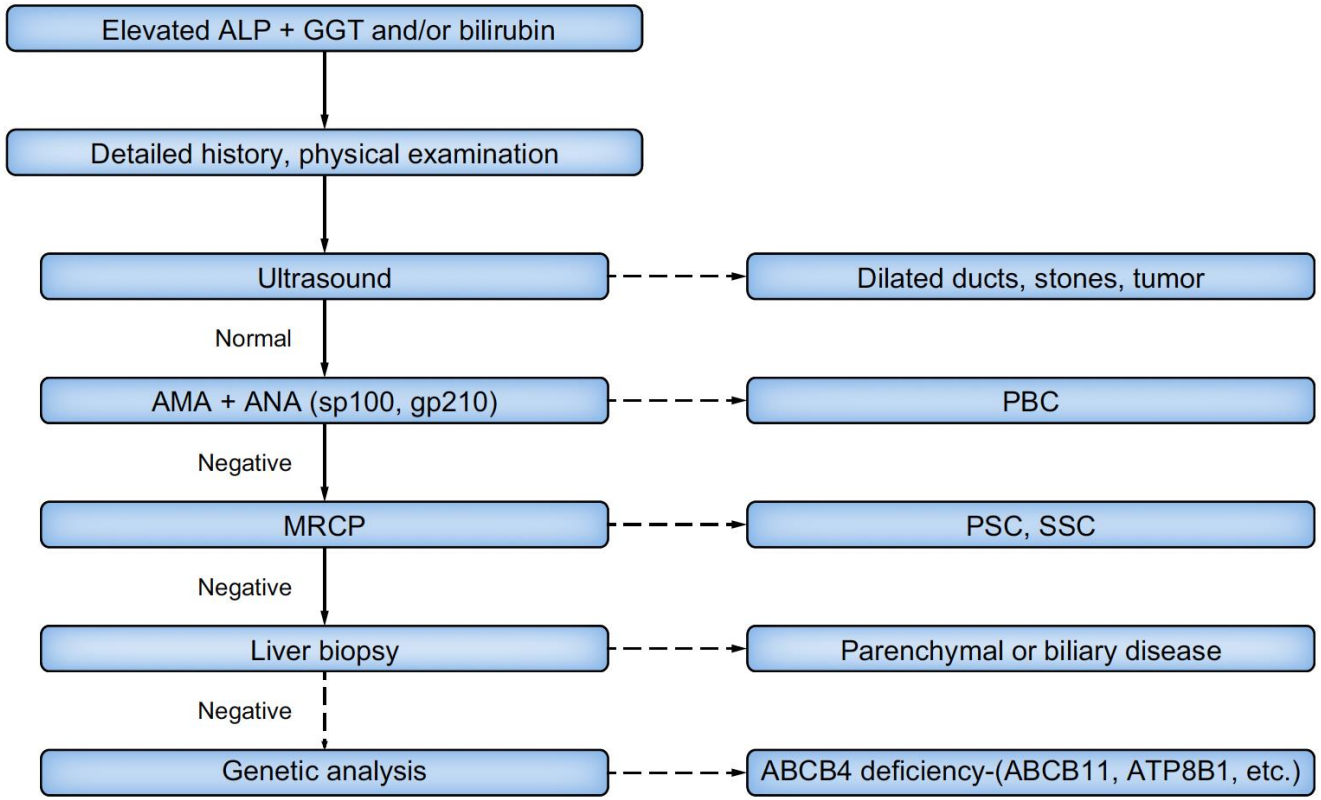


Estrategia diagnóstica CEP



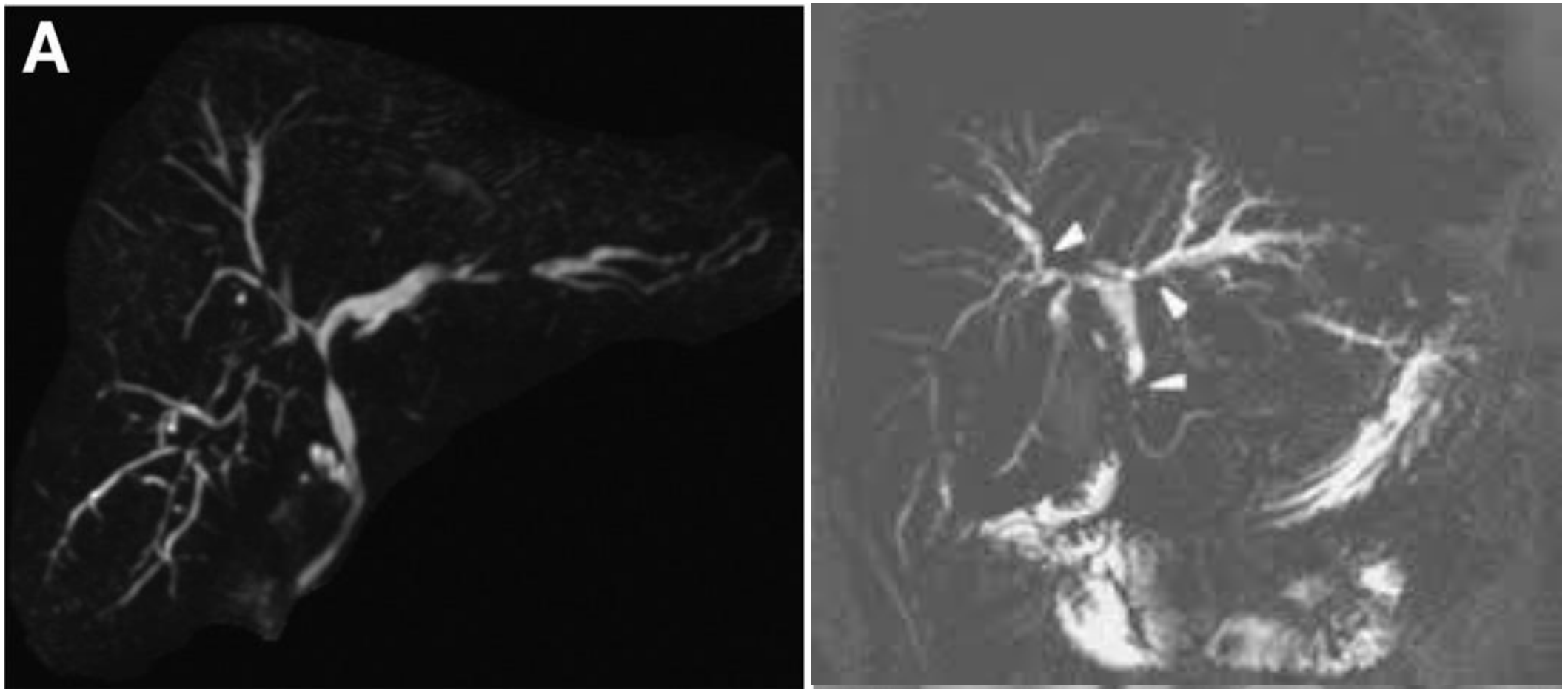
Recommendations

- In adult patients presenting with elevated serum markers of cholestasis, a diagnosis of large duct PSC should be made in the presence of typical findings of sclerosing cholangitis on high-quality cholangiography and after exclusion of secondary causes. The preferred diagnostic test is magnetic resonance cholangiopancreaticography (MRCP) **(LoE 2, strong recommendation, 93% consensus).**
- A diagnosis of small duct PSC should be considered in patients with elevated serum markers of cholestasis of unknown cause, normal high-quality cholangiography, and compatible histology of PSC, particularly in those with concomitant inflammatory bowel disease (IBD) **(LoE 3, strong recommendation, 88% consensus).**
- Autoantibodies should not be used to diagnose or risk-stratify people with PSC **(LoE 4, strong recommendation, 100% consensus).**

EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

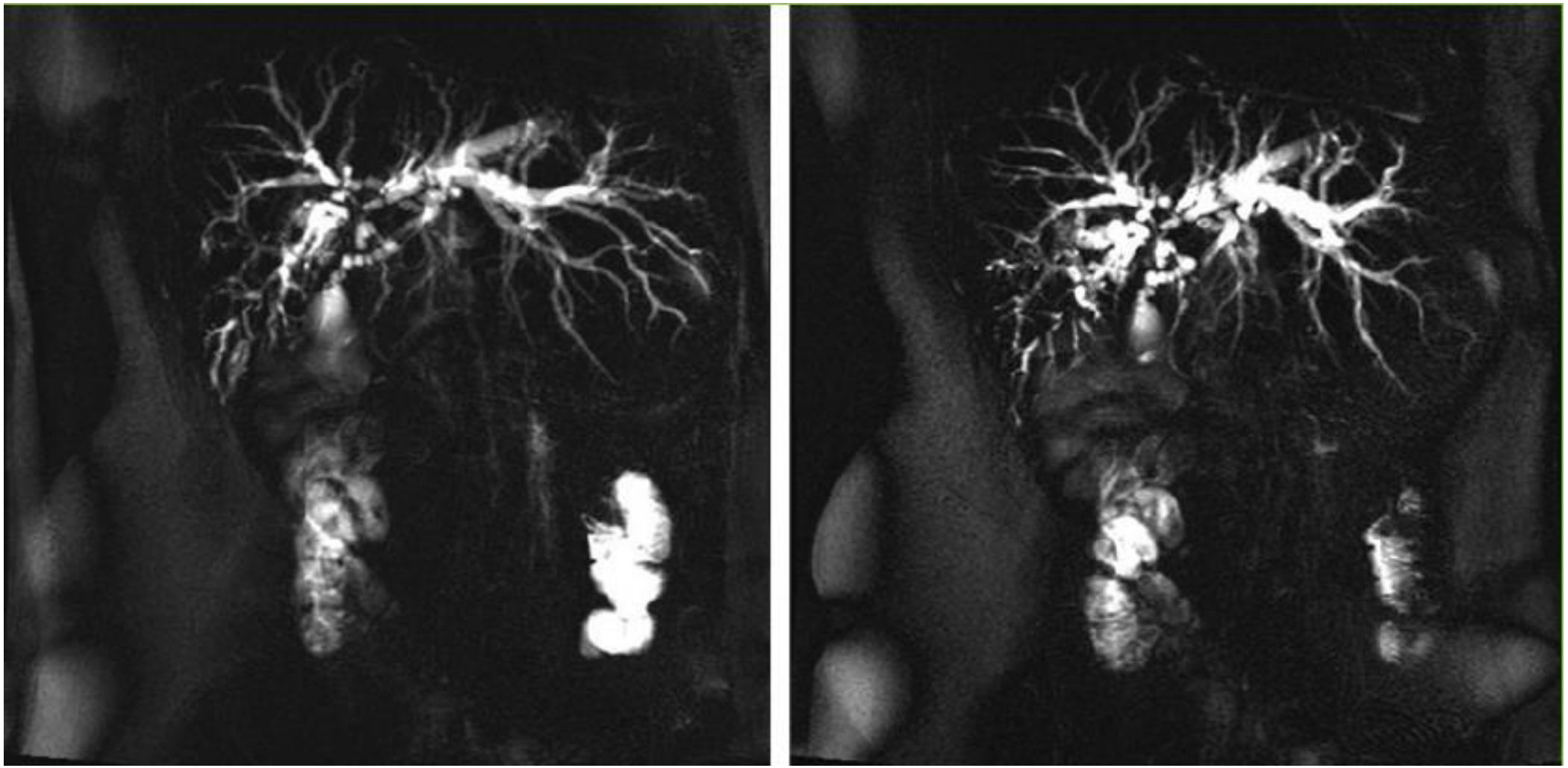
Estrategia diagnóstica CEP

- El diagnóstico inicial de la enfermedad debe basarse en los hallazgos de la RNM

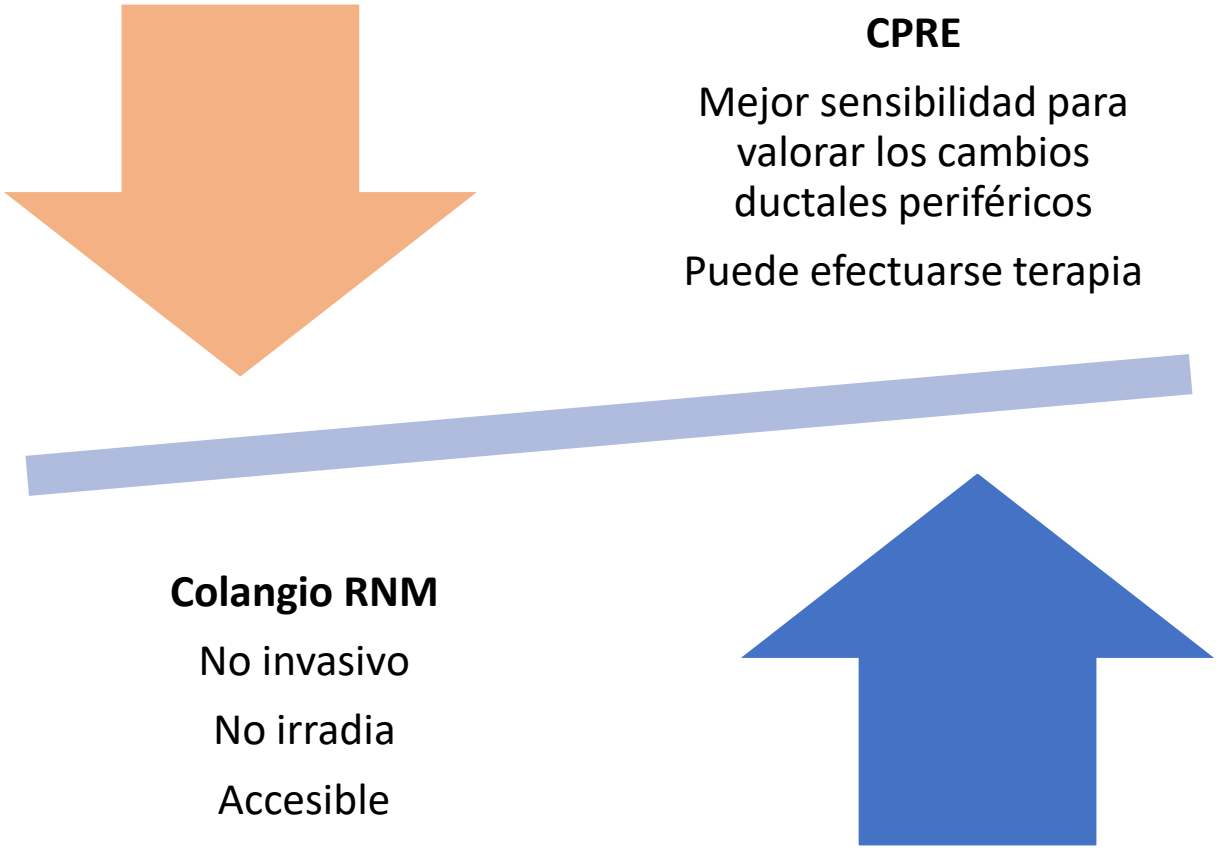


EASL Clinical Practice Guidelines: …..J Hepatol 2009; 51: 237–67.
Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of PSC. Hepatology 2010; 51: 660–78.

Estrategia diagnóstica CEP



Colangio RNM vs CPRE



CPRE

Mejor sensibilidad para valorar los cambios ductales periféricos

Puede efectuarse terapia

Falsos (+)
- CPRE: Distensión biliar incompleta
- MRE: Cirrosis

Falsos (-):
- CPRE: Estenosis marcadas
- MRE: Cambios iniciales

Colangio RNM

No invasivo

No irradia

Accesible

No es un marcador adecuado de actividad de la enfermedad y/ de progresión

Lazaridis et al NEJM 2016 / Schramm et al Hepatology 2017 / Tenca et al. Liv International 2018

¿Cuándo está indicada una CPRE?

- La práctica de una **CPRE solo está indicada para el diagnóstico inicial** en dos circunstancias (las guías de la EASL y AASLD avalan este punto de vista):
  - En sujetos con EII, alta sospecha de CEP y RNM de calidad normal.
  - Sospecha de colangiocarcinoma asociado.

- **En pacientes con una CEP ya diagnosticada,** para evaluar cambios en la clínica, laboratorio o en la imagen, con la intención de:
  - Identificar la localización y extensión de las estenosis.
  - Reconocer potenciales segmentos atróficos.
  - Identificar y tratar estenosis asociadas a abcesos / microabcesos
  - Identificar potenciales variantes anatómicas

- **Es muy útil hacer una colangio-RNM antes de la CPRE para tener una "hoja de ruta"**

23. ERCP may be indicated for the evaluation of relevant strictures as well as new-onset or worsening pruritus, unexplained weight loss, worsening serum liver test abnormalities, rising serum CA 19-9, recurrent bacterial cholangitis, or progressive bile duct dilation. MRI/MRCP should be considered prior to ERCP to clarify the need for biliary intervention and guide the technical approach.
24. Antimicrobial prophylaxis should be administered during the periprocedure period in patients with PSC undergoing ERCP.

The choice between biliary balloon dilation with and without stenting should be left to the endoscopist's discretion. In cases where a plastic biliary stent is placed, the stent should generally be removed within 4 weeks following placement.

EASL Clinical Practice Guidelines: …..J Hepatol 2009; 51: 237–67.
Chapman R, Fevery J, Kalloo A, et al. Hepatology 2010; 51: 660–78. Schramn C et al. Hepatology 2017.
Bowlus CL et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023; 77: 659-702.

¿Cuándo está indicada una biopsia hepática?

- A liver biopsy should be performed in adults suspected of having PSC whose high-quality MRCP is normal, to confirm or exclude small duct PSC (**LoE 4, strong recommendation, 88% consensus**).
- A liver biopsy should be considered in people with PSC and co-existing features of AIH including markedly elevated transaminases, high IgG levels, and positive autoantibodies compatible with AIH (**LoE 4, strong recommendation, 92% consensus**).

- El diagnóstico de la enfermedad no precisa de la práctica de una biopsia hepática. Esta es particularmente útil en dos circunstancias:
  - Sospecha de CEP intrahepática (CEP pequeño ducto) con RNM normal.
  - Elevada sospecha de CEP con RNM de alta calidad normal. **Sujetos con CU y alteración PFH.**
  - Sospecha de síndrome de solapamiento con HAI.

GPT > 5 x LSN

IgG > 2x LSN

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Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of PSC. Hepatology 2010; 51: 660–78.
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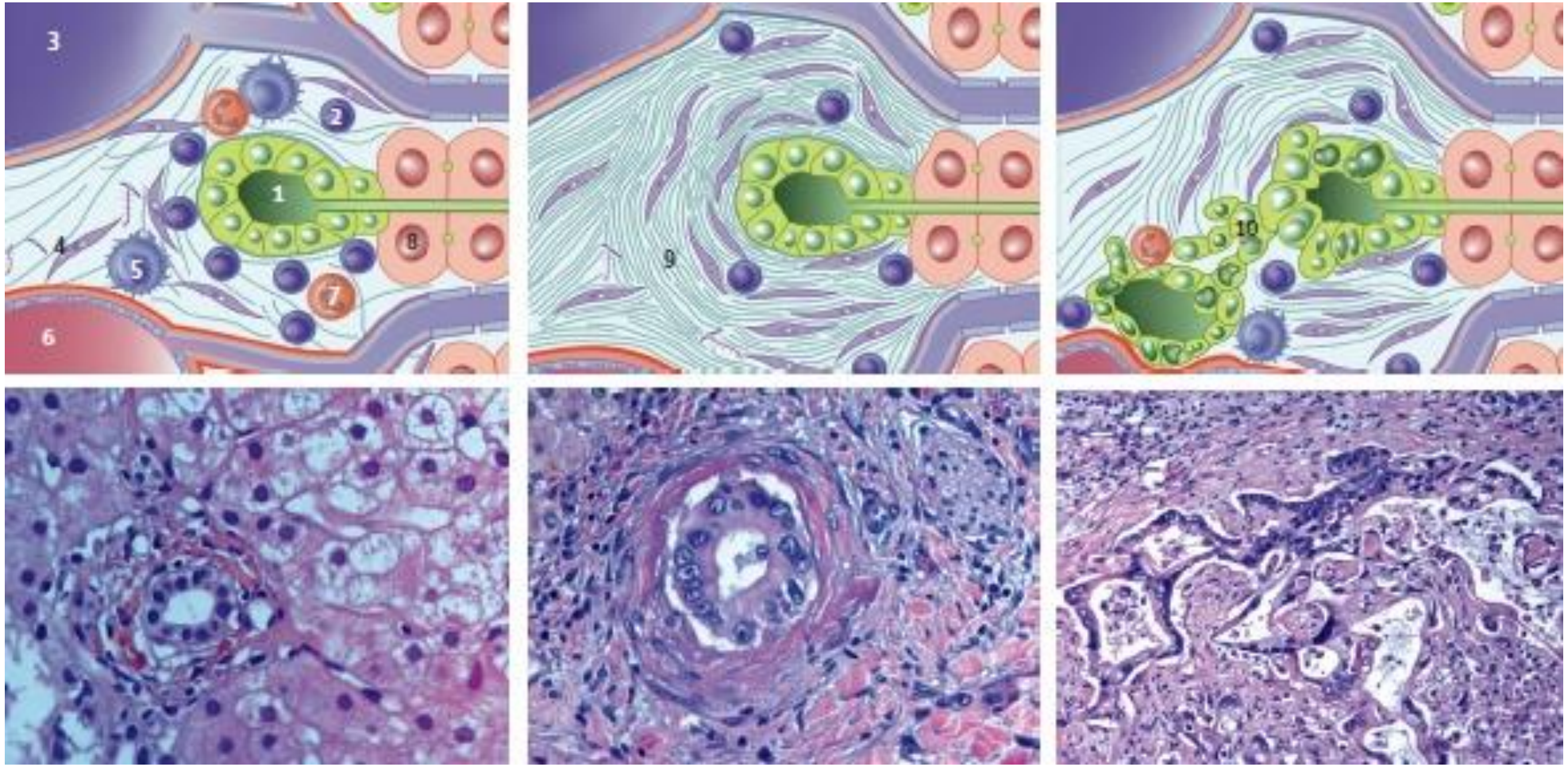


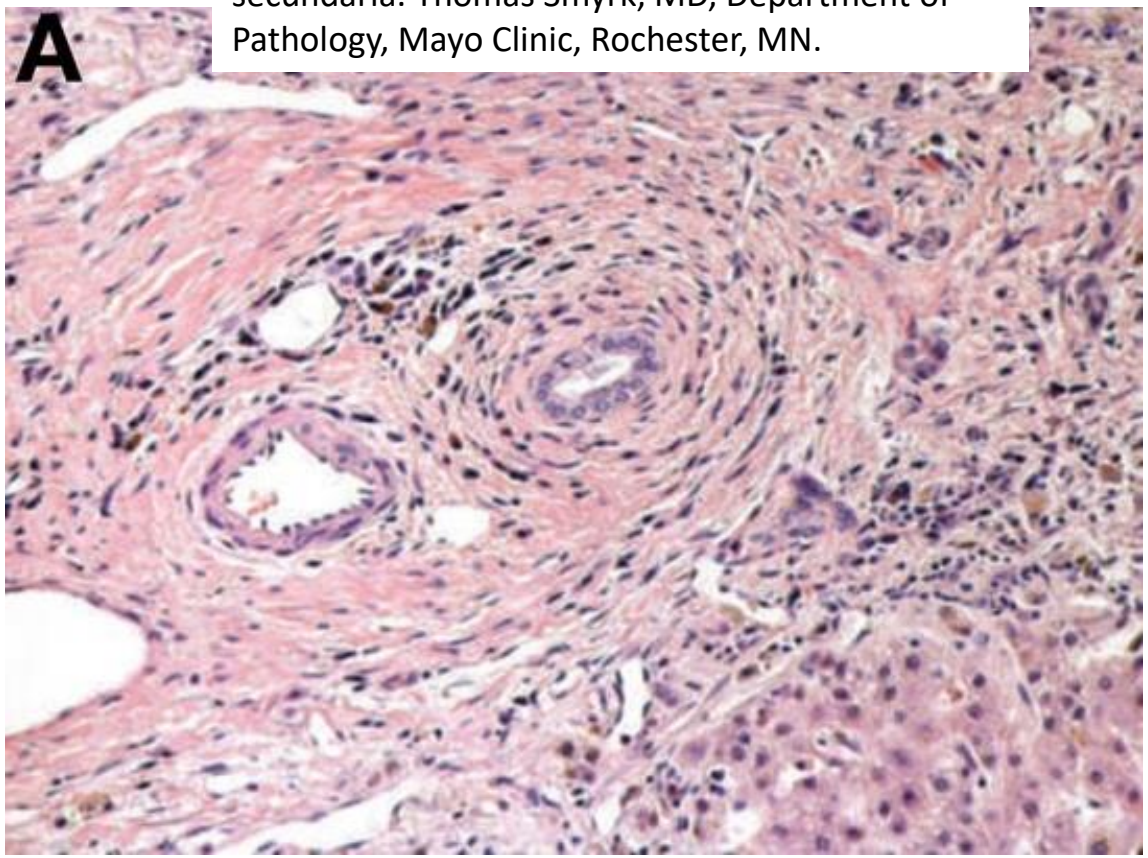
Inicialmente, solo se observan mínimos cambios epiteliales y algunas células inflamatorias. Esta lesión evoluciona hacia la típica colangitis obliterante, no supurativa con considerable fibrosis periductular . Si la lesión persiste, tiende a producirse displasia y, finalmente, un colangiocarcinoma.

1 Conducto biliar. 2 Linfocitos . 3. V. porta. 4. Fibroblastos. 5. Macrófagos. 6 . Arteria 7. PMN. 8. Hepatocitos. 9. Colágeno. 10. Colangiocarcinoma .

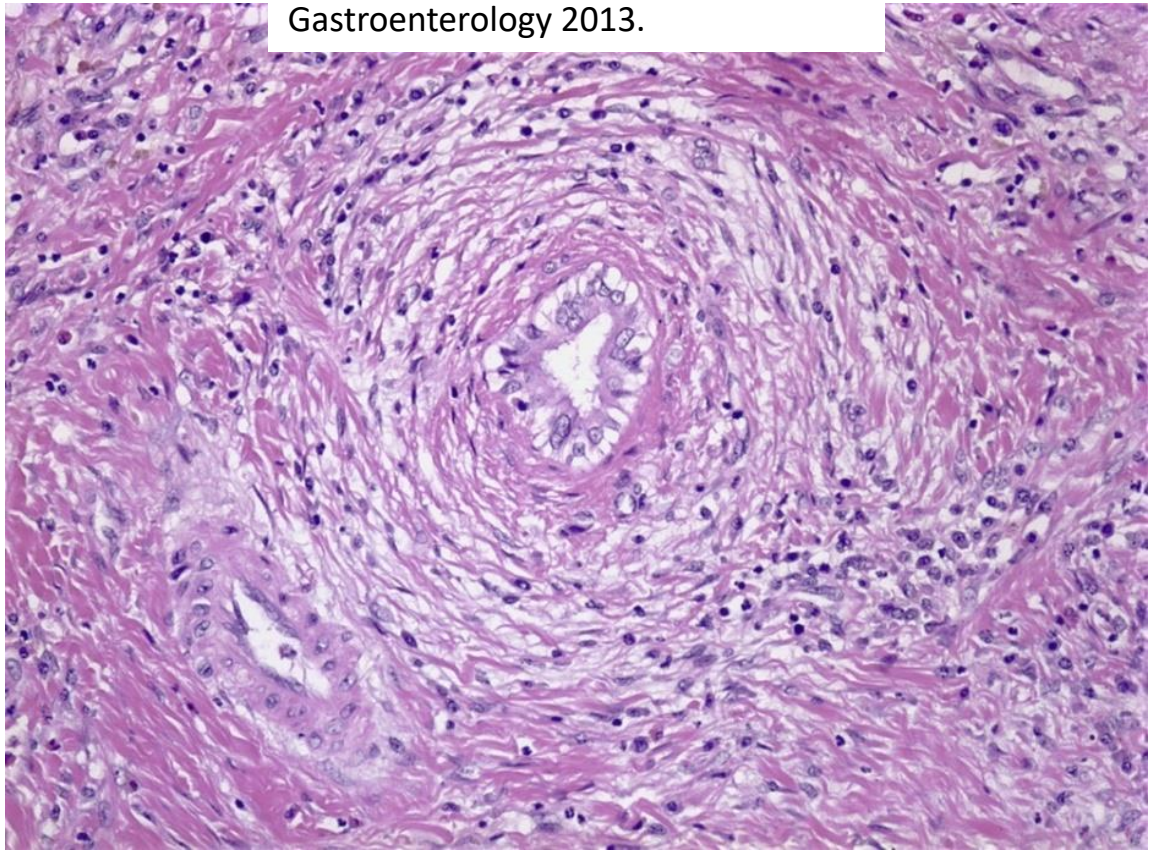
Hirschfield GM, et al. Primary sclerosing cholangitis. Lancet 2013; 382: 1587 - 1589

Biopsia hepática en pacientes con CEP

Fibrosis en capas de cebolla y obstrucción ductal secundaria. Thomas Smyrk, MD, Department of Pathology, Mayo Clinic, Rochester, MN.



Fibrosis ductal concéntrica. Gastroenterology 2013.



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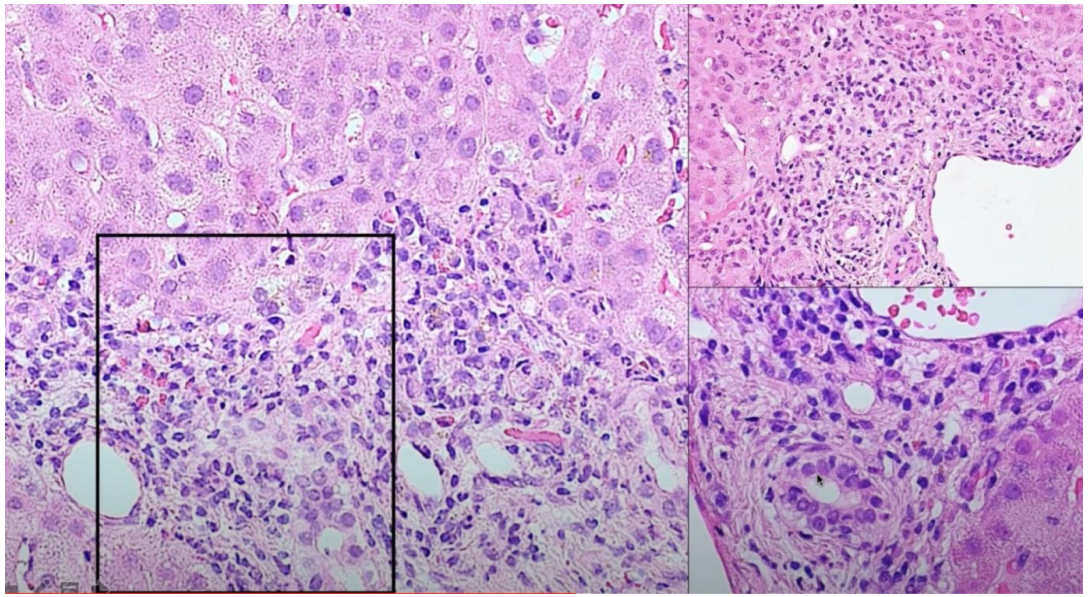
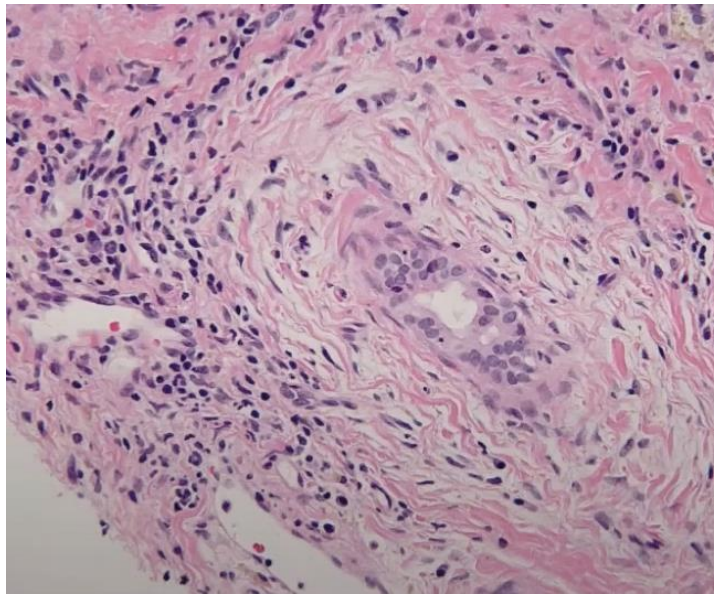
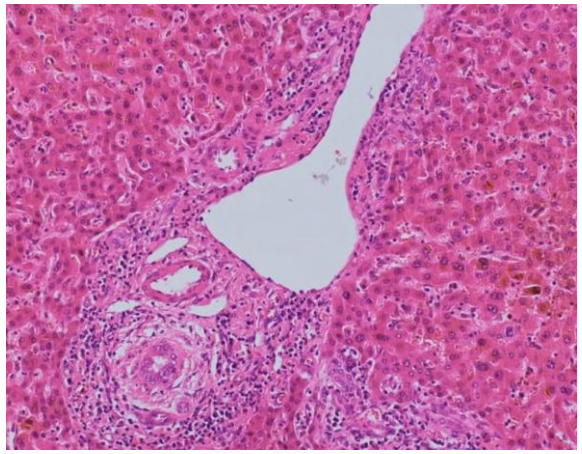
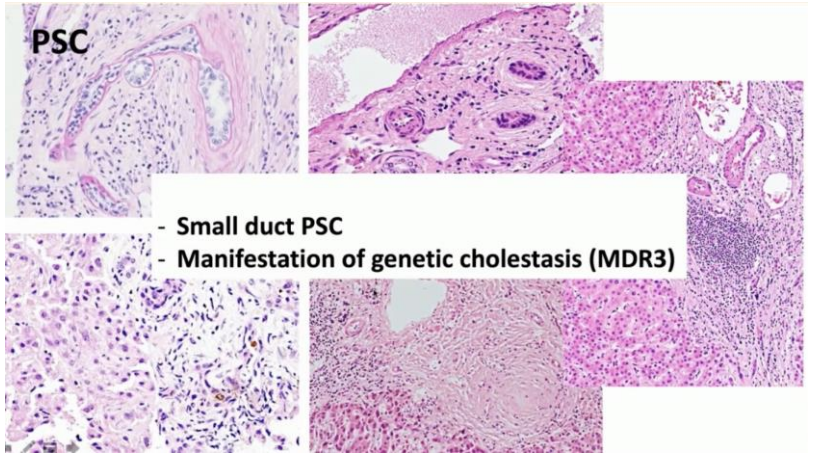
Biopsia hepática en pacientes con CEP

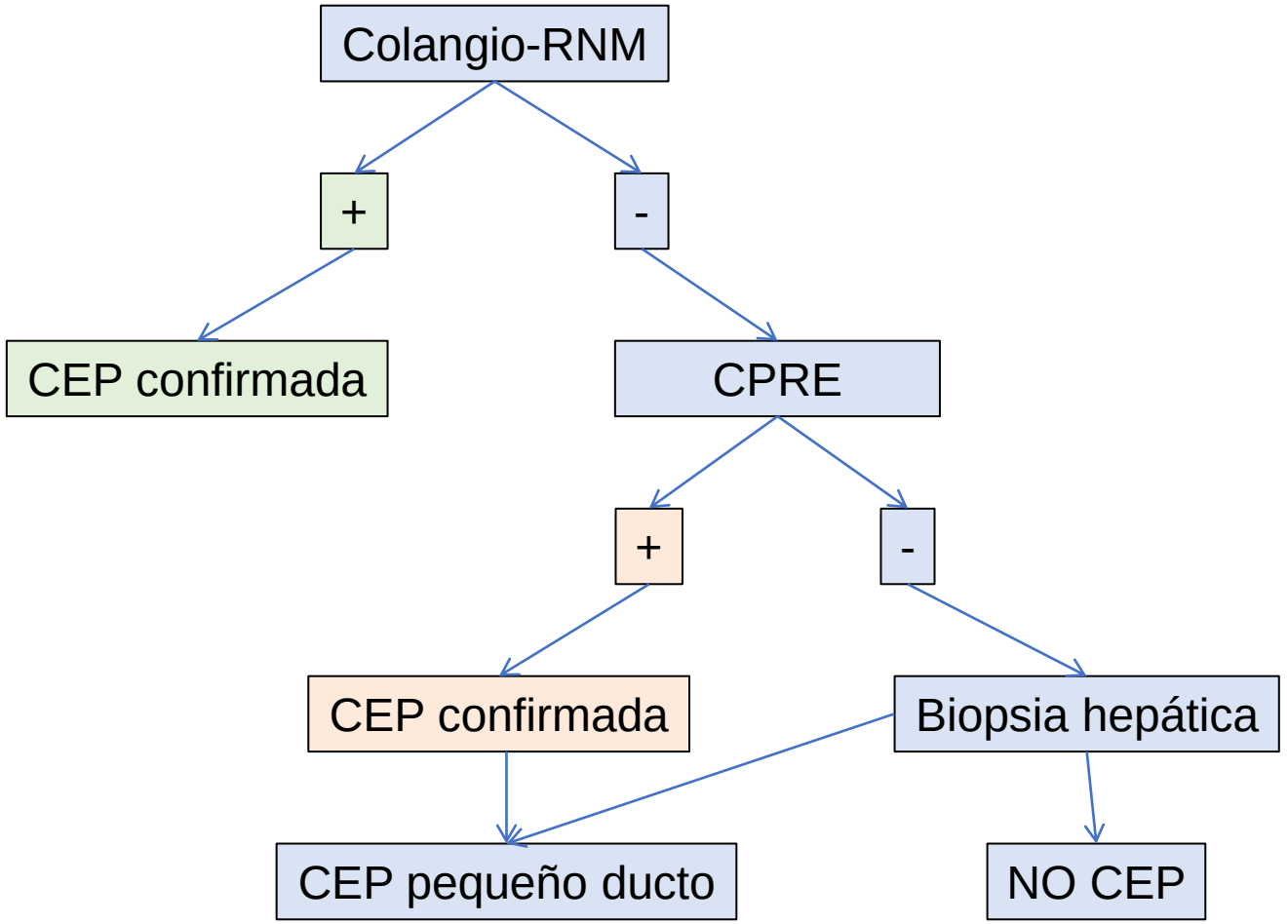








Biopsia hepática en pacientes con CEP



Aabakken L, et al. Endoscopy 2017.

Valor de los autoanticuerpos en el diagnóstico de la CEP

Autoanticuerpo	Prevalencia (%)
ANCA	50 - 80
ANA	7 – 77
AML	13 – 20
Anti-endotelio	35
Anticardiolipina	4-66
Anti-tiroideos	4 – 66
Factor reumatoide	15

- Autoantibodies should not be used to diagnose or risk-stratify people with PSC **(LoE 4, strong recommendation, 100% consensus).**

Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of PSC. Hepatology 2010; 51: 660–78.
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IgG4 y CEP

Dos posibilidades MUY diferentes

- CEP con elevación de IgG4 (subtipo de CEP)
- Enfermedad por IgG4

Recommendation

- Determination of serum IgG4 is suggested in every adult patient with large duct sclerosing cholangitis at the time of diagnosis **(LoE 3, weak recommendation, 91% consensus).**

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Estenosis intrahepáticas y/o extrahepática y/o intrapancreáticas

(Criterios diagnósticos HISORt; histología, serología, imagen, afectación orgánica y respuesta al tratamiento).

- Resección pancreática previa
- Bx pancreática sugestiva de PAI

Imagen típica de PAI +
Elevación IgG4

Dos o más de los siguientes:

- Elevación IgG4
- Imágenes sugestivas PAI
- Afectación otro órgano
- Bx biliar con más de 10 IgG4 células +

Uno de los siguientes después de 4S de tto esteroideo:

-Marcado mejoría estenosis
- Disminución <x2 PFH
-Disminución significativa de Ca 19.9 e IgG4

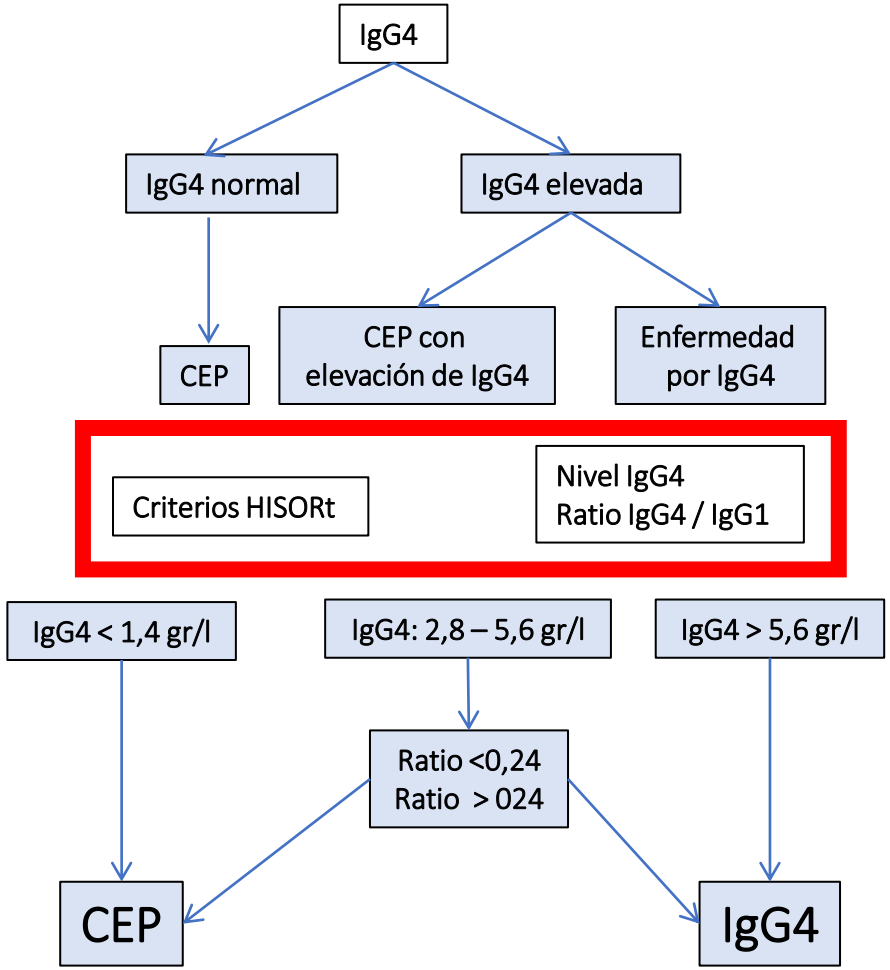
Dx definitivo Colangitis asociada a IgG4

Si NO existe respuesta: Suspende los esteroides y descarta un colangiocarcinoma.

Ghazale A, et al. Gastroenterology 2008. Boonstra K, et al. Hepatology 2014

IgG4 y CEP

- No se conoce con certeza el dintel de IgG4
- **En todos los pacientes con CEP se deben determinar los niveles de IgG4:**
  - Diagnosticar / excluir una enfermedad por IgG4 (mejor pronóstico).
  - Para perfilar de forma adecuada una forma particular de la enfermedad , con niveles elevados de IgG4 sin criterios diagnósticos de enfermedad sistémica por IgG4. La elevación de IgG4 en la CEP se asocia a peor pronóstico.



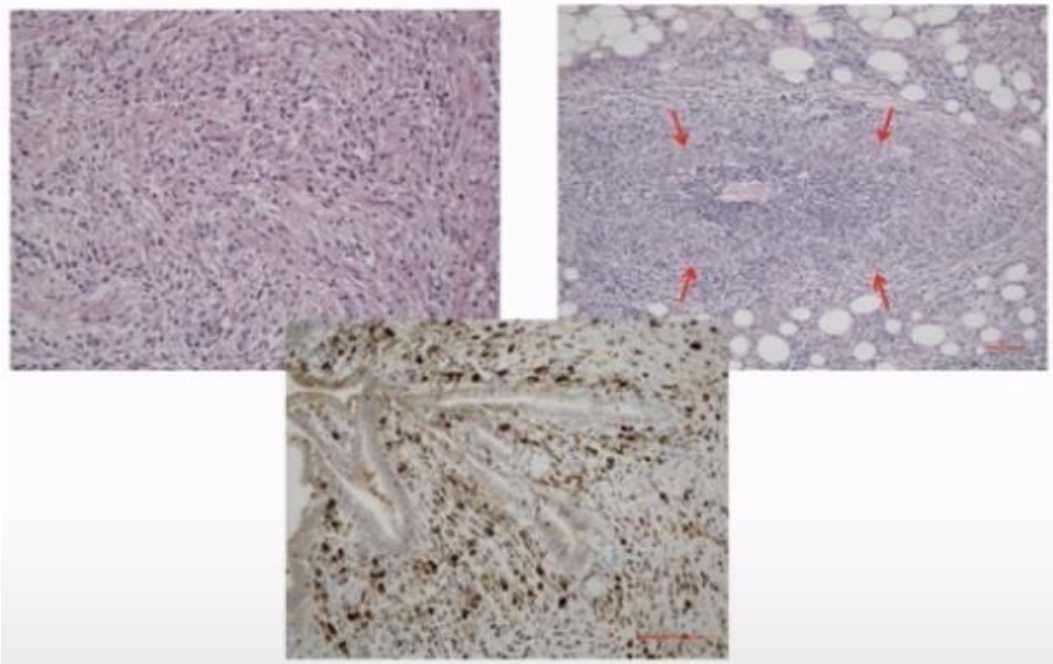
Stone JH, Zen Y, Deshpande V. IgG4-Related Disease. NEJM 2012;366:539-51.
Boonstra K, et al. Hepatology 2014

IgG4 y CEP

Table 2 Clinical parameters in differentiating IgG4-related sclerosing cholangitis (IgG4-SC) from primary sclerosing cholangitis (PSC)

Clinical feature supportive of IgG4-SC or PSC	PSC	IgG4-SC
Male sex	+	++
Younger age	++	+
Pancreatic mass or enlargement on CT	–	++
Pancreatic ductal abnormalities	+/-	+++
Raised serum IgG4	+/-	++
Ampullary biopsy with >10 IgG4 plasma cells per high power field	–	+++
Liver/tissue biopsy with >10 IgG4 plasma cells per high power field	+/–	+++
Pancreatic exocrine insufficiency	–	++
Other associated systemic fibrosclerotic disease	–	++
Cholangiographic changes	++	++
Presence of inflammatory bowel disease	++	+/–
Improvement with steroid treatment	+/–	+++

IgG4> 4 LSN
IgG4/IgG1> 0,24



-Infiltrado linfoplasmocitario con células plasmáticas IgG4 (>10/campo)
- IgG4/IgG >40%
- Fibrosis estoriforme
- Flebitis obliterativa

Kamisaka T et al. J Hepatobiliary Pancreat Sci 2019 / Chapman MH, et al. Gut 2019

IgG4 y CEP

Recommendations

- Predniso(lo)ne (0.5 to 0.6 mg/kg/d) is recommended as the first-line therapy for untreated active IRC. Treatment response should be evaluated after (2 to) 4 weeks, prior to predniso(lo)ne tapering, by clinical, biochemical and/or radiological criteria **(LoE 4, strong recommendation, 100% consensus).**
- Maintenance treatment of IRC is suggested with steroid-sparing immunosuppressants for up to 3 years (*e.g.* azathioprine, 6-mercaptopurine, mycophenolate mofetil) and potentially beyond, starting during predniso(lo)ne tapering, to reduce the risk of IRC relapse. Rituximab can alternatively be considered when relapse has occurred **(LoE 5, weak recommendation, 100% consensus).**

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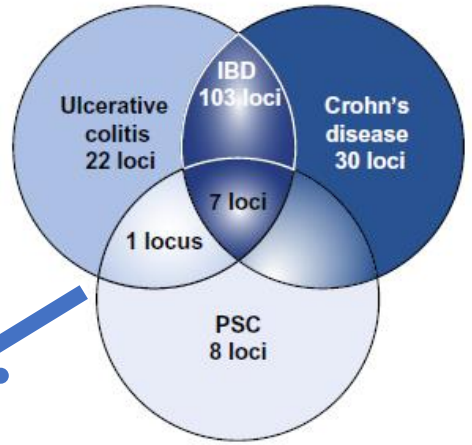
Fenotipar la CEP

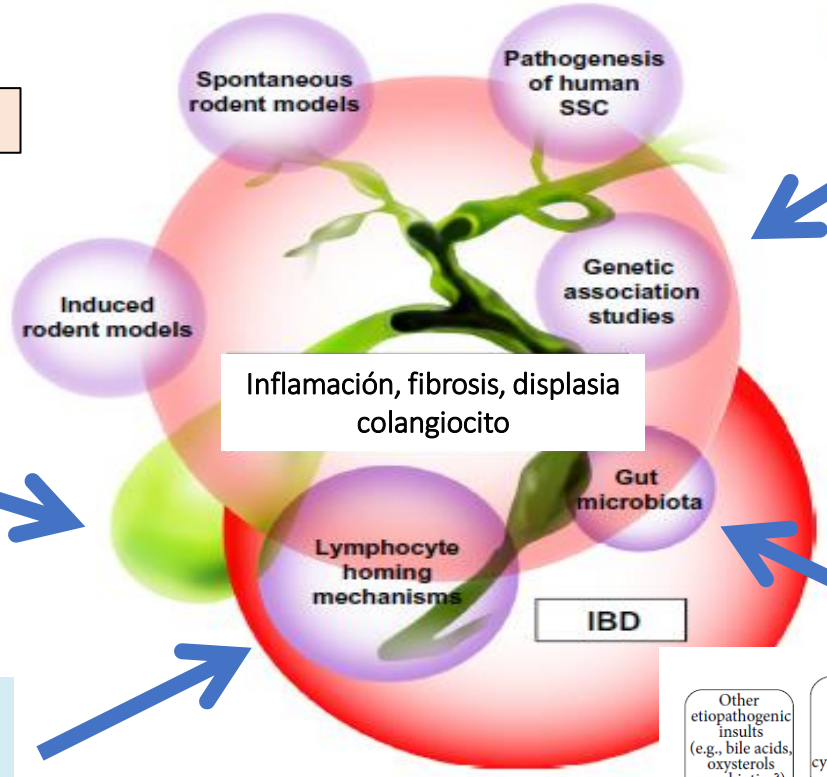
Gran variabilidad fenotípica
Diferentes modelos espontáneos e inducidos



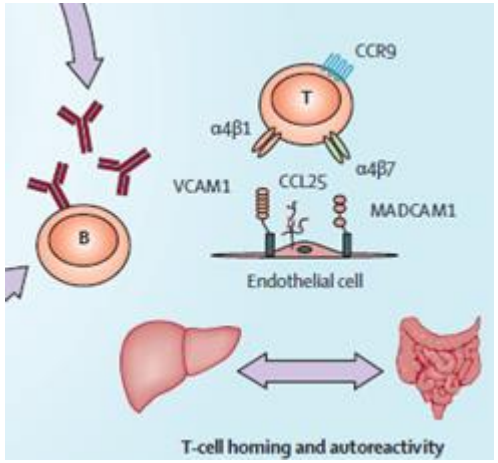
Genéticos

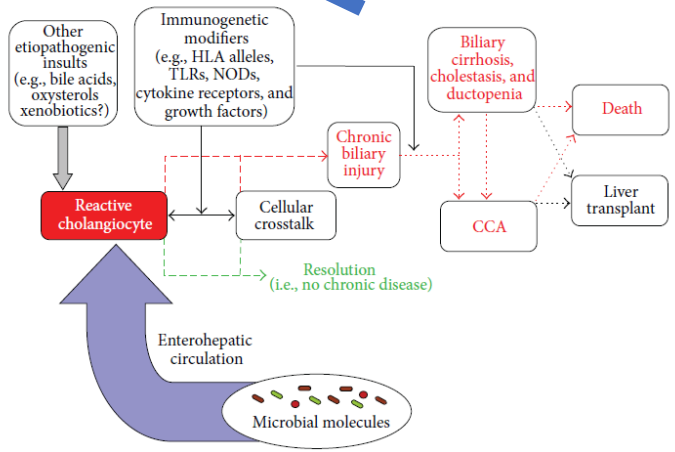
No genéticos

Homeostasis ácidos biliares



Inflamación, fibrosis, displasia colangiocito





¿Manifestación biliar de la aterosclerosis?

Fenotipar la CEP

1. **Colangitis esclerosante primaria típica; variabilidad inducida por:**
   - Edad, / etnia / sexo
   - Hallazgos colangiográficos
   - Existencia de EII o no

2. **Colangitis esclerosante e IgG4.**
   - CEP relacionada con IgG4
   - Enfermedad por IgG4

3. Solapamiento HAI / CEP:

- Del 1 al 17% de todas las CEP.
- Cerca del 50% son niños.
- El desarrollo de la enfermedad puede ser secuencial.
- Está indicada una prueba terapeútica con corticoides o IS.

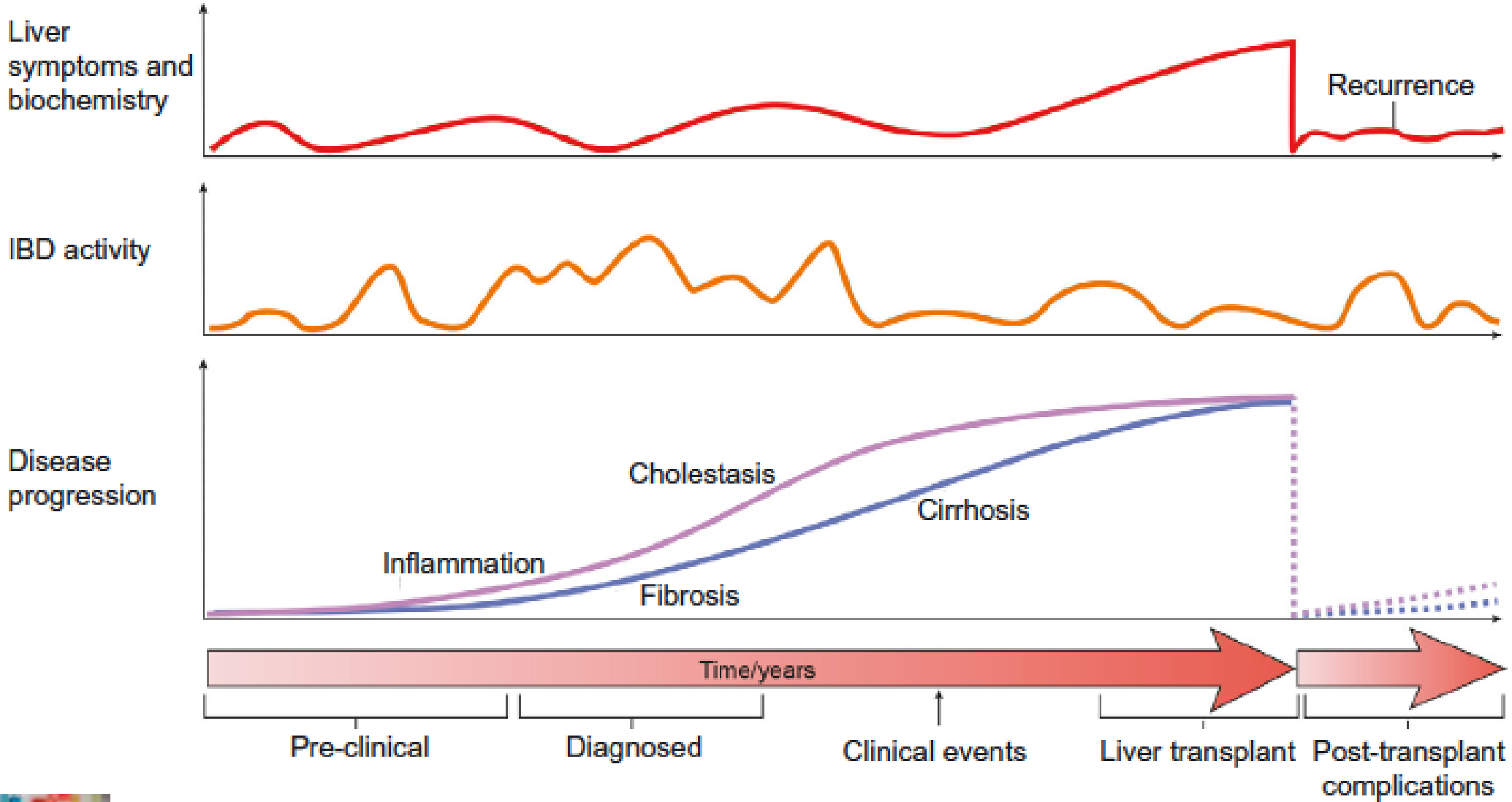
4. CEP de pequeño ducto:

- 10% de todos los casos / Similar distribución edad y sexo.
- Curso más benigno
- 20% progresan a CEP de ductos de gran tamaño

	CEP pequeño ducto (n= 83)	CEP clásica (n= 157)
Muerte	11 (13,3%)	45 (28,7%)
TxH	8 (9,6%)	33 (21%)
Colangiocarcinoma	1 (1,2%)	19 (12%)

Eato JE, et al. Gastroenterology 2013;145:521–536 / Sarkar, Bowlus. Clin Liv Dis 2016
Luth et al. J Clin Gastro 2008. Culver et al. Alim Phar Ther 2011 / Bjomssom et al. Gastroenterology 2008

Estadificación (pronóstico / historia natural) de la CEP



Karlsen TH, Folseraas T, Thorburn D, Vesterhus M. J Hepatology 2017; 67: 1298–1323

Estadificación (pronóstico) de la CEP

Table 5. Rational approaches to non-invasive risk stratification in PSC.

Level of applicability	Prognostic tools
High (High applicability, robust validation)	○ Baseline (early *vs.* advanced) disease stage as defined by biochemical (bilirubin, albumin, platelets, prothrombin time) and imaging analyses ○ Small duct PSC *vs.* classical PSC
Moderate (High applicability, further validation pending)	○ ALP ○ LSM by VCTE ○ ELF test ○ MRI/MRCP
Indeterminate (Insufficient applicability and/or validation)	○ Age, gender and type of IBD ○ AIH features ○ IgG4 serum levels ○ PSC-specific prognostic scores* (except for Mayo Risk Score in advanced PSC)

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ELF test, serum enhanced liver fibrosis test; IBD, inflammatory bowel disease; LSM, liver stiffness measurement; MRCP, magnetic resonance cholangiopancreaticography; VCTE, vibration-controlled transient elastography.
*Likely to move to higher level of applicability in the near future.

"Low risk" of events:

- Small duct PSC and no evidence of cirrhosis

OR

- Classical PSC and (all to be present): asymptomatic with normal bilirubin, albumin, platelets, and PT, ALP <1.5 ULN, LSM (VCTE) <6.5 kPa (or ELF test <7.7), limited biliary changes on MRI/MRCP.

"Significant risk" of events if any present:

- Symptomatic, ALP >1.5 ULN, abnormal bilirubin, albumin, platelets or PT, LSM (VCTE) >9.9 kPa (or ELF test >10.6), extensive biliary changes (especially intra-hepatic biliary dilatation) on MRI/MRCP.

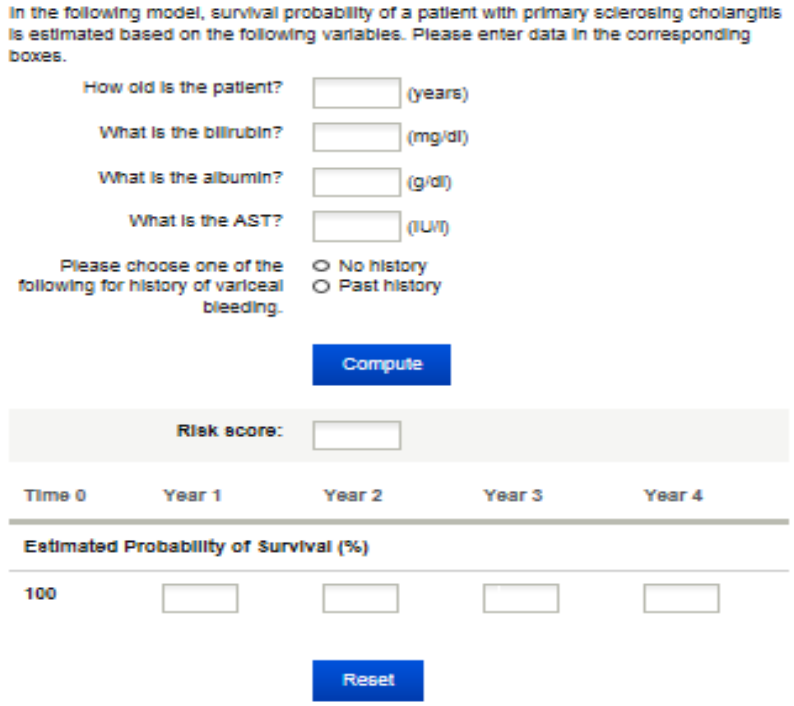
EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

Estadificación (pronóstico / historia natural) de la CEP

1. Modelos predictivos basados en parámetros clínicos muy fáciles de obtener.

2. Modelos predictivos de supervivencia basados en la disminución de la FA en pacientes tratados con UDCA.

3. Modelos predictivos del desarrollo de VE.


In the following model, survival probability of a patient with primary sclerosing cholangitis is estimated based on the following variables. Please enter data in the corresponding boxes.

How old is the patient? (years)

What is the bilirubin? (mg/dl)

What is the albumin? (g/dl)

What is the AST? (IU/l)

Please choose one of the following for history of variceal bleeding. ○ No history ○ Past history

Compute

Risk score:

Time 0	Year 1	Year 2	Year 3	Year 4
Estimated Probability of Survival (%)				
100				

Reset

Extraordinaria variabilidad fenotípica: Dificultad para adivinar la progresión de la enfermedad.
Los modelos pronósticos son útiles para evaluar el seguimiento de grupos de pacientes, pero NO deben utilizarse para predecir la evolución de la enfermedad en un paciente concreto.

Al Mamari S, et al. Improvement of serum…. J Hepatol 2013; 58: 329-334.
Kim WR, et al. A revised natural history model for PSC. Mayo Clin Proc 2000; 75: 688-94.
Treeprasertsuk S et al. The predictors of the presence of varices… Hepatology 2010: 51; 1302-1310

Estadificación (pronóstico / historia natural) de la CEP

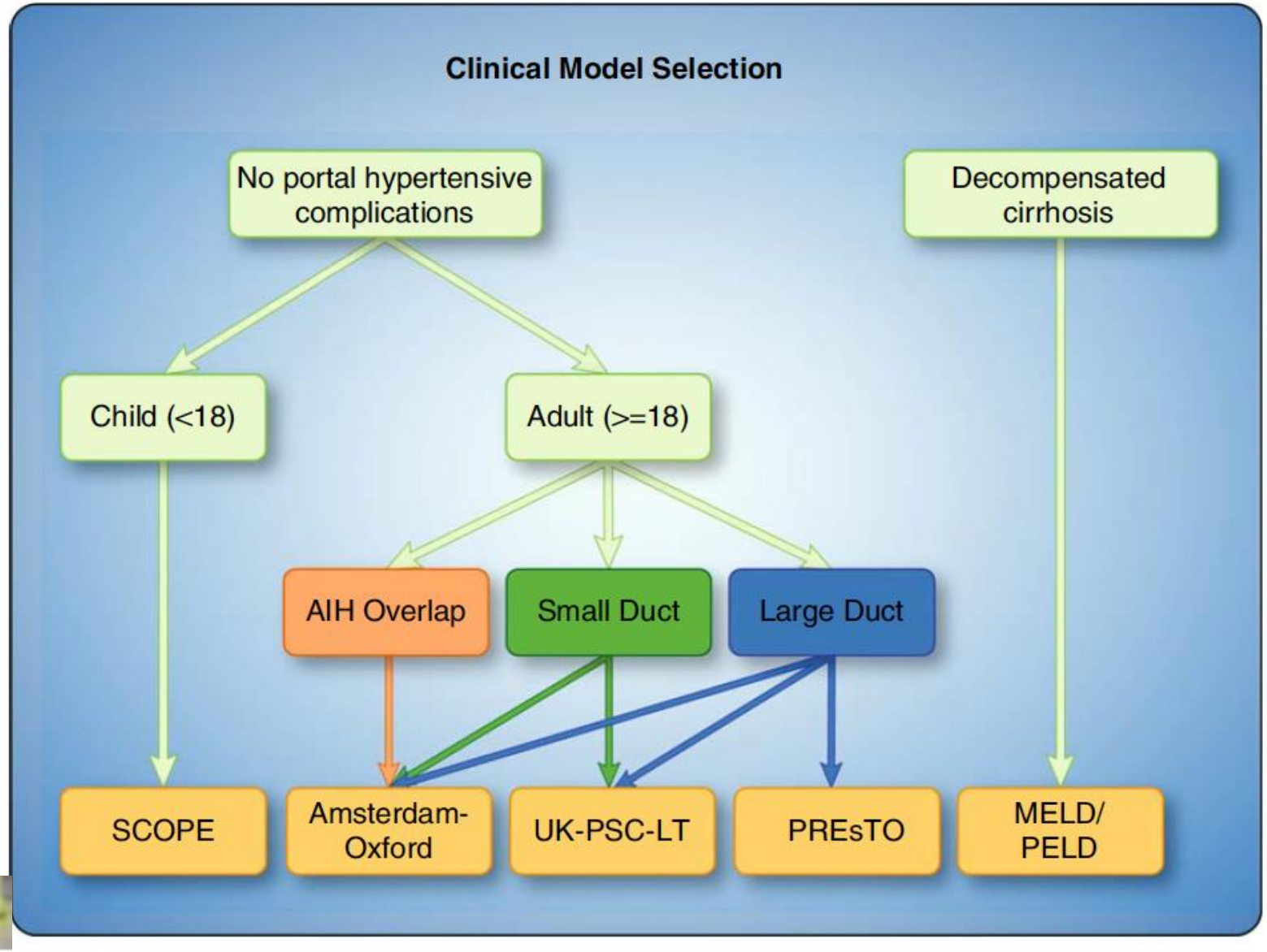
TABLE 3 Validated clinical prognostic models of PSC

	Models Amsterdam-Oxford 2017[230]	UK-PSC 2019[231]	PREsTO 2020[232]	SCOPE 2020[162]
Variables	Age Bilirubin Albumin AST ALP Platelets PSC subtype (large-duct or small-duct)	Age Bilirubin Albumin ALP Platelets Presence of extrahepatic biliary disease History of variceal hemorrhage	Age Bilirubin Albumin AST ALP Platelets Hemoglobin Sodium Years since PSC diagnosis	Bilirubin Albumin Platelets GGT Cholangiography (large-duct or small-duct involvement)
Endpoint	LT or liver-related death by 15 years	Short term: death or LT by 2 years Long term: death or LT by 10 years	Hepatic decompensation (ascites, variceal hemorrhage, encephalopathy) by 5 years	Portal hypertensive complications, biliary complications, CCA, listing for LT, or death from liver disease by 5 years
Risk thresholds[a]	Lower risk: < 1.58 Higher risk: ≥ 1.58	Lower risk: < 1.46 Higher risk: ≥ 1.46	Lower risk: < 20% Higher risk: ≥ 20%	Lower risk: 0–5 Higher risk: 6–11
Website	https://sorted.co/psc-calculator/	http://www.uk-psc.com/resources/the-uk-psc-risk-scores/	rtools.mayo.edu/PRESTO_calculator/	Scopeindex.net

[a]Lower-risk group cutoffs were selected to identify patients with approximately 10% or less risk of transplant or death within 5 years. Cutoffs were not reported for the PREsTO model; however, approximately twice as many patients developed decompensation as were transplanted in follow-up, making a 20% risk of decompensation a reasonable approximation of a 10% risk of transplant or death.

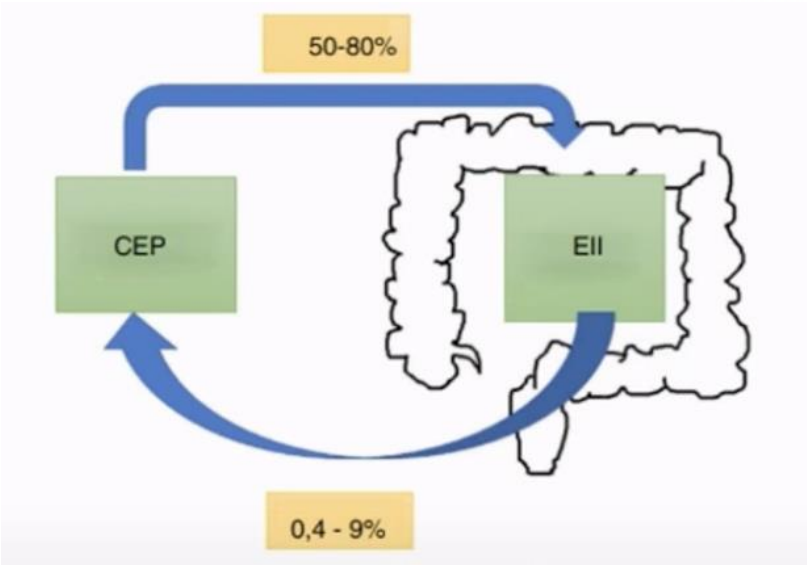
Bowlus CL et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023; 77: 659-702.

Estadificación (pronóstico / historia natural) de la CEP



Bowlus CL et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023; 77: 659-702.

Enfermedad inflamatoria intestinal y CEP



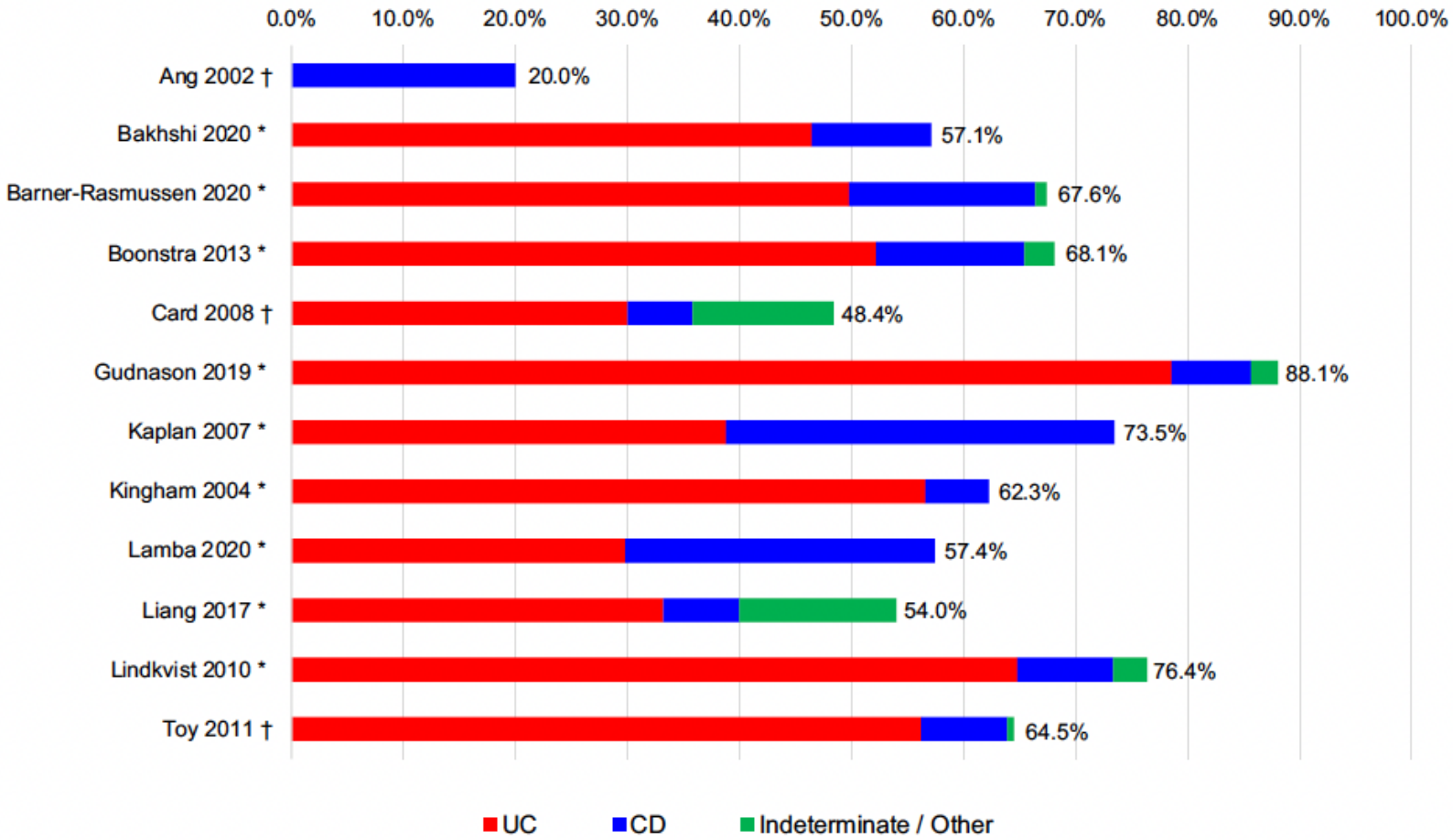
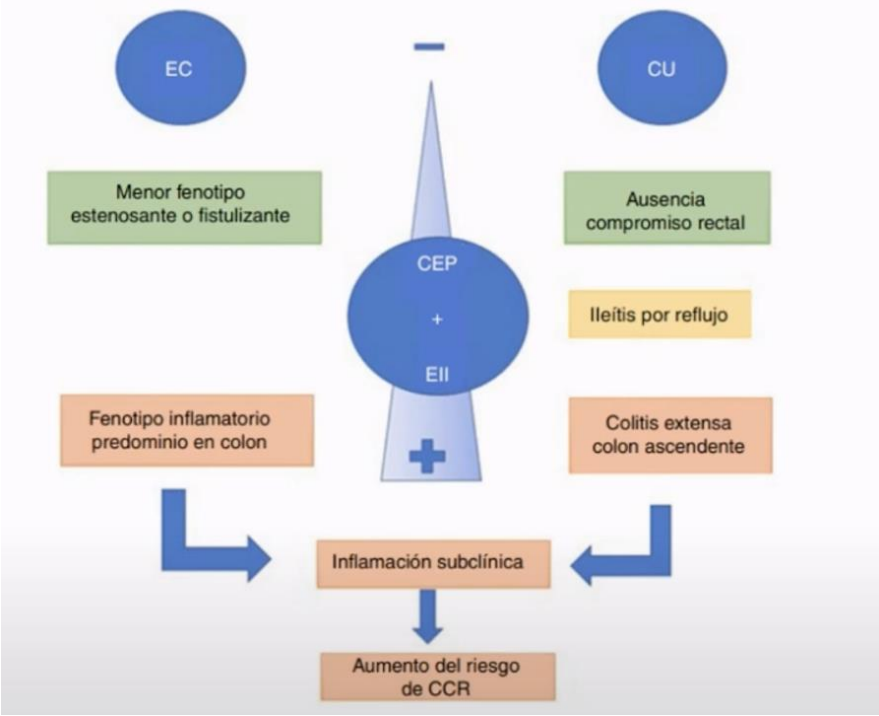
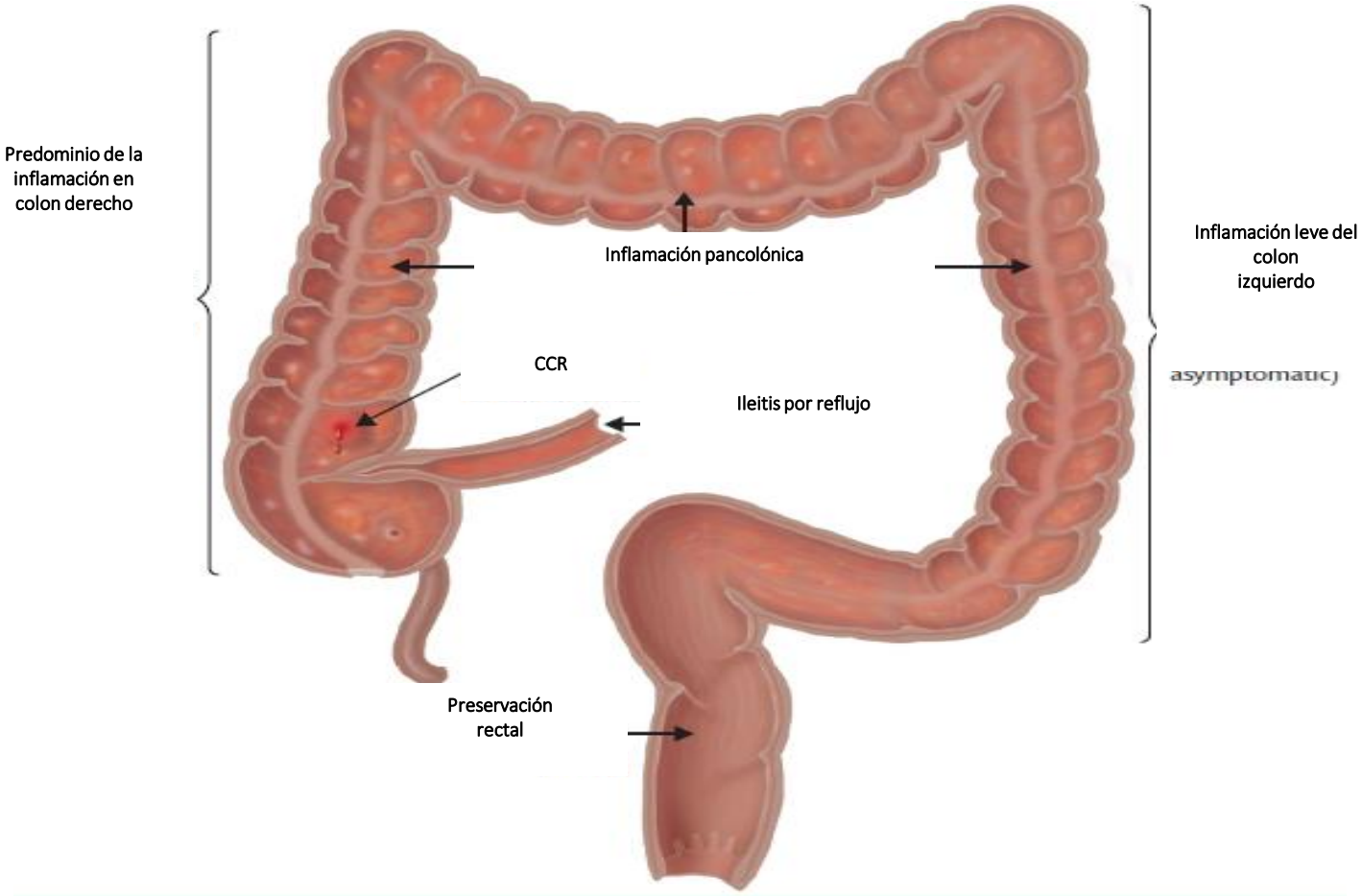


Figure 3. IBD comorbidity among PSC cohorts. Infographic detailing the proportion of patients with PSC who developed concomitant IBD according to subtype. *Proportion among incident cases. †Proportion among total cases.

Trivedi PJ, Bowlus CL, Yimam KK, Razavi H, Estes C. Epidemiology, Natural History, and Outcomes of Primary Sclerosing Cholangitis: A Systematic Review of Population-based Studies. Clin Gastroenterol Hepatol. 2021:S1542-3565(21)00919-8.

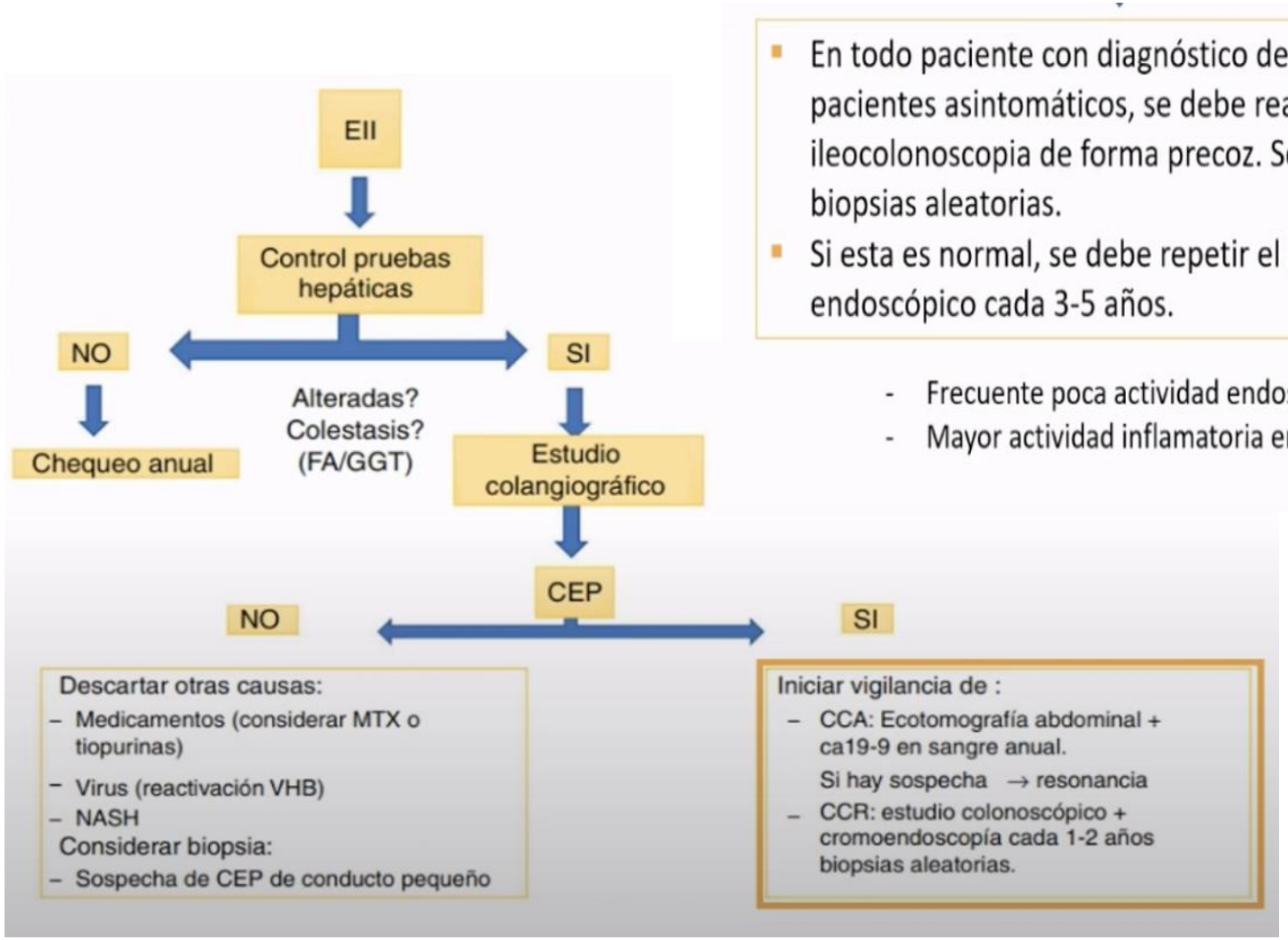
Enfermedad inflamatoria intestinal y CEP





Gideon M Hirschfi eld et al. Lancet 2013; 382
Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of PSC. Hepatology 2010; 51: 660–78
Chaman MH et al Gut 2016 / Lindor et al Am I Gastroentero! 2015
Weismüiller TI et al Gastroenterol 2017 / Nuñez P et al. Gastroenterol Henatol 2019

Enfermedad inflamatoria intestinal y CEP



- En todo paciente con diagnóstico de CEP, incluso en pacientes asintomáticos, se debe realizar una ileocolonoscopia de forma precoz. Se deben incluir biopsias aleatorias.
- Si esta es normal, se debe repetir el procedimiento endoscópico cada 3-5 años.

- Frecuente poca actividad endoscópica.
- Mayor actividad inflamatoria en Bx.

Gideon M Hirschfi eld et al. Lancet 2013; 382
Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of PSC. Hepatology 2010; 51: 660–78
Chaman MH et al Gut 2016 / Lindor et al Am I Gastroentero! 2015
Weismüiller TI et al Gastroenterol 2017 / Nuñez P et al. Gastroenterol Henatol 2019

Enfermedad inflamatoria intestinal y CEP

- Ileocolonoscopy with biopsies from all colonic segments including the terminal ileum, regardless of the presence of lesions, is recommended at the time of PSC diagnosis **(LoE 3, strong recommendation, 100% consensus).**
- A diagnostic colonoscopy can be considered every 5 years in people with PSC where no IBD is present or whenever complaints suspicious for IBD occur **(LoE 5, weak recommendation, 92% consensus).**
- Annual surveillance (or every 1 to 2 years in individualised patients without inflammatory activity) colonoscopy with biopsies is recommended in all adult PSC-IBD patients regardless of the duration of IBD or liver transplant status **(LoE 3, strong recommendation, 92% consensus).**

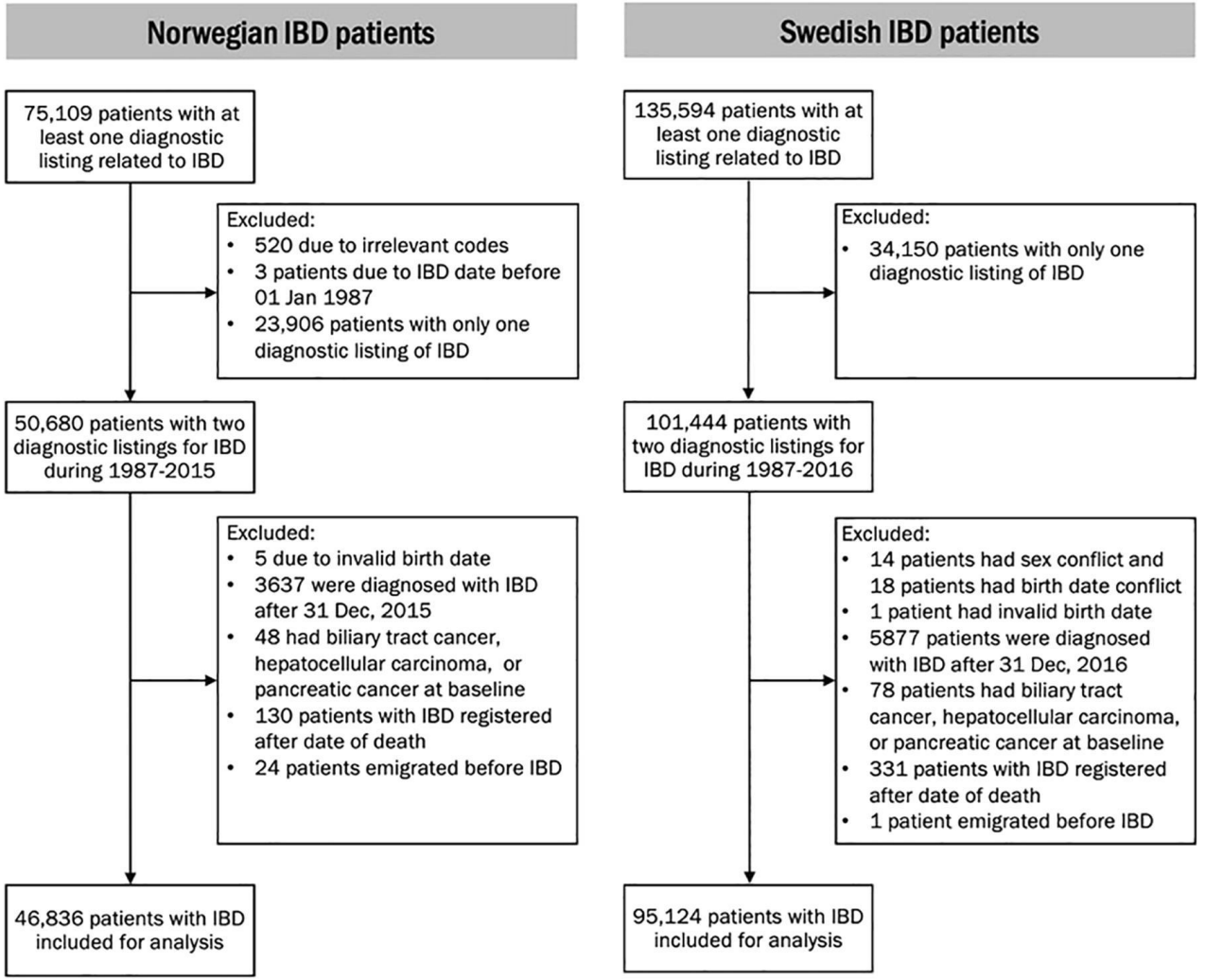
22. In patients with PSC in whom IBD is diagnosed, high-definition surveillance colonoscopy with biopsies should start at age 15 years and be repeated at 1-year to 2-year intervals to evaluate for colonic dysplasia.

- Treatment of PSC-related IBD in line with current practice guidelines with the goal of achieving mucosal healing is recommended **(LoE 3, strong recommendation, 92% consensus).**

- Colectomy is recommended in patients with high-grade colonic dysplasia or neoplasia or if symptomatic colonic inflammatory activity persists despite optimum medical therapy. Colectomy may also be considered in confirmed low-grade dysplasia at repeated occasions and/or at multiple locations **(LoE 3, strong recommendation, 79% consensus).**

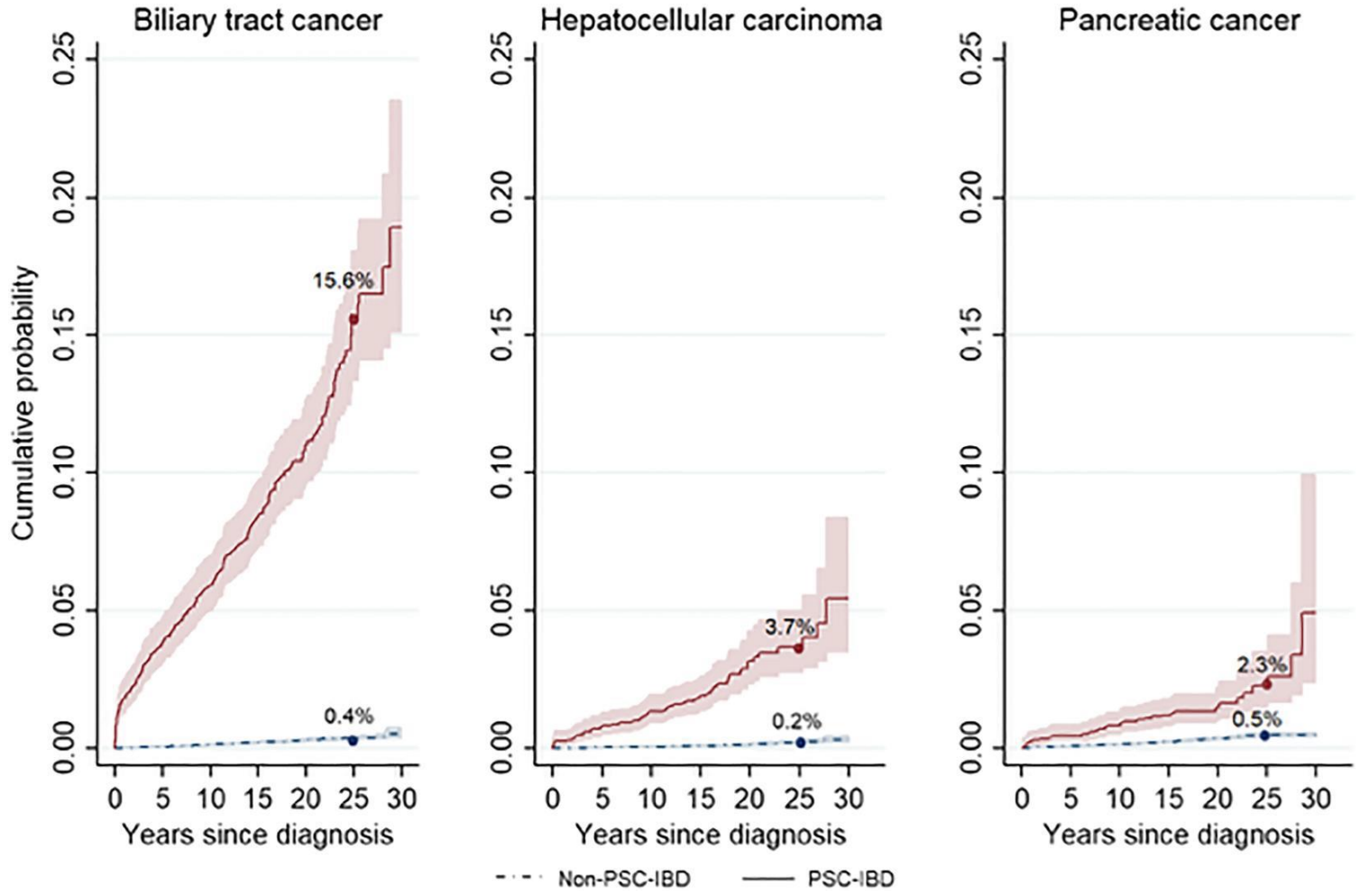
EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.
Bowlus CL et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023; 77: 659-702.

CEP como enfermedad preneoplásica



Yu J, et al. Risk of hepato-pancreato-biliary cancer is increased by primary sclerosing cholangitis in patients with inflammatory bowel disease: A population-based cohort study. United European Gastroenterol J. 2022 Feb 2. doi: 10.1002/ueg2.12204. Epub ahead of print. PMID: 35107865.

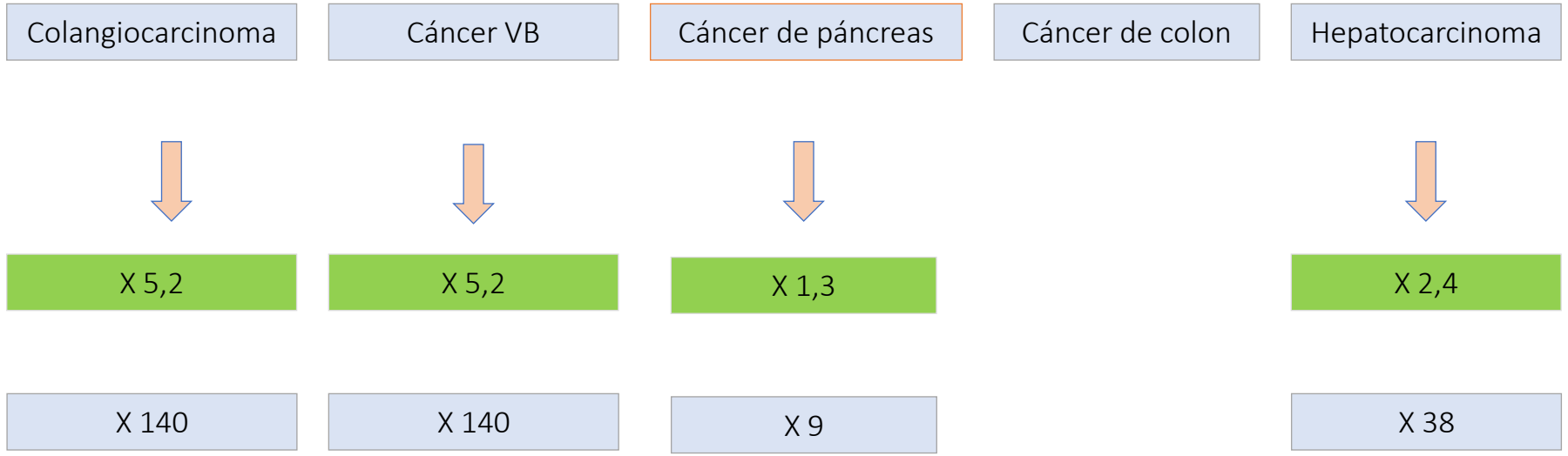
CEP como enfermedad preneoplásica



Yu J, et al. Risk of hepato-pancreato-biliary cancer is increased by primary sclerosing cholangitis in patients with inflammatory bowel disease: A population-based cohort study. United European Gastroenterol J. 2022 Feb 2. doi: 10.1002/ueg2.12204. Epub ahead of print. PMID: 35107865.

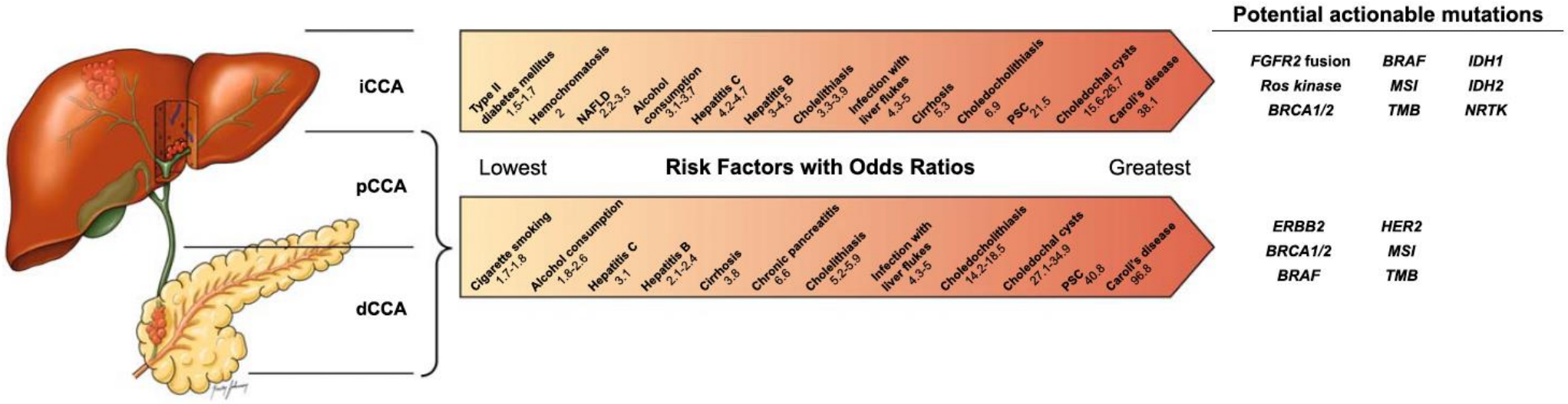
CEP como enfermedad preneoplásica

Tumores potencialmente asociados a la colangitis esclerosante primaria.



Yu J, et al. Risk of hepato-pancreato-biliary cancer is increased by primary sclerosing cholangitis in patients with inflammatory bowel disease: A population-based cohort study. United European Gastroenterol J. 2022 Feb 2. doi: 10.1002/ueg2.12204. Epub ahead of print. PMID: 35107865.

CEP como enfermedad preneoplásica. Colangiocarcinoma.



Colangiocarcinoma (RR x 160 respecto a la población general). Estretegia de cribado: RNM anual + Ca-19-9 (+CEA).

Estenosis dominante o incremento de los niveles de Ca 19.9 (sin colangitis bacteriana):

- CRPE + citología convencional y FISH si es posible:
- No dx: Repetir RNM + Ca 19.9 y/o CPRE a los 3-6 meses
- La citología sistemática de rutina detecta colangiocarcinoma con elevada especificidad pero baja sensibilidad.

Navaneethan U et al. Gastrointest Endosc. 2013. Bangarulingam et al. Hepatology 2010.

Bowlus CL et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023; 77: 659-702.

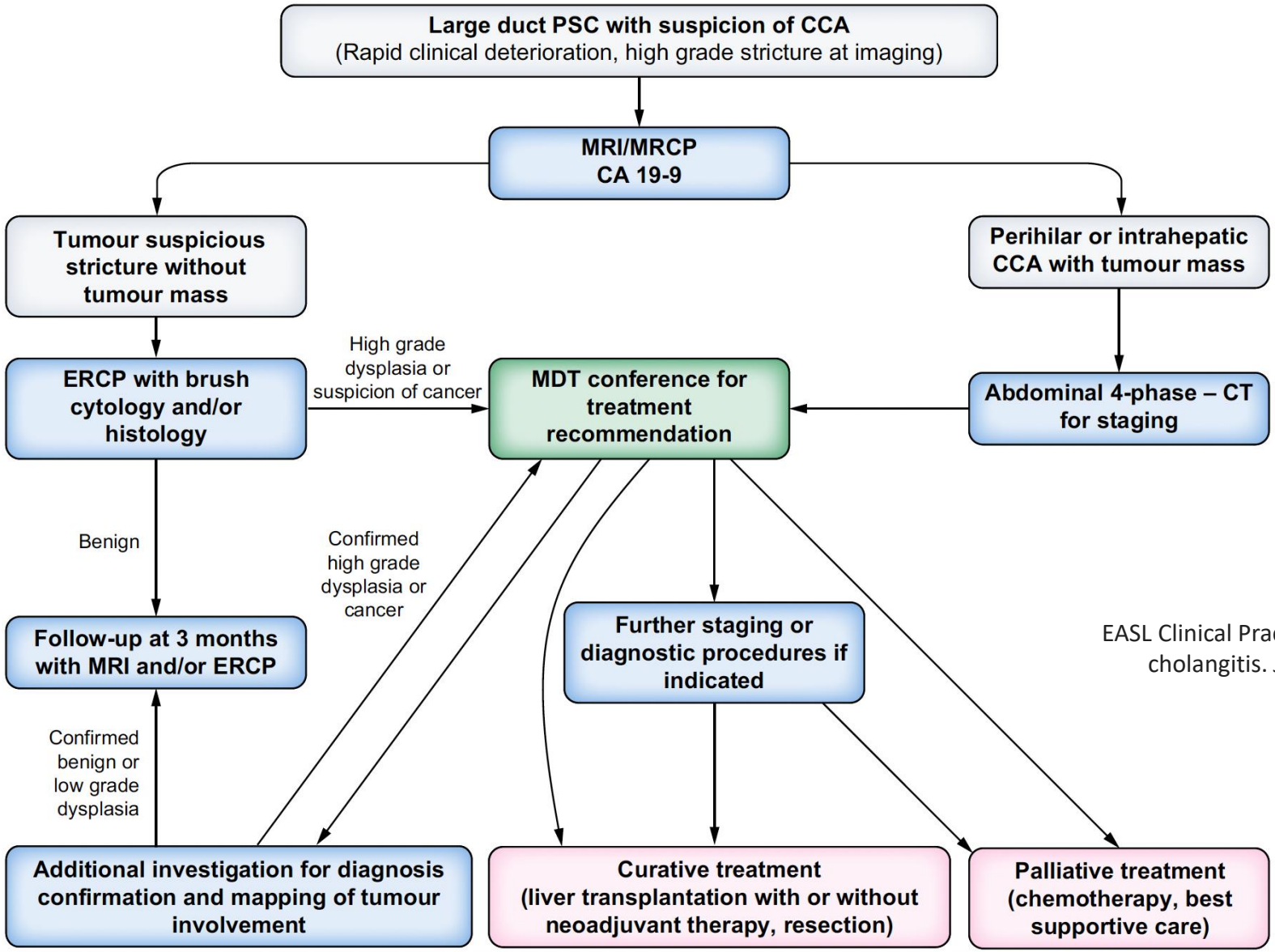
CEP como enfermedad preneoplásica. Colangiocarcinoma.

- CCA must be suspected in i) newly diagnosed PSC with high-grade stricture(s) and in ii) known PSC with worsening of signs or symptoms, progressive stricture(s) or a new mass lesion identified on imaging **(LoE 4, strong recommendation, 93% consensus).**
- Diagnostic work-up by an experienced multidisciplinary team is recommended in people with PSC and suspected CCA **(LoE 5, strong recommendation, 100% consensus).**
- Contrast-enhanced, cross-sectional imaging is recommended as the initial diagnostic test when CCA is suspected, potentially followed by ERCP with ductal sampling (brush cytology, endobiliary biopsies) for diagnosis and staging of the suspected CCA **(LoE 1, strong recommendation, 96% consensus).**
- Serum CA 19-9 can be assessed in all patients where CCA is suspected and fluorescence *in situ* hybridisation (FISH) or equivalent chromosomal assessments can be considered when brush cytology and/or histology are equivocal **(LoE 3, weak recommendation, 91% consensus).**

- Referral to a specialised centre is recommended when CCA or high-grade dysplasia is confirmed. In a multidisciplinary approach, therapeutic options including liver transplantation, liver resection, irradiation, brachy- or systemic therapy or combinations should be considered **(LoE 3, strong recommendation, 96% consensus).**

EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

CEP como enfermedad preneoplásica. Colangiocarcinoma.



EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

CEP como enfermedad preneoplásica. Cáncer VB.

Cáncer vesícula biliar (RR x 30 – 40 respecto a la población general).

- RNM o ecografía anual.
- 60% de las lesiones polipoides son malignas.
- La sensibilidad para cáncer de los pólipos > 8 mm de diámetro es del 100% y la especificidad del 70%

- Si se identifica un pólipo en la VB:

  - Tamaño igual o superior a 8 mm de diámetro: Colecistectomía.
    - Alta frecuencia morbilidad (40%)
    - Child > 7 puntos predice complicaciones precoces

  - Tamaño menor de 8 mm de diámetro:
    - Función hepática normal. Colecistectomía.
    - Observación resto casos.

18. CCA and gallbladder carcinoma surveillance should be performed annually and include abdominal imaging, preferably by MRI/MRCP with or without serum CA 19-9. Surveillance is not recommended for patients with PSC under 18 years of age or with small-duct PSC.
19. Intraductal tissue sampling for cytology and FISH should be performed routinely during ERCP for relevant strictures.
20. Cholecystectomy should be considered for patients with PSC with gallbladder polyps >8 mm, preferably at an experienced center in patients with advanced disease. Polyps ≤8 mm may be monitored with US every 6 months.
21. Patients with PSC with cirrhosis should undergo HCC surveillance consistent with current AASLD guidelines.

- Cholecystectomy is recommended in people with PSC with gallbladder polyps greater or equal to 8 mm in size and smaller polyps growing in size, due to the high risk of malignancy or dysplasia **(LoE 4, strong recommendation, 89% consensus).**

Razumilava et al. Hepatology 2011. Eaton et al.AJG 2012. Said et al. J Hepatol 2007.
EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.
Bowlus CL et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023; 77: 659-702.

CEP como enfermedad preneoplásica. Otros tumores.

Hepatocarcinoma.

- Incremento del riesgo similar a otros pacientes con cirrosis hepática (1,5% / año)
- Igual seguimiento (ya recomendado para la VB).

Cáncer colorectal (x 10).

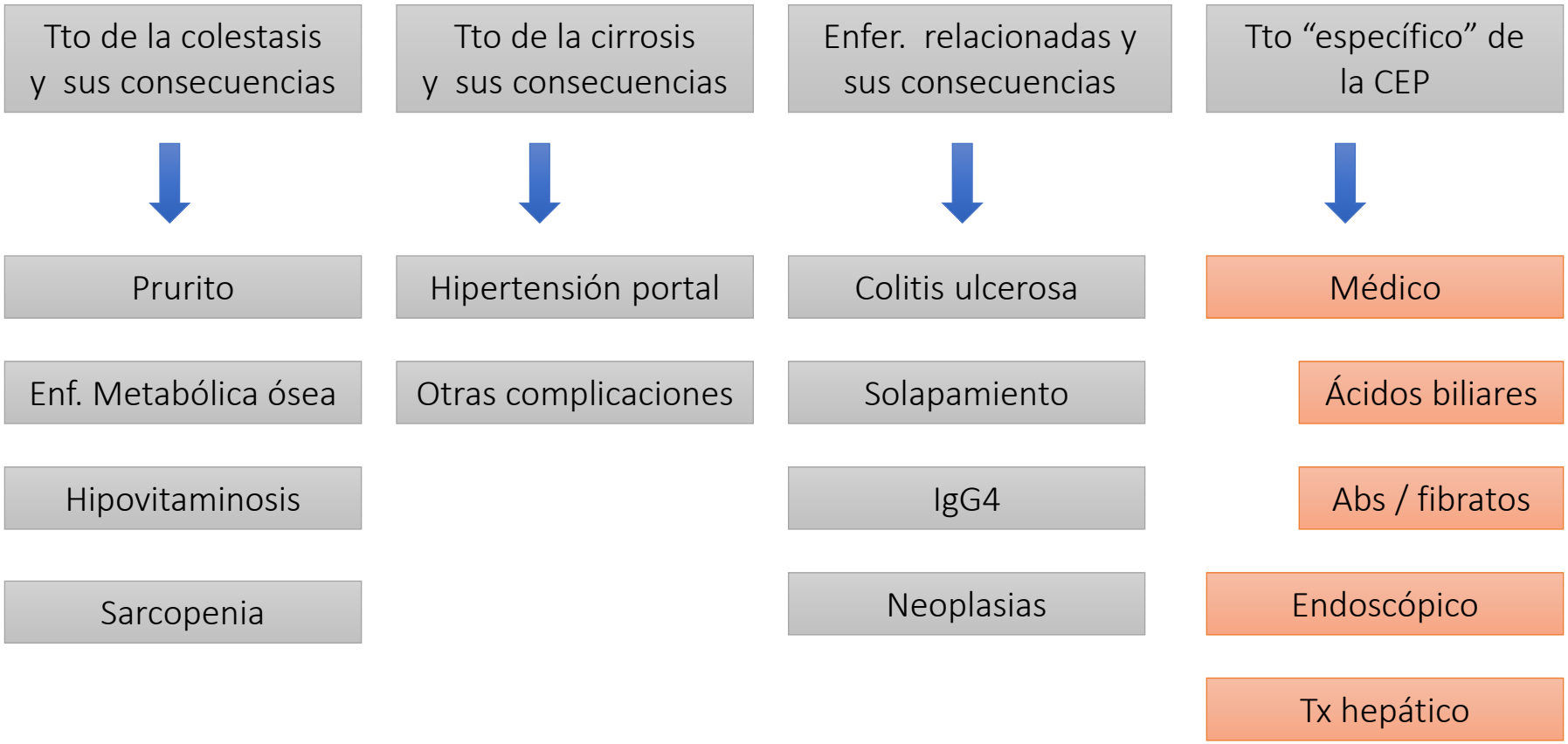
- Colonoscopia más biopsias múltiples cada 1-2 años.
- Si se identifica displasia manejar en función de las guías de la AGA.
- Control anual después del TxH.
- Control anual del reservorio ileoanal y/o de la ileostomía

- Ileocolonoscopy with biopsies from all colonic segments including the terminal ileum, regardless of the presence of lesions, is recommended at the time of PSC diagnosis **(LoE 3, strong recommendation, 100% consensus).**
- A diagnostic colonoscopy can be considered every 5 years in people with PSC where no IBD is present or whenever complaints suspicious for IBD occur **(LoE 5, weak recommendation, 92% consensus).**
- Annual surveillance (or every 1 to 2 years in individualised patients without inflammatory activity) colonoscopy with biopsies is recommended in all adult PSC-IBD patients regardless of the duration of IBD or liver transplant status **(LoE 3, strong recommendation, 92% consensus).**

MÁSTER EN HEPATOLOGÍA

EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

Esquema general de tratamiento de la CEP



Tratamiento ”específico” de la CEP. Ácidos biliares.

El único tratamiento “específico” que se administra en los pacientes con una CEP es, habitualmente, el UDCA. Sin embargo:

1. No existe una evidencia suficiente acerca de la bondad de este tratamiento (contraindicado en las guías AASLD) o sin evidencia suficiente en las guías EASL.

2. Las dosis altas pueden asociarse a un agravamiento de la enfermedad, por lo que en este momento se deben considerar contraindicadas.

3. Es controvertida la potencial acción quimioprotectora del UDCA sobre el CCR.

4. Están en evaluación otros tratamientos basados en ácidos biliares como el nor-UDCA.

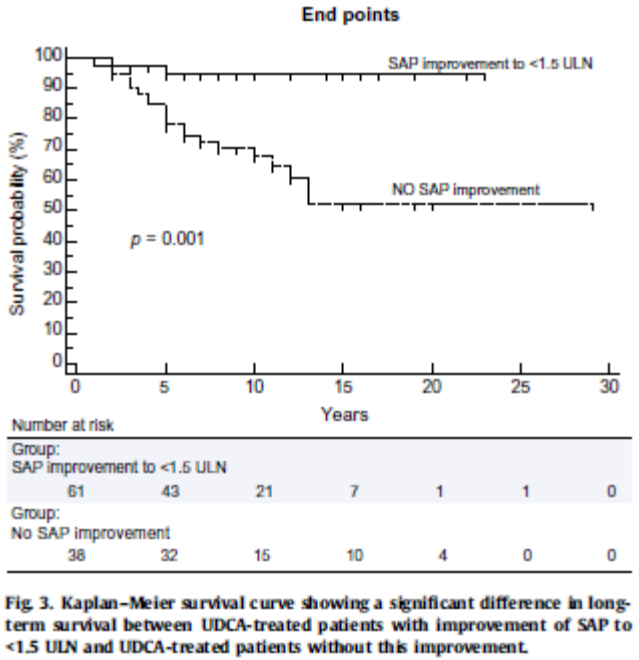


Fig. 3. Kaplan–Meier survival curve showing a significant difference in long-term survival between UDCA-treated patients with improvement of SAP to <1.5 ULN and UDCA-treated patients without this improvement.

Al Mamari S, et al. Improvement of serum…. J Hepatol 2013; 58: 329-334

Tratamiento ”específico” de la CEP. Ácidos biliares.

- UDCA at doses of 15-20 mg/kg/d can be given since it may improve serum liver tests and surrogate markers of prognosis. Available data does not allow for a firmer recommendation **(LoE 1, weak recommendation, 76% consensus).**
- UDCA at doses of 28-30 mg/kg/d should not be given **(LoE 1, strong recommendation, 100% consensus).**

- Las evidencias acerca de una potencial disminución del riesgo de cáncer de colon y/o del desarrollo de colangiocarcinoma en los pacientes tratados con UDCA son muy bajas.

- Se están evaluando otras terapias basadas en ácidos biliares como el norUDCA (ácido nurocólico, ácido obeticólico, cilofexor y aldafermina), pero los resultados son todavía muy preliminares.

EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

Tratamiento ”específico” de la CEP. Corticoides e inmunosupresores.

Colangitis esclerosante e IgG4.

- CEP relacionada con IgG4
- Enfermedad por IgG4

Solapamiento HAI / CEP:

- Del 1 al 17% de todas las CEP.
- Cerca del 50% son niños.
- El desarrollo de la enfermedad puede ser secuencial.
- Está indicada una prueba terapeútica con corticoides o IS.

- Use of corticosteroids/immunosuppressives/biologics is not suggested for the routine treatment of PSC **(LoE 4, weak recommendation, 96% consensus).**
- In people with PSC with biochemically (ALT, IgG, auto-antibodies) and histologically suggestive features of AIH, it is suggested to consider corticosteroids or other immunosuppressive therapies under close monitoring **(LoE 3, weak recommendation, 88% consensus).**
- It is not suggested to use corticosteroids or immunosuppressive therapies in people with PSC with mildly elevated serum IgG4 (<2x ULN) **(LoE 5, weak recommendation, 91% consensus).**

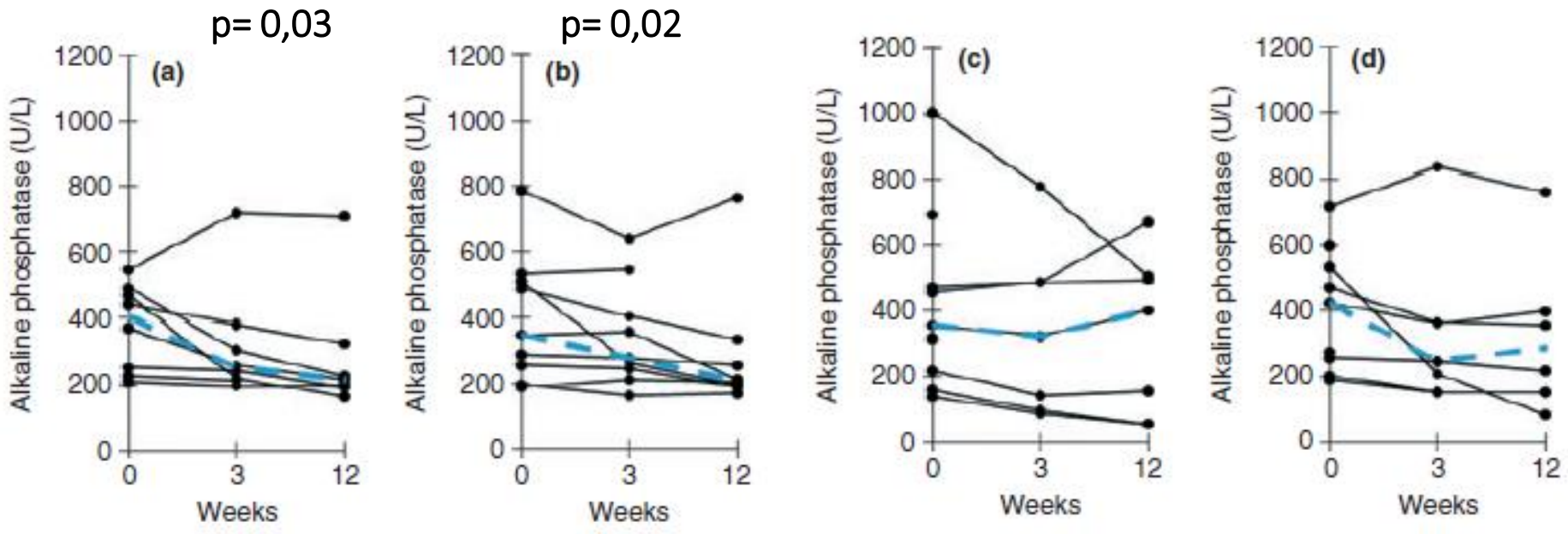
EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

Tratamiento ”específico” de la CEP. Corticoides e inmunosupresores.

Drug	year	n	Antibiotic dose	Treatment duration	Change in ALP	Other
Metronidazole +UDCA vs. placebo + UDCA	2004	80	600-800 mg/day	36 months	- 52%	50% on MTZ/UDCA had AEs
Minocycline	2009	16	200 mg/day	12 months	- 20%	25% discontinued due to AEs
Vancomycin	2008	14	50 mg/kg (**kids**)	Up to 54 months		**Normalization of GGT and ALT in non cirrhotics**
Vancomycin vs. metronidazole	2013	18 vs. 17	Vanco: 125 or 250 mg qid MTZ: 250 or 500 mg tid	12 weeks	- 42% - 10%	6 patients discontinued study due to AE, 4 in MTZ group
Vancomycin	2016	29	125 mg qid	12 weeks	- 45%	
Rifaximin	2017	16	550 mg bid	12 weeks	No change	

Farikka et al. Hepatology 2004; Silveira et al. Am J Gastro 2009; Davies et al. J Pediatr Gastroenterol Nutr 2008; Tabibian et al. AP&T 2013; Rahimpour et al. J Gastrointestin Liver Dis 2016; Tabibian et al. Am J Ther 2017

Tratamiento ”específico” de la CEP. Corticoides e inmunosupresores.



Variación en FA en los grupos de pacientes con dosis altas y bajas de vancomicina y metronidazol.
(a) Dosis baja de vancomicina, (b) Dosis alta de vancomicina,
(c) Dosis baja de metronidazol, (d) Dosis metronidazol.

Tabibian JH,. Aliment Pharmacol Ther 2013; 37: 604–612

Tratamiento ”específico” de la CEP. Corticoides e inmunosupresores.

- **NO indicados en la actualidad**

- Muy pocos datos; estudios con pocos pacientes
- ¿Qué antibiótico?
- ¿Qué dosis?
- ¿Cuánto tiempo tiempo debe durar el tratamiento?
- ¿Cuál es su eficacia?
- ¿Quién se beneficia de este tratamiento?

- Long-term use of antibiotics is not recommended for treatment of PSC in the absence of recurrent bacterial cholangitis **(LoE 3, strong recommendation, 100% consensus).**

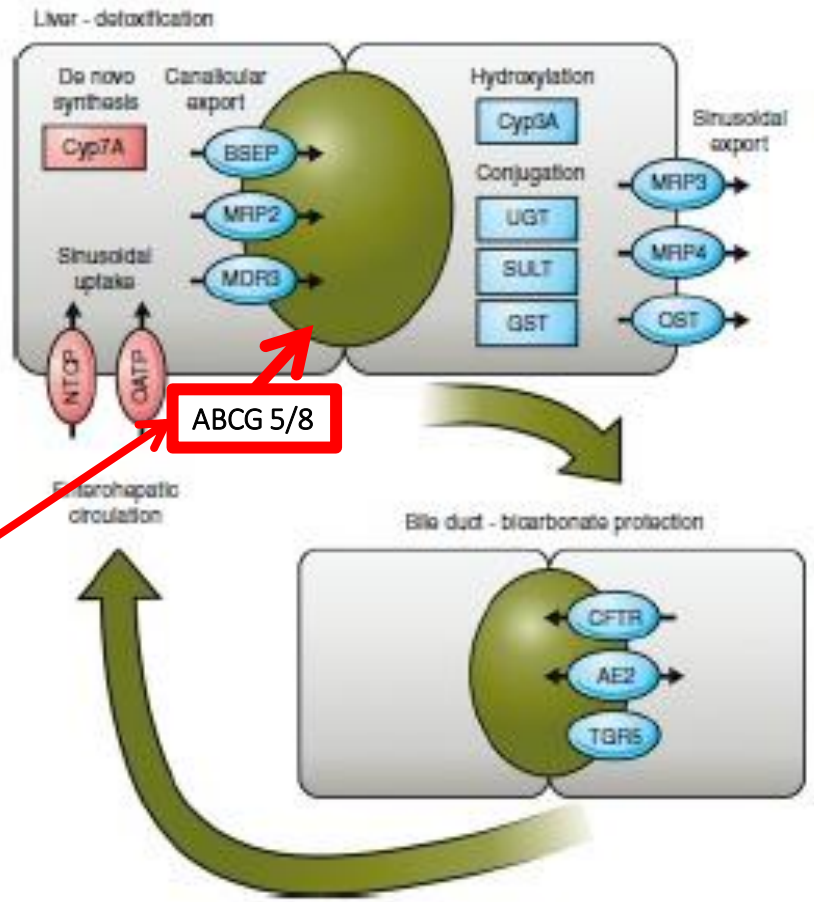
EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

Tratamiento ”específico” de la CEP. Corticoides e inmunosupresores.

Concepto: Fibratos disminuyen la concentración de FA de origen hepático (1993).

Mecanismo:

- Agonista PPAR alfa, delta, gamma (agonista pan-PPAR).
- Agonista PXR



Hirschfield GM, et al. Gastroenterology 2013; 144: 1357–1374.
Karlsen et al. TH. Aliment Pharmacol Ther 2014; 39: 282–301
Honda et al. Hepatology 2013: 57: 1931 – 1941.
Ghonem NS, Boyer JL. Hepatology 2013; 57: 1691-1971.

Tratamiento ”específico” de la CEP. Corticoides e inmunosupresores.

Table 1. Summary of Prospective Clinical Studies Testing the Efficacy of Bezafibrate as Adjunct Therapy in Patients With Chronic Cholestatic Liver Disease Not Responding Adequately to UDCA Monotherapy

Author (Reference)	Daily BF Dose	Daily UDCA Dose	UDCA (n), UDCA+BF (n) (Diagnosis)	Bezafibrate Safety	Therapeutic Outcomes of Adjunct Bezafibrate
Nakai et al.[18]	400 mg	600 mg	13, 10 (PBC)	No side effects	↓ ALP, γ-GTP, and IgM
Kanda et al.[19]	400 mg	600 mg	11, 11 (PBC)	Polydipsia (n = 1), resolved w/o therapy interruption	↓ ALP and pruritis
Ohmoto et al.[20,21]	400 mg	600 mg	11, 6 (PBC)[20] 10, 10 (PBC)[21]	Not reported	↓ serum markers of hepatic fibrosis[20]; ↓ ALP, γ-GTP, ALT,

Table 2. Summary of Prospective Clinical Studies Testing the Efficacy of Fenofibrate as Adjunct Therapy in Patients With Chronic Cholestatic Liver Disease Not Responding Adequately to UDCA Monotherapy

Author (Reference)	Daily FF dose	Daily UDCA dose	UDCA (n), UDCA+ FF (n) (diagnosis)	Fenofibrate Safety	Therapeutic Outcomes of Adjunct Fenofibrate
Ohira et al.[7]	150-200 mg	600-900 mg	7, 7 (PBC)	No side effects	↓ ALP, γ-GTP, IgM, pruritis, and fatigue
Dohmen et al.[4]	< 60 kg:100 mg; > 60 kg:150 mg	600 mg	9, 9 (PBC)	No side effects	↓ ALP, γ-GTP, IgM, and AMA
Levy et al.[6]	160 mg	13-15 mg/kg	20, 20 (PBC)	Heartburn (n = 2): study withdrawal	↓ ALP, IgM, AST, TGs, and serum cytokines
Han et al.[5]	200 mg	13-15 mg/kg	22, 22 (PBC)	Pruritis (n = 1): interruption, symptoms resolved, then FF restarted	↓ ALP, γ-GTP, ALT, AST, cholesterol, and TGs
Liberopoulos et al.[9]	200 mg	600 mg	4, 6 (PBC)	No side effects	↓ ALP, γ-GTP, ALT, cholesterol and TGs

Ghonem NS, Boyer JL. Hepatology 2013; 57: 1691-1971

Tratamiento ”específico” de la CEP. Corticoides e inmunosupresores.

Bezafibrato + UDCA vs Placebo + UDCA

- 67% of patients on BZF normalized ALP vs. 0 on placebo
- 30% of patients on BZF normalized all liver chemistries vs. 0 on placebo
- 75% improvement in itching score vs. 0% for patients on placebo
- Improvements in markers of fibrosis and liver stiffness on BZF group

Corpechot C et al. AASLD 2017. LB-01.

Tratamiento ”específico” de la CEP. Corticoides e inmunosupresores.

- NO indicados en la actualidad

- Muy pocos datos; estudios con pocos pacientes
- ¿Cuánto tiempo tiempo debe durar el tratamiento?
- ¿Cuál es su eficacia?. No hay datos a largo plazo.
- ¿Cuál es su toxicidad?. No hay datos a largo plazo
- ¿Quién se beneficia de este tratamiento?

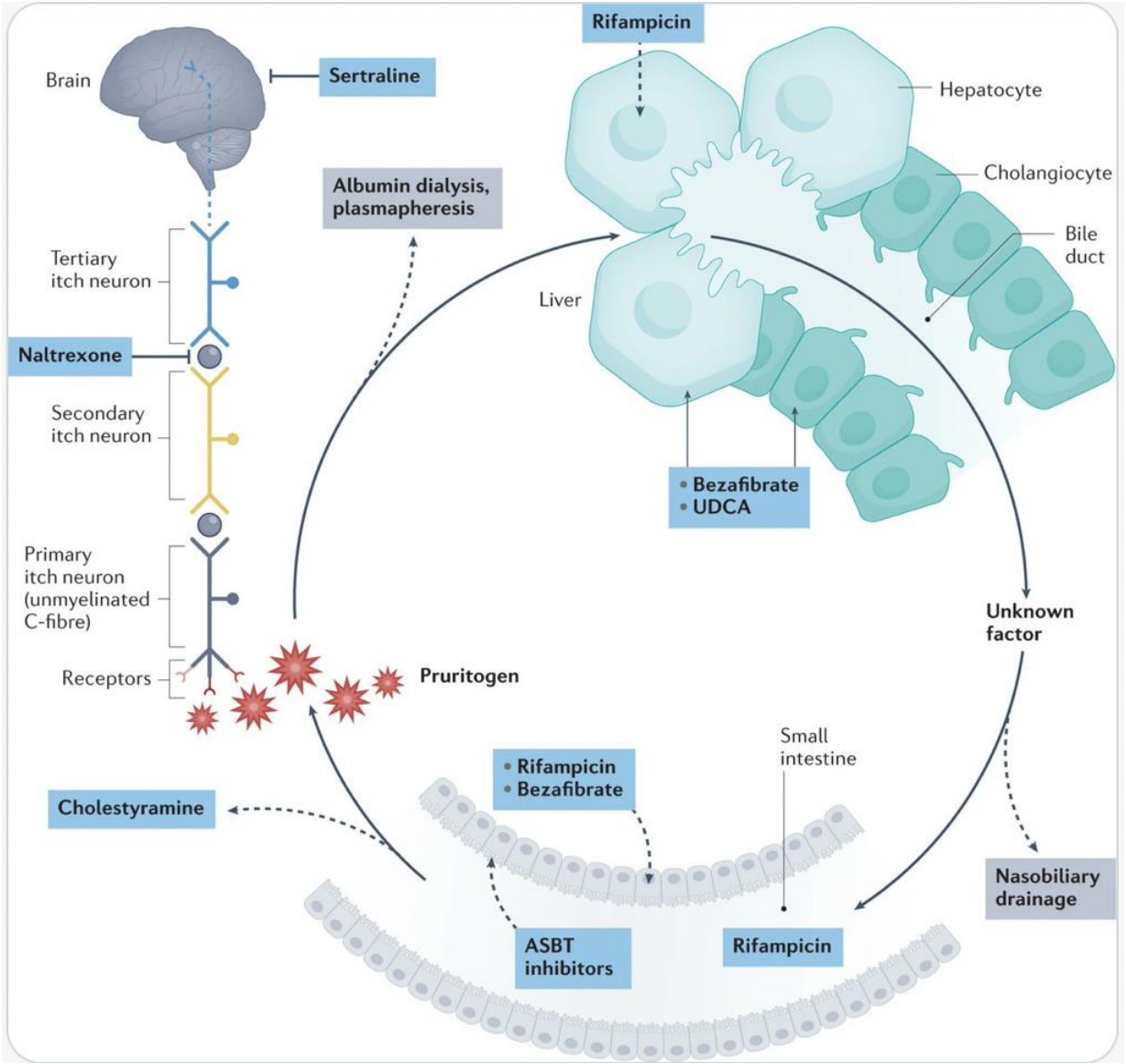
- Pero……..Disminuye la FA

Tratamiento ”específico” de la CEP.

11. All patients with PSC should be considered for participation in clinical trials.
12. In patients not eligible or interested in clinical trials with persistently elevated ALP or GGT, UDCA 13–23 mg/kg/day can be considered for treatment and continued if there is a meaningful reduction or normalization in ALP (GGT in children) and/or symptoms improve with 12 months of treatment.
13. Currently, there is insufficient evidence to recommend the use of oral vancomycin for the treatment of PSC.
14. Patients with PSC with a diagnosis of concurrent AIH should be treated according to the AASLD AIH guidelines.
15. Antibiotics should be used for bacterial cholangitis with consideration for MRCP to rule out relevant strictures.
16. ERCP should be performed for bacterial cholangitis if there is an inadequate response to antibiotics.
17. Upper endoscopy to screen for varices should be performed if the LS is >20 kPa by TE or the platelet count is $\leq 150{,}000/mm^3$.

Bowlus CL et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023; 77: 659-702.

Tratamiento de algunos problemas muy relevantes de la CEP. Prurito.



Beuers U, Wolters F, Oude Elferink RPJ. Mechanisms of pruritus in cholestasis: understanding and treating the itch. Nat Rev Gastroenterol Hepatol. 2023 Jan;20(1):26-36. doi: 10.1038/s41575-022-00687-7. Epub 2022 Oct 28. PMID: 36307649.

Tratamiento de algunos problemas muy relevantes de la CEP. Prurito.

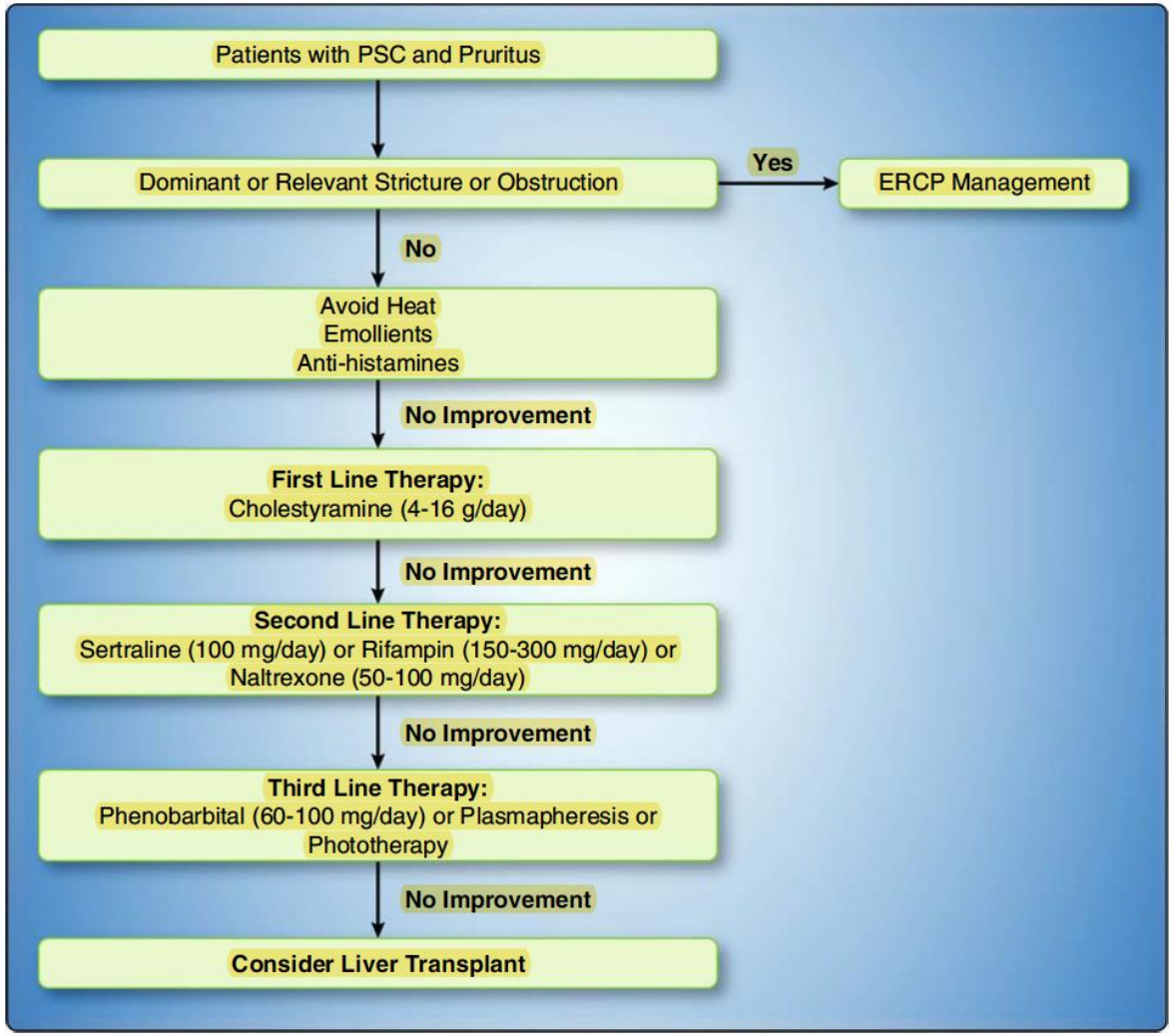
Table 6. Medical treatment of pruritus in sclerosing cholangitis.

Evidence	Drug	Potential side effect	References
1st line	Bezafibrate (400 mg daily)	Renal insufficiency, myalgia, myopathy, hepatitis	219
2nd line	Rifampicin (150-300 mg/d)	Hepatitis	20,51
3rd line	Naltrexone (12.5-50 mg/d)	Opioid withdrawal syndrome	20,51
No evidence for PSC	Anion exchange resins (cholestyramine [4 g once to four times daily], colesevelam [1,250-1,875 mg twice daily]; 4 hours separate from other medication)	Abdominal discomfort	20,51
No evidence for PSC	Sertraline (50-75 mg/d)		20,51
Experimental	ASBT inhibitors	Diarrhoea	
Experimental	Selective PPARα and PPARδ agonists		

- It is recommended to exclude relevant bile duct strictures in large duct sclerosing cholangitis as the cause of progressive pruritus. If present and reachable, relevant strictures should be treated by endoscopic balloon dilatation (or stenting, if balloon dilatation alone is insufficient) after brushing **(LoE 4, strong recommendation, 95% consensus).**
- Pharmacological treatment of moderate to severe pruritus in sclerosing cholangitis with bezafibrate or rifampicin is recommended **(LoE 4, strong recommendation, 83% consensus).**

EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

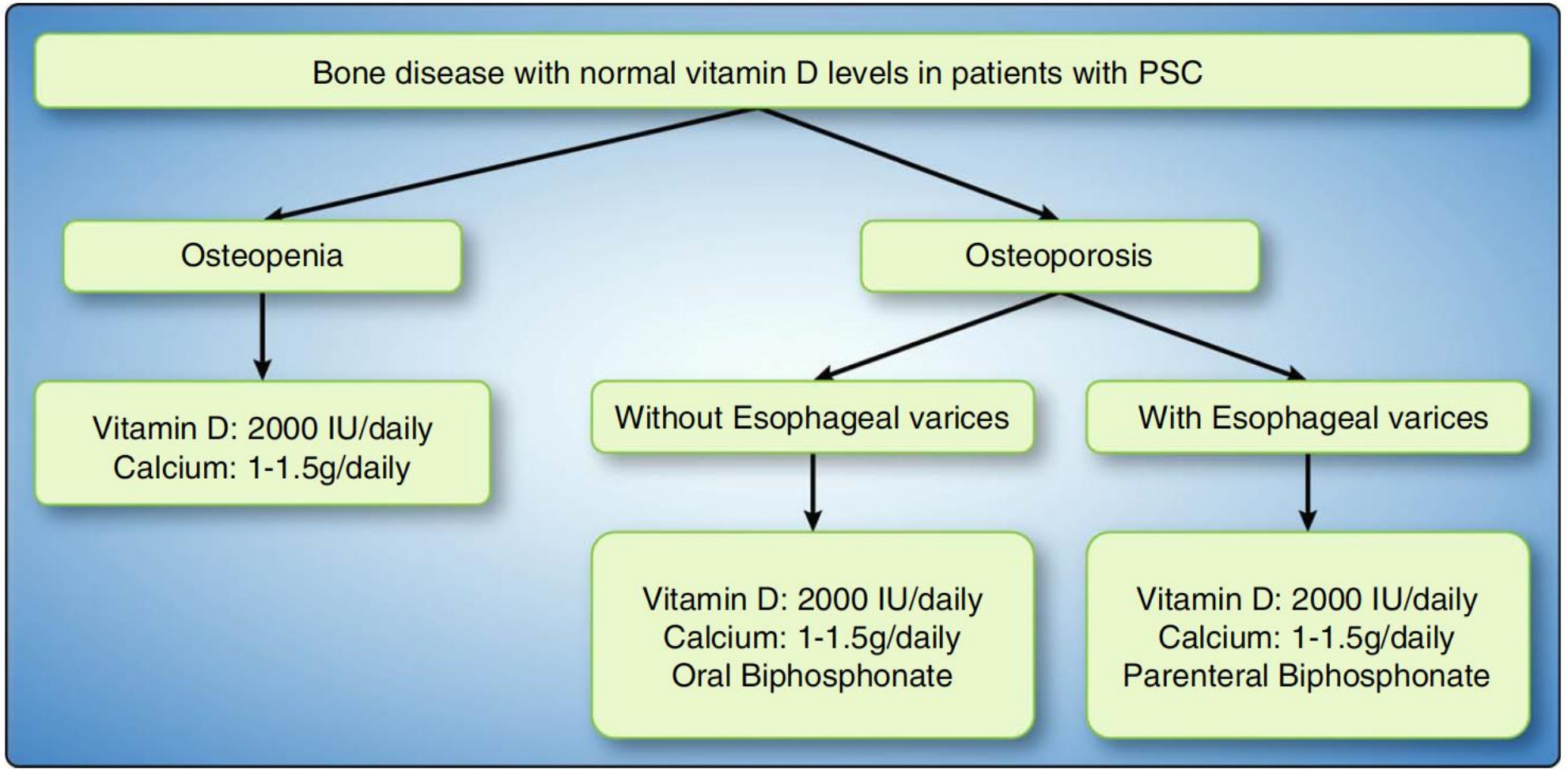
Tratamiento de algunos problemas muy relevantes de la CEP. Prurito.



26. Bile acid sequestrants should be used as initial therapy for patients with PSC who have pruritus that does not respond to conservative measures such as heat avoidance, emollients, and antihistamines. Alternatives for refractory pruritus include sertraline 100 mg daily, naltrexone titrated to a dose of 50–100 mg daily, and rifampin 150–300 mg twice daily.
27. Management of IBD in patients with PSC is similar to that in those without PSC. Active management of IBD and surveillance of colon cancer should continue in the posttransplant period.
28. Nutritional assessments, including but not limited to biometrics and lipid-soluble vitamin levels, should be performed at PSC diagnosis and yearly thereafter with nutritional intervention and vitamin supplementation as needed.
29. Bone density examinations should be performed to exclude osteopenia or osteoporosis at diagnosis and at 2-year to 3-year intervals thereafter based on risk factors.

Bowlus CL et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023; 77: 659-702.

Tratamiento de algunos problemas muy relevantes de la CEP. Enf. osea.



Bowlus CL et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023; 77: 659-702.

Tratamiento de algunos problemas muy relevantes de la CEP. Defícit vitamínicos.

TABLE 4 Clinical manifestations of vitamin deficiencies and recommended supplementations[355,356]

Vitamin	Clinical symptoms	Recommend daily doses (children) Repletion	Maintenance	Recommend daily doses (adults) Repletion	Maintenance	Comments
Vitamin A	Night blindness, xerophthalmia	5000–10,000 IU daily	1500–5000 IU daily	5000–100,000 IU daily × 2 weeks	1500–5000 IU daily	Frequent monitoring to avoid hypervitaminosis A
Vitamin D[d]	Osteomalacia,[a] osteoporosis,[b] Rickets,[c] tetany in children	4000–8000 IU daily	400–2000 IU daily	*Serum 25(OH)D < 12 ng/ml*		
				50,000 IU weekly × 8 weeks	800 IU daily	May require higher doses or use of hydroxylated vitamin D metabolites
				Serum 25(OH)D 12–20 ng/ml		
				800–1000 IU daily	800–1000 IU daily	
				Serum 25(OH)D 20–30 ng/ml		
				600–800 IU daily	600–800 IU daily	
Vitamin E	Neuropathy, ataxia, progressive neuromuscular disorder, hemolytic anemia	100–200 mg daily	15–25 mg daily	200–2000 mg daily	15 mg daily	
Vitamin K	Hypoprothrombinemia, bone disease (impaired osteoblast function)	2–5 mg i.v. × 3 days	2–5 mg daily	2.5–10 mg daily	5–10 mg oral weekly to daily	Monitor by INR or plasma phylloquinone

Note: Water-miscible formulas are recommended for supplementation.
Abbreviation: INR, international normalized ratio.
[a]Defective mineralization of the preformed osteoid occurs in both adults and children.
[b]Bone mineral density T-score < 2.5 present in 4%–10% of patients with PSC.
[c]Defective mineralization of the growth plate in growing children.
[d]Vitamin D_3 should be used for treatment and supplementation due to its greater bioavailability and affinity for vitamin D–binding protein.

Bowlus CL et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology 2023; 77: 659-702.

Tratamiento de algunos problemas muy relevantes de la CEP. Estenosis dominante.

Concepto

- Estenosis < 1,5 mm del colédoco.
- Estenosis < 1 mm de hepático der / iz

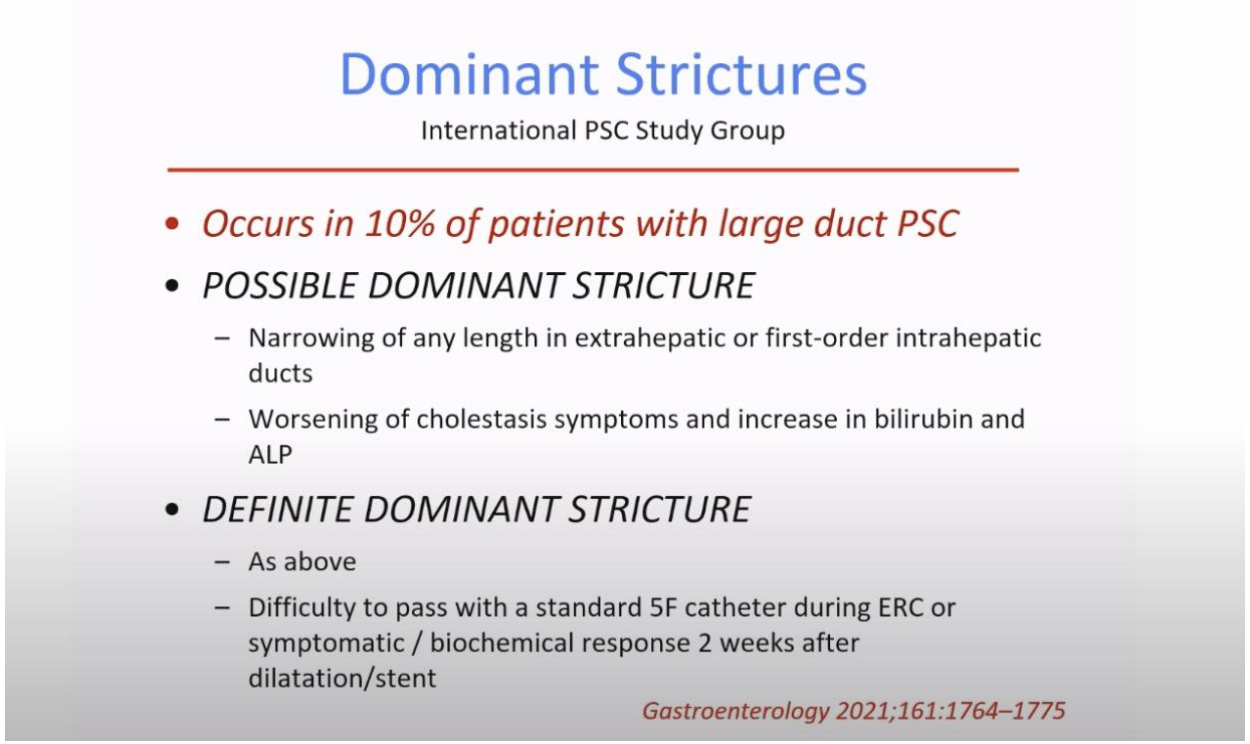
¿Siempre es precisa la actuación?.

- Progresión de la colestasis.
- Colangitis de repetición.
- Prurito refractario
- Se debe descartar de forma sistemática un colangiocarcinoma

Table 7. Definition and nomenclature of strictures in primary sclerosing cholangitis.

Type	Definition
Relevant stricture	A high-grade biliary stricture on imaging in the common bile duct or hepatic ducts with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis.
High-grade stricture	A biliary stricture on MRI/MRCP with >75% reduction of duct diameter in the common bile duct or hepatic ducts.

MRCP, magnetic resonance cholangiopancreaticography.



EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

Estenosis dominante ¿es siempre preciso el tratamiento endoscópico?

¿Cual es la mejor actitud terapéutica?.

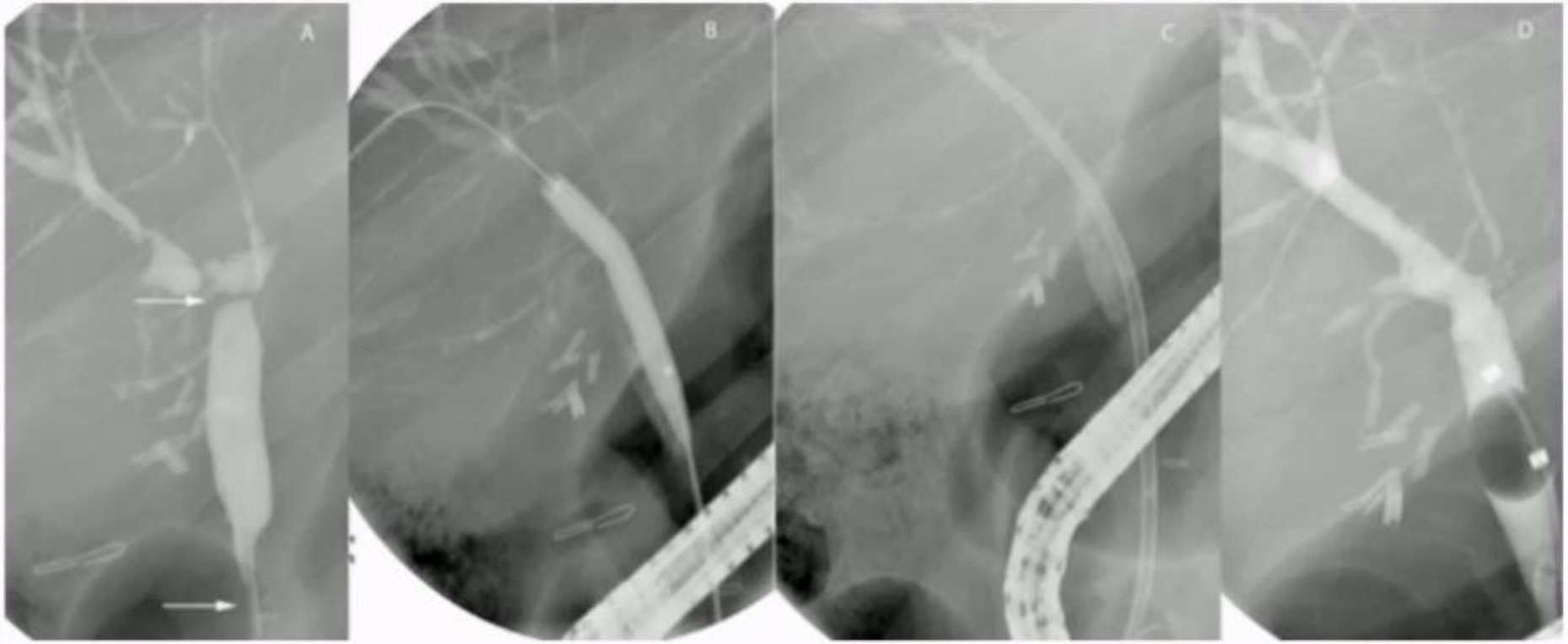
- Dilatación simple
- Dilatación más colocación de stent temporal (uno o varios / una o más veces).
- Siempre, profilaxis antibiótica a corto plazo (¿puede ser útil a largo plazo?.
- ¿y si no es posible lo anterior?. Colangiografía transhepática (rendez-vous) / Hepaticoyeyunostomía.

¿Cual es el riesgo de la actuación sobre la vía biliar?

- Colangitis de repetición (1%).
- Pancreatitis (5-7%).
- Los factores asociados al riesgo de pancreatitis / colangitis post-CPRE son: Cirrosis, Enfermedad de Crohn, solapamiento HAI, realización de esfinterotomía, experiencia del médico.

Alkhatibb et al. Dig Dis Sci 2011; 56: 3685
Clinical Gastroenterology and Hepatology 2013; 11: 898-907

Estenosis dominante ¿es siempre preciso el tratamiento endoscópico?



(A) Dominant strictures (B) Balloon dilatation of the strictures. (C) Placement of a 10F plastic biliary stent above the hilar stricture. (D) Stricture resolution noted on follow-up cholangiogram.

Estenosis dominante ¿es siempre preciso el tratamiento endoscópico?

Posibilidades de tratamiento:

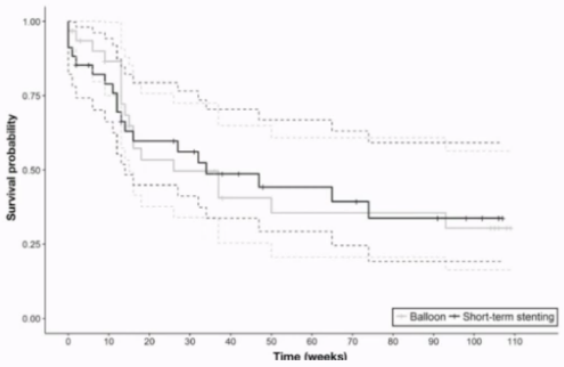
- Esfinterotomía
- Dilatación con balón sin esfinteerotomía
- Dilatación + stent temporal (poco tiempo)

DILISTENT STUDY

Stenting vs Balloon dilation – Open label trial 9 centers

Primary outcome - cumulative recurrence-free patency of the dominant stricture

- 65 randomized
  - 31 vs 34
- Stent (2weeks) vs balloon
- Cumulative recurrence-free rate did not differ significantly between groups at 24 months
- Study terminated by DSMB early due to high side effects in the stent group-
  - Pancreatitis 24% vs 3.3%
  - Cholangitis 12% vs 3.3%



Gastroenterology 2018;155:752–759

EASL/ESGE Guidelines. 2017
Lindor KD et al. Am J Gastro 2015
AASLD Guidelines, Hepatology. 2010

Estenosis dominante ¿es siempre preciso el tratamiento endoscópico?

Estenosis < 1,5 mm del colédoco.
Estenosis < 1 mm de hepático der / izq

Stenosis with a diameter of ≤1.5 mm in the CBD
or ≤1 mm in the intrahepatic duct within 2cm of main hepatic confluence.

First ERCP session

Consider sphincterotomy

↓

Balloon Dilate to 4 mm

↓

Insert Plastic Stent (7-10Fr)*

→

At 2-4 weeks

↓

Re-dilate (4-8 mm)

2-3 sessions

↓

Follow up

1. *REFRACTORY STRICTURES AFTER FAILURE OF DILATION * three*
2. *CHOLANGITIS*

Lindor KD et al. Am J Gastro 2015
AASLD Guidelines, Hepatology. 2010
EASL/ESGE Guidelines. 2017

Estenosis dominante ¿es siempre preciso el tratamiento endoscópico?

- Prurito intratable
- Colangitis de repetición / ictericia
- Estenosis dominante con colestasis progresiva
- Coledocolitiasis
- Sospecha fundada de colangiocarcinoma

Objetivos.

- Mejorar funcionalidad hepática y retrasar TxH
- Descartar colangiocarcinoma
- Tratar estenosis dominantes

- The indication for endoscopic intervention should ideally be discussed in multidisciplinary meetings of hepatologists, biliary endoscopists and abdominal radiologists. The procedure should be performed by experienced endoscopists **(LoE 5, strong recommendation, 96% consensus).**
- Therapeutic endoscopic intervention is recommended in patients with relevant strictures, defined as high-grade strictures on imaging in the common bile duct or hepatic ducts and signs or symptoms of obstructive cholestasis and/or bacterial cholangitis **(LoE 4, strong recommendation, 87% consensus).**

- Acute bacterial cholangitis should be treated with antibiotics and subsequent biliary decompression if an underlying relevant stricture is present **(LoE 3, strong recommendation, 96% consensus).**

- Law R, Baron TH. CLD 2014
- Thosani, Baneriee. Clin Liv Disease 2015
- EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

Trasplante hepático en pacientes con CEP.

La indicación de TxH en estos pacientes es especialmente difícil.
Es imprescindible una elevada experiencia.

Indicaciones de trasplante hepático :

- Convencionales:
  - Cirrosis hepática descompensada.
- Específicas:
  - Ictericia que no se resuelve con tto endoscópico.
  - Prurito intratable
  - Colangitis bacteriana recidivante.
- Cuestionables:
  - Displasia biliar
  - Colangiocarcinoma hiliar de < 3 cm.

Liver transplantation should be considered for people with PSC and decompensated cirrhosis or hepatocellular carcinoma according to standard guidelines **(LoE 3, strong recommendation, 100% consensus).**

Liver transplantation should be considered for people with PSC with recurrent bacterial cholangitis and/or severe pruritus or jaundice despite endoscopic and pharmacological therapy **(LoE 3, strong recommendation, 100% consensus).**

Liver transplantation can be considered in people with PSC and high-grade biliary dysplasia confirmed by cytology or ductal histology **(LoE 4, weak recommendation, 92% consensus).**

Liver transplantation for early-stage CCA in PSC can be performed within the context of clinical trials **(LoE 4, weak recommendation, 92% consensus).**

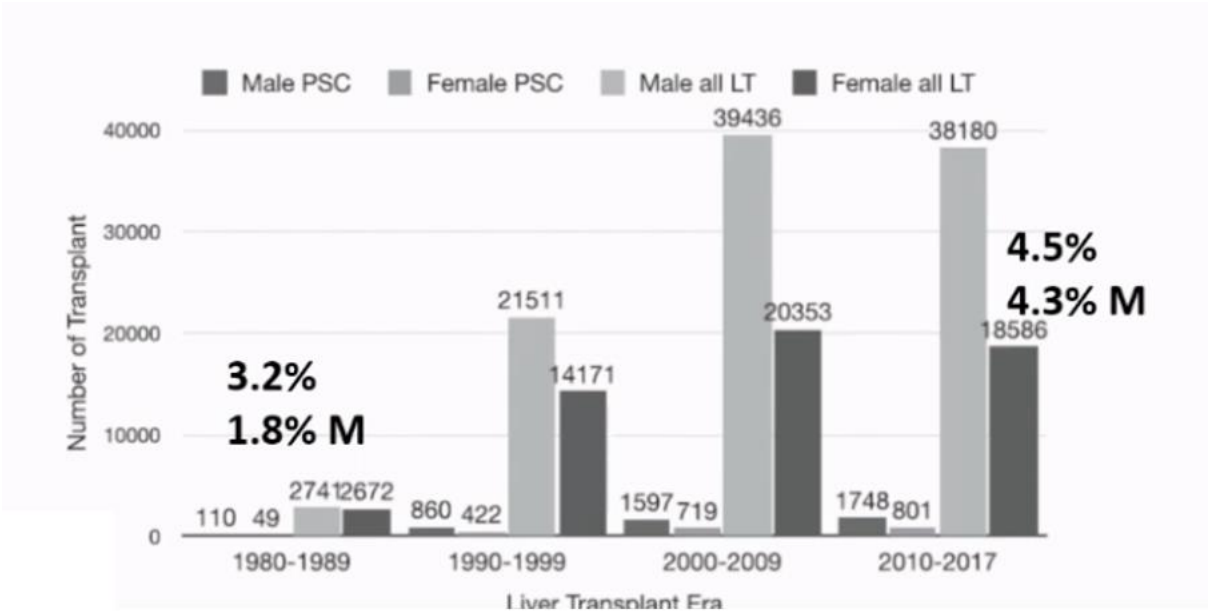
30. LT should be considered in all patients with PSC and complications of end-stage liver disease, recurrent cholangitis, intractable pruritus, or early-stage hepatobiliary cancers.
31. Patients with elevated liver enzymes after transplant should undergo histological and cholangiographic assessments to distinguish rPSC from allograft rejection and/or biliary complications.

Mogl MT et al. Survival without biliary complications after liver transplant for primary sclerosing cholangitis. Exp Clin Transplant 2013; 11: 510-21. Carbone M, Neuberger JM. Autoimmune liver disease, autoimmunity and liver transplantation. J Hepatol 2014; 60: 210-23. Carrion AF, Bhamidimarri KR. Liver transplant for cholestatic liver diseases. Clin Liver Dis 2013; 17: 345-59.
EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

Trasplante hepático en pacientes con CEP.

Liver transplantation in PSC should be performed using a duct-to-duct anastomosis unless anatomical disease location or technical surgical factors warrant a Roux-en-Y hepaticojejunostomy **(LoE 4, strong recommendation, 79% consensus).**

6463 TH por CEP en 159 centros desde 1980 a 2017



Aumento de las indicaciones por CEP en los últimos años-3.2%->4.5%
Diferencias según áreas geográficas
Aumento del número de mujeres con TH por CEP: 1.8%- >4.3%

Berenguer M; et al. Transplantation 2021
EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

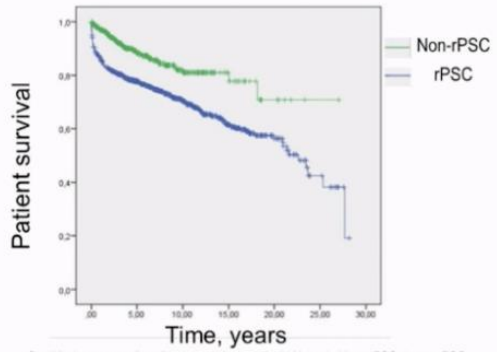
Trasplante hepático en pacientes con CEP. Recidiva post TX.

Objetivos:
1- Evaluar la **supervivencia** a largo plazo
2-Evaluar la necesidad de **RE-TH**
3-Evaluar el **impacto de la recurrencia** de CEP en estos dos aspectos

✓ ELTR, N=478 pacientes

Resultados:
✓ Mortalidad 27% al 1.5 años
✓ Re-TH 15.4%
✓ Supervivencia post- TH 87%, 78% y 70% los 1, 5 y 10 años

Recurrencia CEP fue del **17.5%**
-Menor supervivencia (HR 2.28, IC 95% 1.7.3.1, p<0.001)
-Mayor tasa de re-TH: 34% vs 17% (p<0.0001)



Graphical representation of post transplant survival with and without rPSC. In non-rPSC group T=0 is time of first LTx. In the rPSC group, T=0 is time of diagnosis of rPSC.

Visseren T, J Hepatol 2017, : S200

A diagnosis of recurrent PSC can be made based on progressive biliary strictures on cholangiography and/or histological findings compatible with PSC more than 90 days after liver transplantation upon exclusion of other identifiable causes **(LoE 4, weak recommendation, 92% consensus).**

- No existe tratamiento eficaz para la misma
- AUDC se ha administrado sin evidencia
  - Reducción de CCR—Uso recomendado en pacientes con CEP y CU post-TH
- Tratamiento de las estenosis biliares dominantes y sus síntomas
- En pacientes con CEP y EII →Tratamiento de la EII
- RE-TH

Martin et al Sem Liv Dis 2017

Visseren T, et a. J Hepatol 2017
EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022; 77: 761-806.

CEP. Conclusiones

Diagnóstico e historia natural:

- El diagnóstico de CEP se establece, en pacientes con colestasis, mediante RNM.
- La práctica de una bx hepática y/o de una CPRE se debe restringir a situaciones muy peculiares (CEP ducto pequeño, sospecha de solapamiento).
- Siempre se debe excluir una CE secundaria. No olvides IgG4.
- El fenotipo de la enfermedad es extraordinariamente variable.
- La historia natural es muy difícil de precisar. Los modelos de predicción de progresión NO son útiles para los pacientes individuales.

Tratamiento:

-El papel de los ácidos biliares es controvertido.

-Si existe sospecha de solapamiento con HAI (o de enfermedad por IgG4), se puede hacer un ensayo terapéutico con corticoides y/o inmunosupresores.

-El tto adecuado de las estenosis dominantes es crítico en la evolución de la enfermedad.

-El TxH se debe indicar en las circunstancias mencionadas con anterioridad.

CEP. Conclusiones

- La epidemiología de la indicación por CEP está cambiando-- mayor número de mujeres que llegan al TH
- La supervivencia tras el TH es buena
- La recurrencia de la CEP tras el TH acontece en torno al 20% y se asocia a
  -- mortalidad y re-TH
- No existe un tratamiento específico para la recurrencia de CEP
- En caso de recurrencia, el re-TH es una opción de tratamiento con resultados mejores que otras indicaciones de re-TH
- Implicaciones sobre el curso EII en la evolución post-TH
  -Colectomía pre-TH (protectora)
  -Modificaciones del microbioma
  -Adecuado control de la EII post-TH (tratamientos biológicos)

En mi opinión, los pacientes con una CEP en estadio no inicial deben ser remitidos a centros altamente especializados con unidad de endoscopias avanzada y TxH.

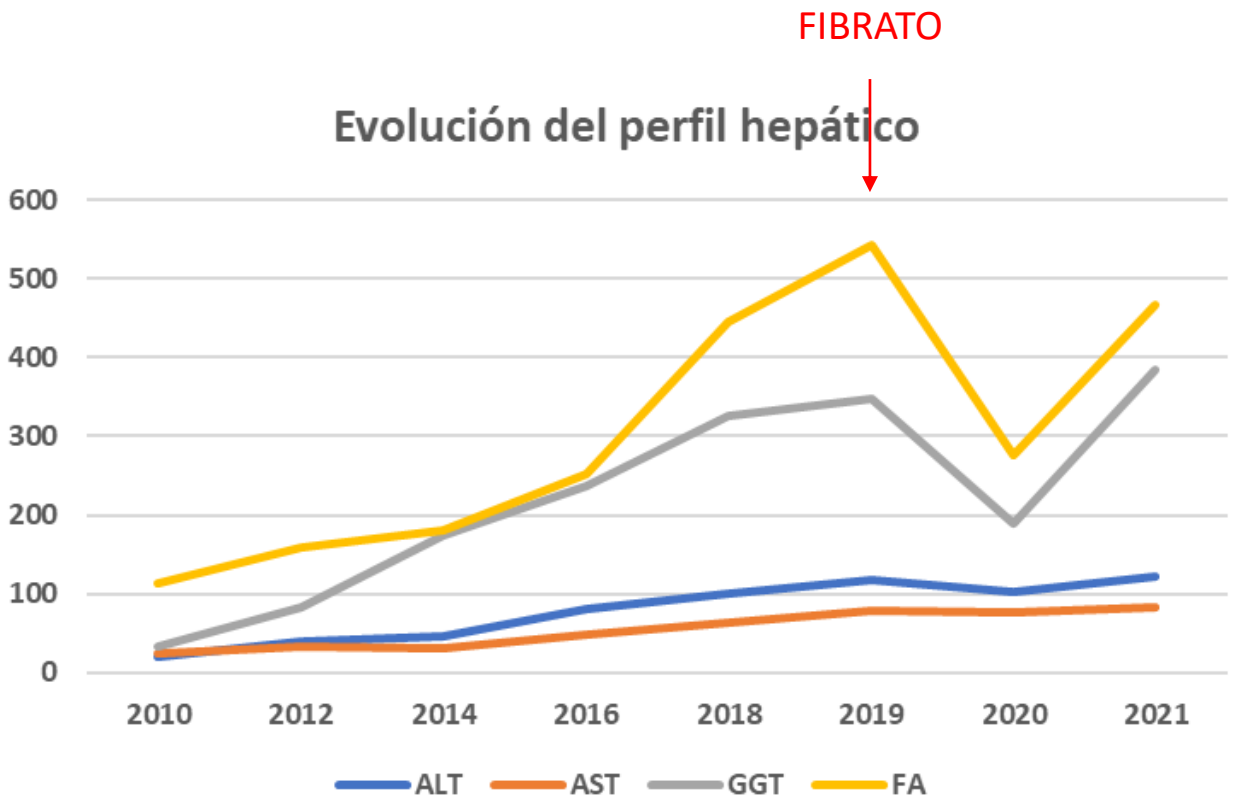
CASO CLÍNICO

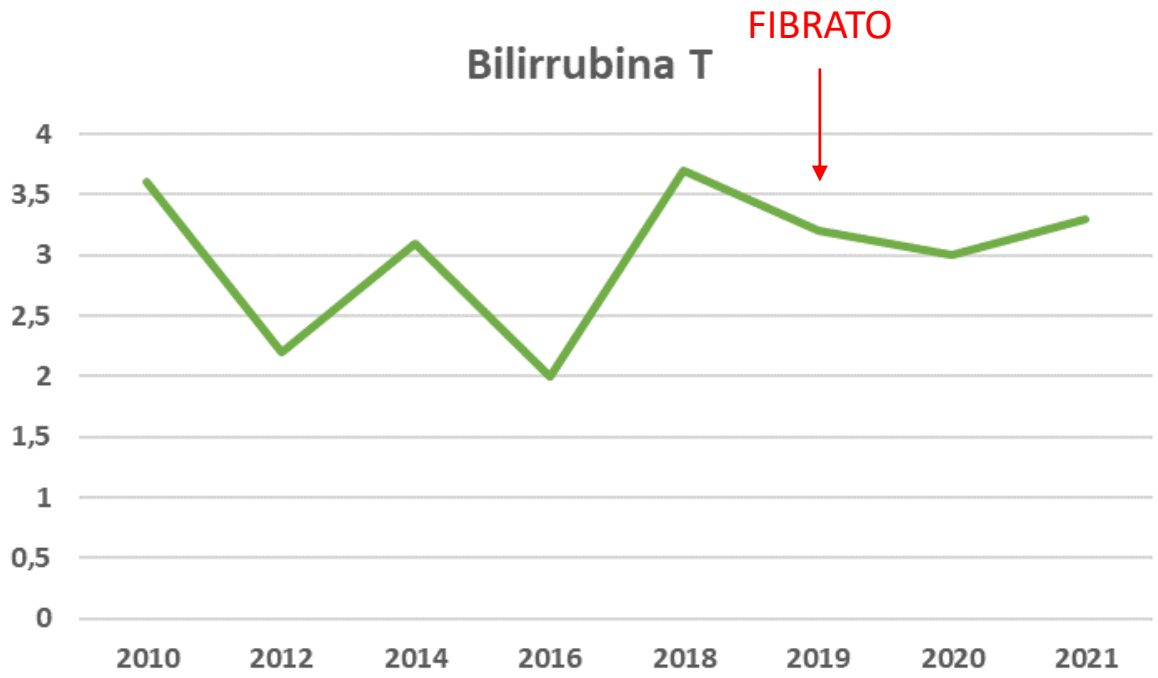
ÓSCAR

HISTORIA EN DIGESTIVO

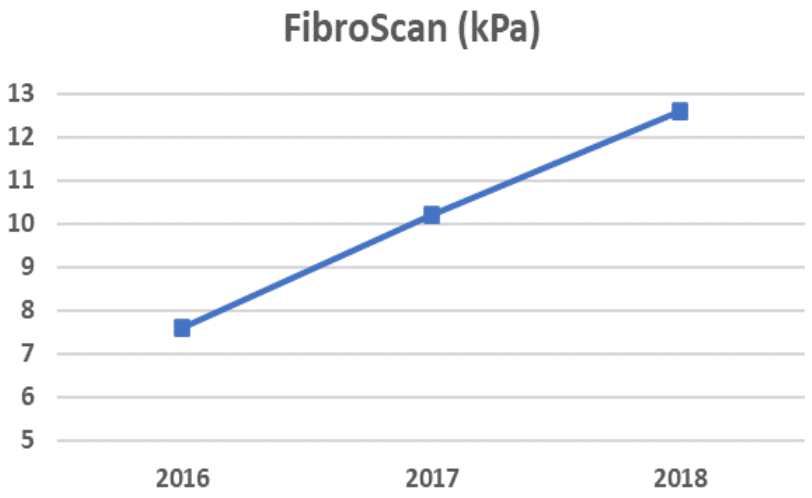
- 38 años
- Sin hábitos tóxicos
- CEP de afectación intrahepática diagnosticado en 2008 en tratamiento con UDCA desde entonces.

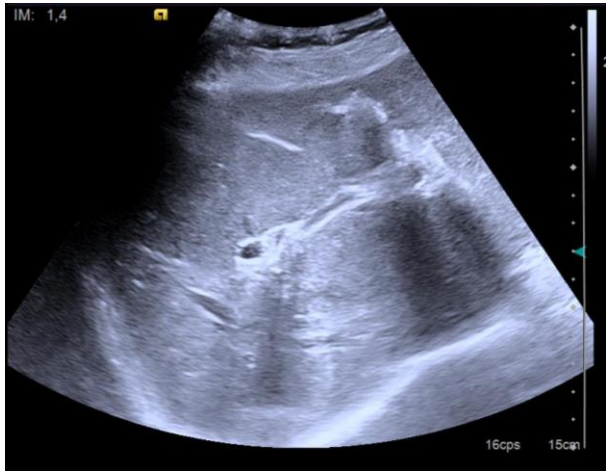
EVOLUCIÓN ANALÍTICA



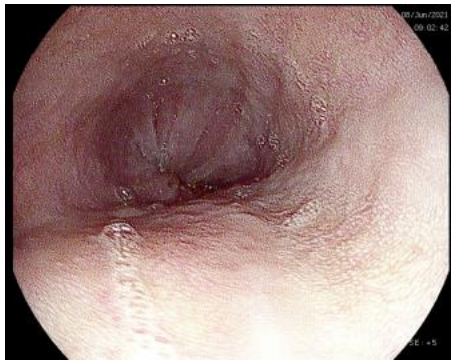


EVOLUCIÓN AFECTACIÓN HEPÁTICA





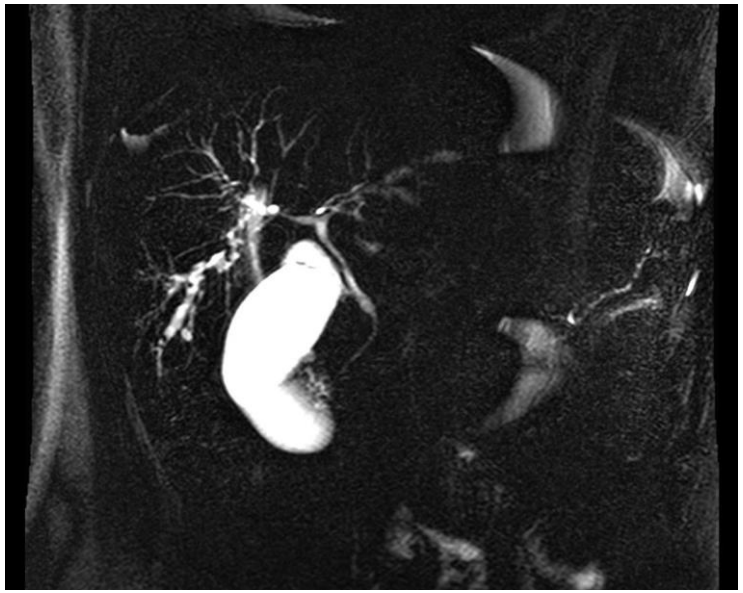
ECO abd (Nov-2019): Hígado con importantes cambios morfológicos en relación con hepatopatía crónica observándose contornos polilobulados. Gran crecimiento del lóbulo caudado. Parénquima es heterogéneo. Bazo de 13,5 cm.



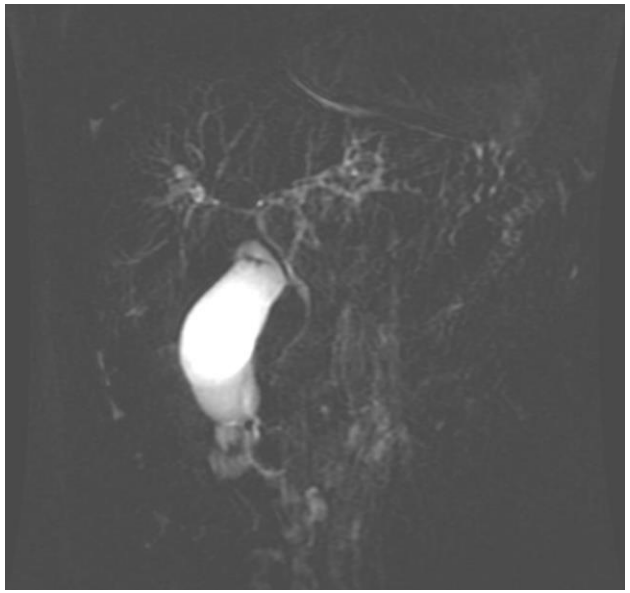
Gastroscopia (Jun-2021): No VVEE. Gastropatía HTP leve.

CIRROSIS (MELD 12) CON HTP

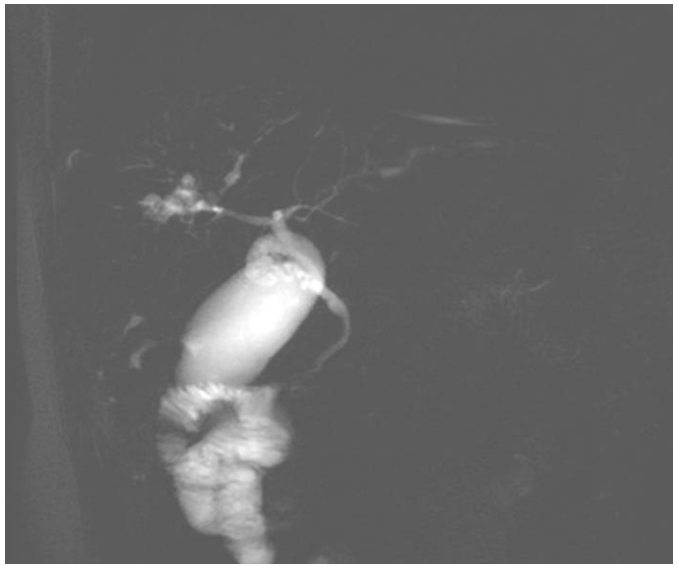
EVOLUCIÓN RADIOLÓGICA



cRMN (2012): Áreas de estenosis segmentaria en varios segmentos intrahepáticos. Litiasis biliar intrahepática en ramas tributarias del segmento VI.



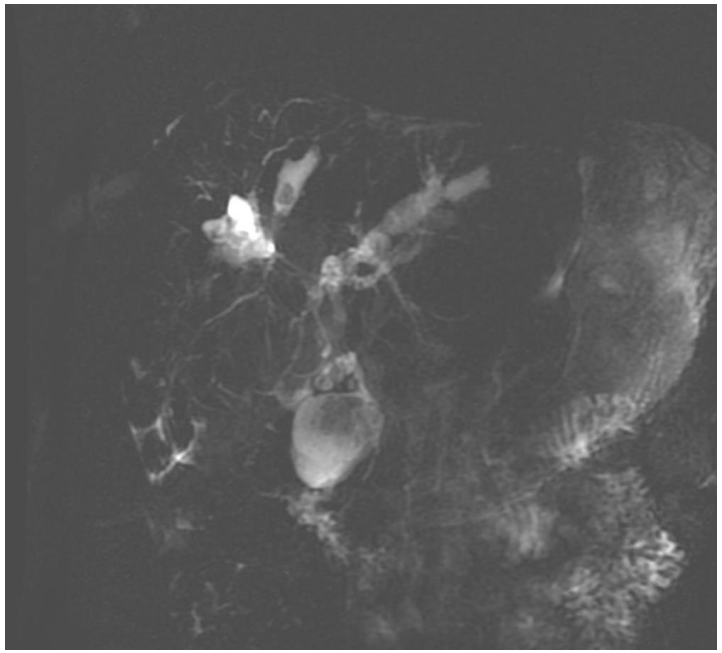
cRMN (2016): Colédoco con bordes discretamente irregulares, con una mínima ectasia en su mitad proximal. Dilatación de la vía biliar intrahepática distal, con áreas de morfología sacular, alternándose con zonas estenóticas. Mayor dilatación de los radicales periféricos principalmente en ramas izquierdas.



cRMN (2018): Mayor alteración de la morfología de la vía biliar, mayor ectasia distal. Defectos de repleción intraluminal en la vía intrahepática mal definidos, y heterogéneos, que se pueden atribuir a microlitiasis / barro biliar.

EVOLUCIÓN RADIOLÓGICA

cRMN (2020): Dilatación llamativa e irregular de la vía biliar que es más marcada en el LHD. Múltiples estenosis, destacando la localizada en la confluencia de los conductos anterior y posterior que condiciona la mayor dilatación de la vía del LHD. Litiasis de 10 milímetros diámetro en el segmento posterior. La vía biliar extrahepática presenta una irregularidad con disminución de calibre, sin condicionar este caso dilatación proximal.

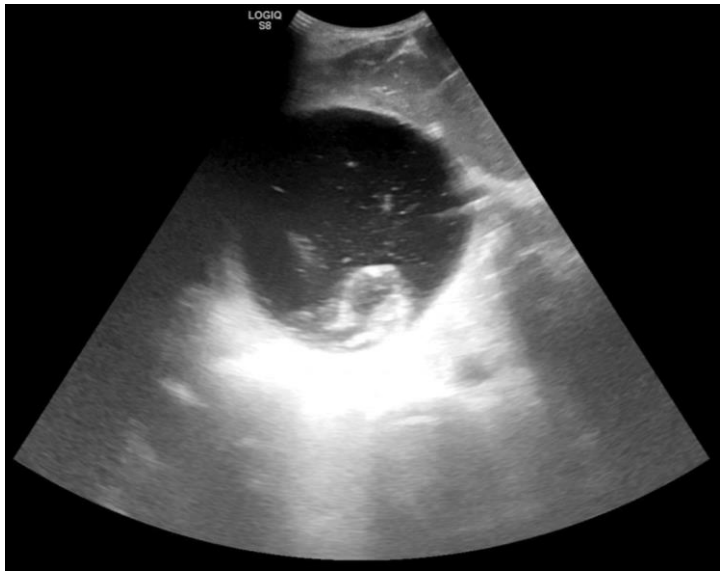


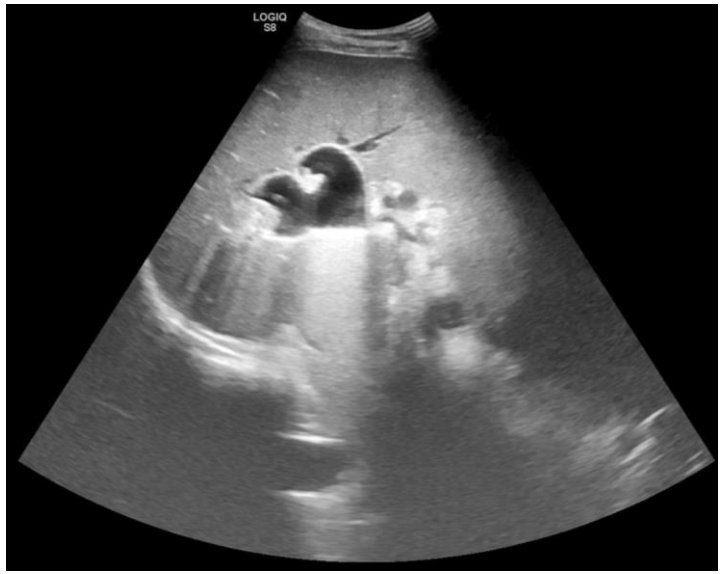
cRMN (04/01/2022): Severa estenosis que afecta a la confluencia de radicales lobares y segmentarios de ambos lóbulos, al hepático común y al colédoco, confiriéndole es un calibre irregular alternando segmentos estenosados con otros mínimamente dilatados. Los radicales periféricos de la totalidad de los segmentos hepáticos presentan marcadas dilataciones de aspecto pseudosacular y su luz está ocupada por material hipointenso que corresponde a litiasis intra biliar / debris / barro biliar.

EPISODIO ACTUAL_ Ingreso el 20 de enero

- **E.A.:** Cuadro de 7 días de evolución de dolor en HD intermitente junto con tumoración a ese nivel, coluria e ictericia marcada. No fiebre. Refiere astenia, pérdida de peso de más de 10 kg e ictericia en los últimos meses. No hiporexia.
- **E.F:**
  - BEG aunque presenta un deterioro marcado del estado físico. CyOx3. Ictericia esclero-cutánea
  - Tº 38ºC (en planta)
  - Abdomen: Masa palpable en hipocondrio derecho, no dolorosa.
- **Pruebas complementarias:**
  - *Bioquímica:* ALT 106. AST 93. GGT 270. FA 612. Bi 13,8 (→ 17). PCR 7 (→ 8,6). Albumina 3,4
  - *Hemograma:* Leucos 6500. Hb 12,1 (→ 10,1)
  - *Coagulación:* AP 32% (→ 53%)

EPISODIO ACTUAL_ Ingreso el 20 de enero





ECO abdomen: La vesícula biliar está marcadamente distendida, alcanzando un diámetro máximo que supera los 10 cm y con contenido ecogénico en su interior. Murphy ecográfico negativo y las paredes de la vesícula no están engrosadas.
Existe una clara dilatación de radicales biliares intrahepáticos izquierdos y derechos apreciándose en algunos de ellos defectos de repleción ecogénicos que sugieren correspondencia con acúmulos de barro biliar / moldes biliares. No se aprecia una clara dilatación de vía biliar extrahepática si bien es difícil la valoración.

10 DIAS ANTES…

Analítica de control

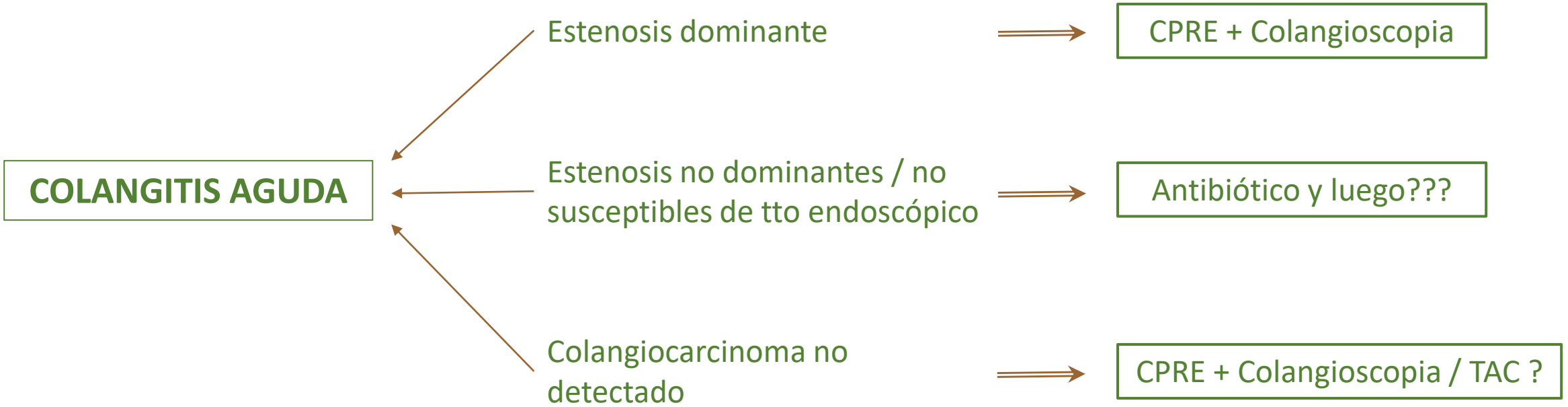
MELD 20 puntos

BIOQUÍMICA GENERAL

Tipo de muestra: **Suero**	*Resultados*		*Unidades*	*Rangos de referencia*		
Glucosa suero	88		mg/dl	74	-	109
Urea suero	27		mg/dl	19	-	49
Creatinina suero	0.78		mg/dl	0.72	-	1.18
Filtrado Glomerular estimado (CKD-EPI)	>90		ml/min/1,73m2		>=	60
	Multiplicar por 1.159 si el individuo es de raza negra					
Sodio suero	136		mEq/l	135	-	145
Potasio suero	4.6		mEq/l	3.5	-	5.1
Ác Úrico suero	4		mg/dl	3.4	-	7
ALT (GPT) suero	**143**	↑↑	U/l	10	-	49
AST (GOT) suero	**135**	↑	U/l	14	-	35
GGT suero	**318**	↑	U/l	6	-	73
Fosfatasa Alcalina (ALP) suero	**633**	↑	U/l	46	-	116
Bilirrubina Total suero	**9.4**	↑	mg/dl	0.3	-	1.2
Bilirrubina Directa suero	**7.3**	↑↑	mg/dl	0	-	0.3
LDH suero	170		U/l	120	-	246
Triglicéridos suero	112		mg/dl	35	-	150
Colesterol suero	160		mg/dl	120	-	200
HDL Colesterol suero	**<20**	↓	mg/dl	40	-	60
Proteínas Totales suero	8		g/dl	5.7	-	8.2
Albúmina suero	4		g/dl	3.2	-	4.8
Calcio suero	9.8		mg/dl	8.7	-	10.4
Hierro suero	**23**	↓	µg/dl	65	-	175
Transferrina suero	272		mg/dl	215	-	365
Capacidad total de fijación de hierro suero (cálculo)	345		µg/dl	254	-	472
Indice de Saturación de Transferrina suero	**6**	↓	%	15	-	50
Ferritina suero	**405**	↑	ng/ml	22	-	322

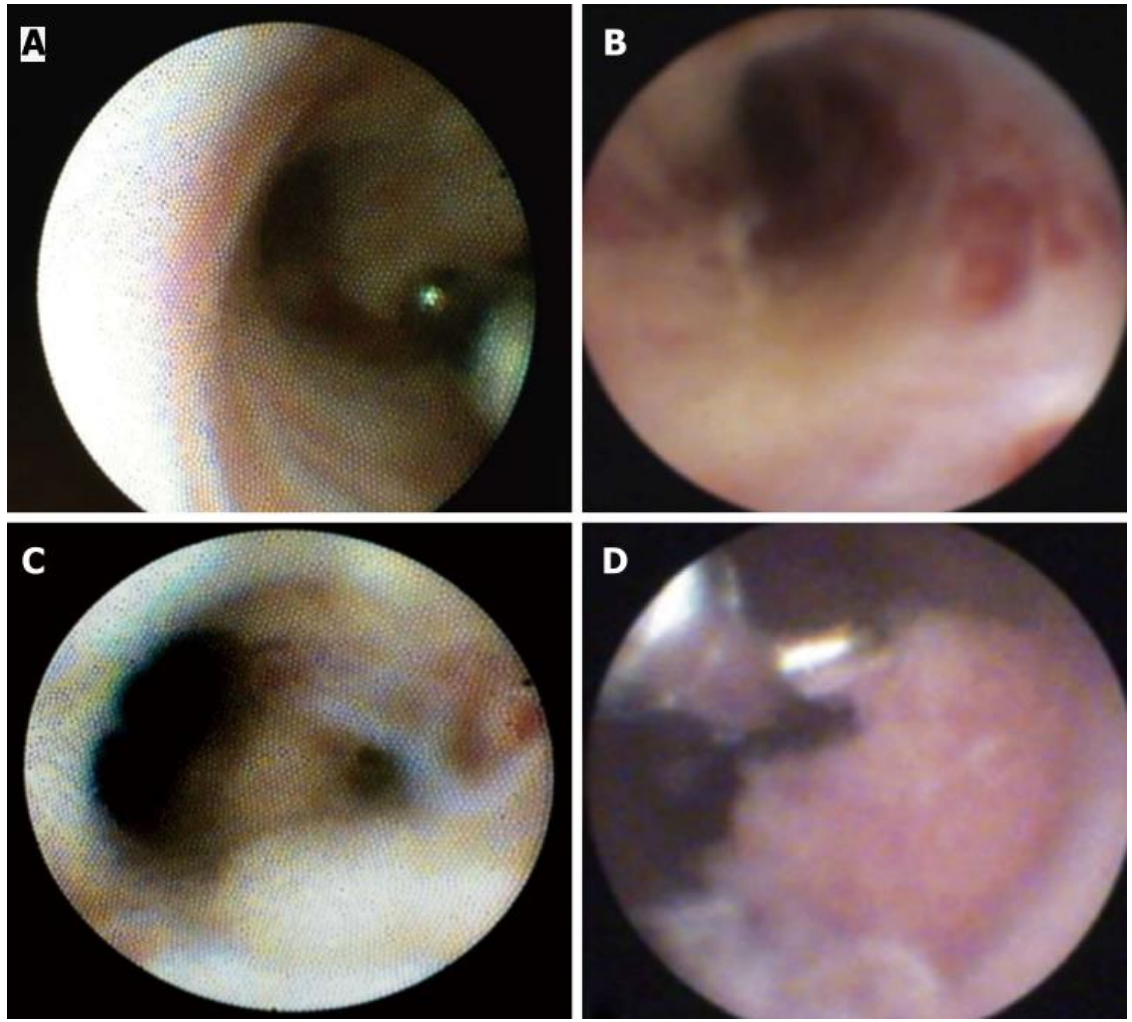
DIAGNÓSTICO Y MANEJO

Progresión de la CEP (14 años) con desarrollo de cirrosis e hipertensión portal y complicado actualmente con:



Colangitis esclerosante primaria.

¿Puede cambiar el spyglass este concepto?.



Un único explorador.

Canal de trabajo e irrigación.

Mayor sensibilidad.

Dx dirigido.

Pero:
- No es excesivamente caro, lleva 10 años en el mercado y se conoce y usa poco (¿?)

World J Gastrointest Endosc 2014 April 16; 6(4): 137-143

Colangitis esclerosante primaria.

¿Puede cambiar el spyglass este concepto?.

Table 2 Types of choledochoscopy

Type of choledochoscopy	Advantages	Disadvantages
Peroral (endoscopic)	Natural orifice	(1) Technical expertise; (2) Sedation or anesthesia; and (3) Not possible in patients with previous gastric resections or Roux-en-Y gastric bypass
Percutaneous transhepatic (interventional radiology)	(1) Shorter scope length; (2) Repeated with ease; and (3) Therapeutic interventions	(1) Need dilated intra-hepatic ducts; and (2) Risk of bleeding, bile leak, tumor seeding, biliary fistula and skin excoriation
Percutaneous transenteric *via* access loop (interventional radiology, surgical)	(1) Shorter scope length; (2) Repeated with ease; (3)Therapeutic interventions; (4) Ductal dilatation not necessary; and (5) In patients with RPC	(1) Previous access loop creation; and (2) Risk of small bowel injury, peritonitis, biliary fistula and skin excoriation
Intra-operative transcystic (surgical)	(1) Avoid CBD incision; (2) Therapeutic interventions; (3) Can document CBD clearance; and (4) It can be done laparoscopically	(1) The spiral valve of Heister; (2) Anatomy of the cystic duct; (3) Size of the cystic duct; (4) Need thin scopes (3 mm); (5) Technical expertise; and (6) Risks of bleeding, bile leak
Intra-operative transcholedochal (surgical)	Most direct access	(1) Need dilated extra-hepatic biliary system; (2) Risk of bleeding, bile leak; (3) Can put an internal stent; and (4) Can put T tube

Lee T, Teng TZJ, Shelat VG. Choledochoscopy: An update. World J Gastrointest Endosc. 2021 Dec 16;13(12):571-592. doi: 10.4253/wjge.v13.i12.571. PMID: 35070020; PMCID: PMC8716986.

Colangitis esclerosante primaria.

¿Puede cambiar el spyglass este concepto?.

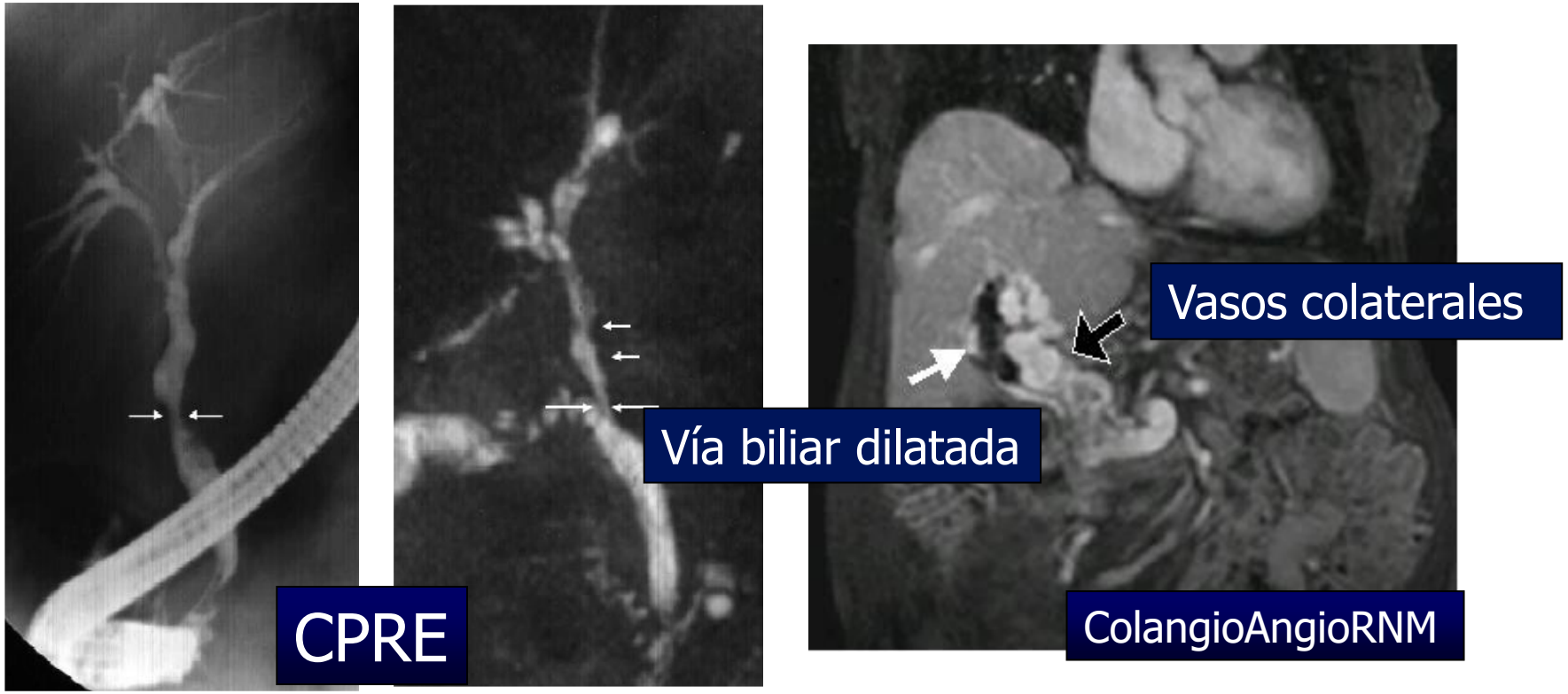
Table 3 Diagnostic and therapeutic indications for choledochoscopy

Diagnostic indications	Therapeutic indications
Visual impression and visually-guided biopsies of: (1) Indeterminate biliary strictures (IBS); (2) Dominant strictures in primary sclerosing cholangitis (PSC); and (3) IgG4-related sclerosing cholangitis (IgG4-SC)	Stone fragmentation: (1) Electrohydraulic lithotripsy (EHL); and (2) Laser lithotripsy (LL)
Precise preoperative mapping of the extent of tumor involvement in CCA	Ablative therapies in cholangiocarcinoma (CCA): (1) Radiofrequency ablation; (2) Photodynamic therapy; (3) Nd:YAG laser ablation; and (4) Argon plasma coagulation
Choledochal cysts	Cystic duct stent placement
Intraductal papillary neoplasms of the bile duct	Guidewire passage through strictures, surgically altered anatomy
Cholangioadenoma	Resection of ductal masses
Biliary papillomatosis	Retrieval of migrated ductal stents
Eosinophilic cholangitis	Gallbladder stenting and drainage
Biliary varices	
Right Hepatic Artery Syndrome	
Congenital pancreaticobiliary maljunction	
Post-liver transplant ductal ischemia	
Tissue sampling and visual evaluation for infections: (1) Cytomegalovirus; and (2) HIV	
Evaluation of intrahepatic biliary tracts during minimally invasive surgery	

Lee T, Teng TZJ, Shelat VG. Choledochoscopy: An update. World J Gastrointest Endosc. 2021 Dec 16;13(12):571-592. doi: 10.4253/wjge.v13.i12.571. PMID: 35070020; PMCID: PMC8716986.

Dx/d colangiopatía portal.

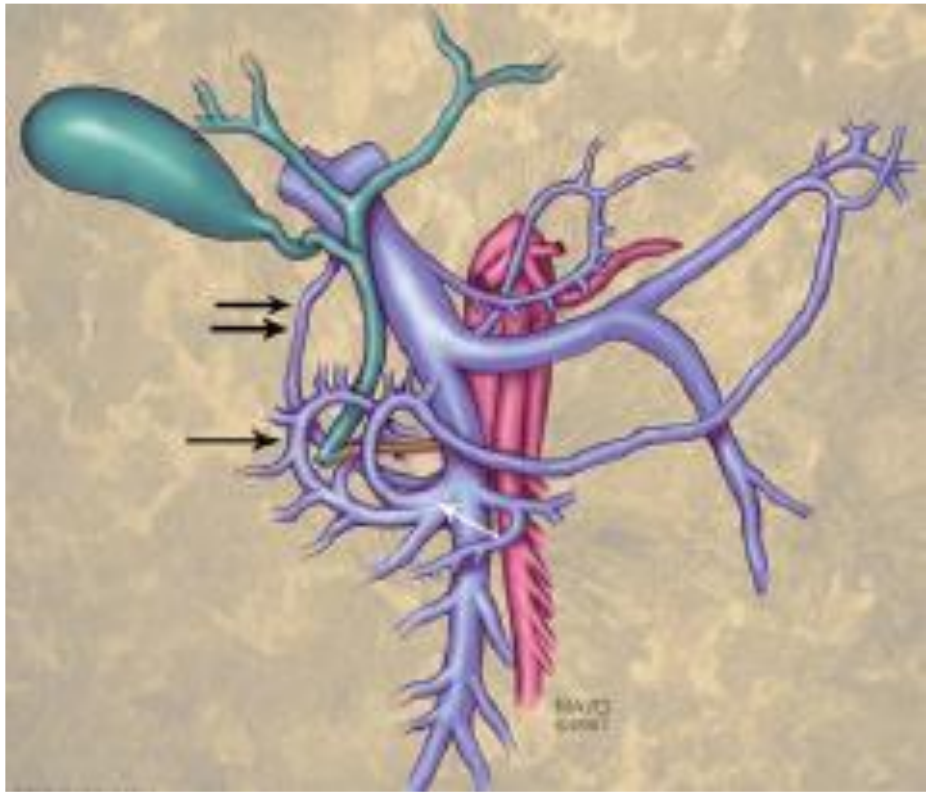
- Alteraciones de la vía biliar (estenosis, angulación dilatación, etc) que desarrollan los pacientes con cavernomatosis portal atribuida a la compresión de la vía biliar por colaterales

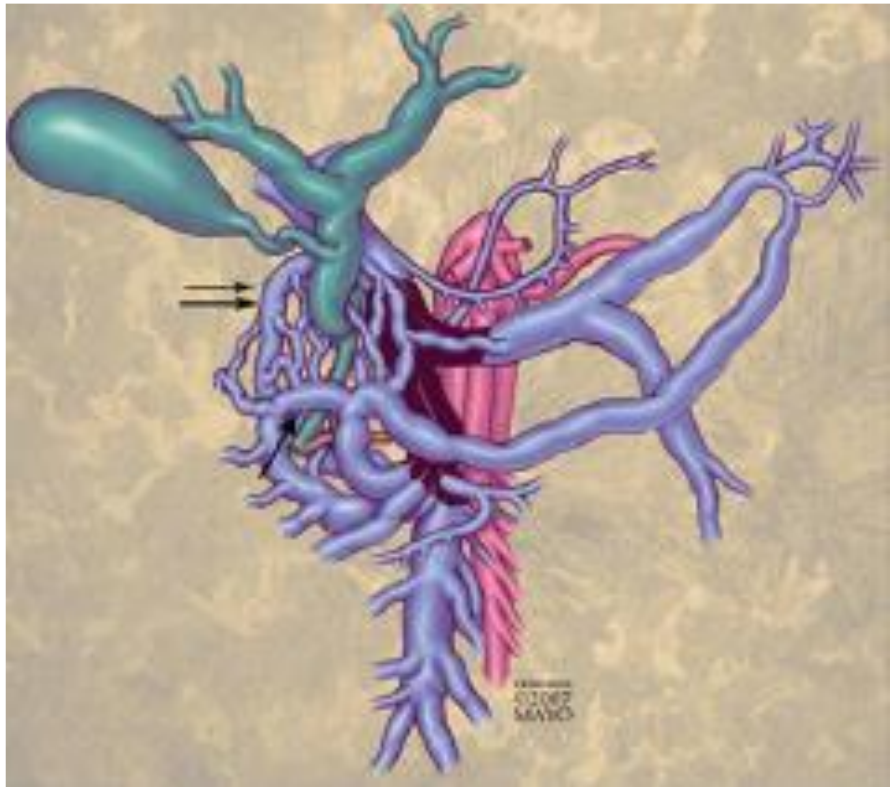


Cortesia Dr. JC García Pagán

Estrategia diagnóstica en la CEP.

Dx/d colangiopatía portal.



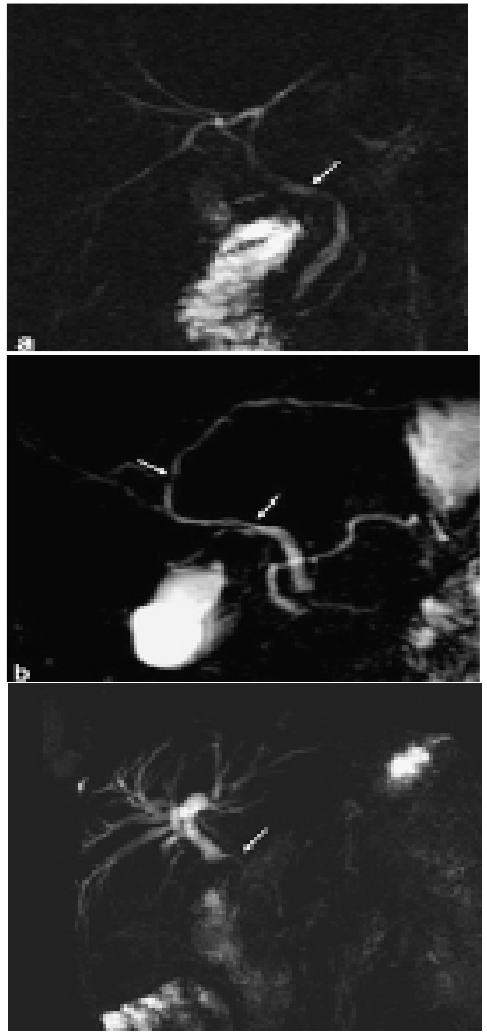


Cortesia Dr. JC García Pagán

Estrategia diagnóstica en la CEP.

Clasificación de la colangiopatía portal.

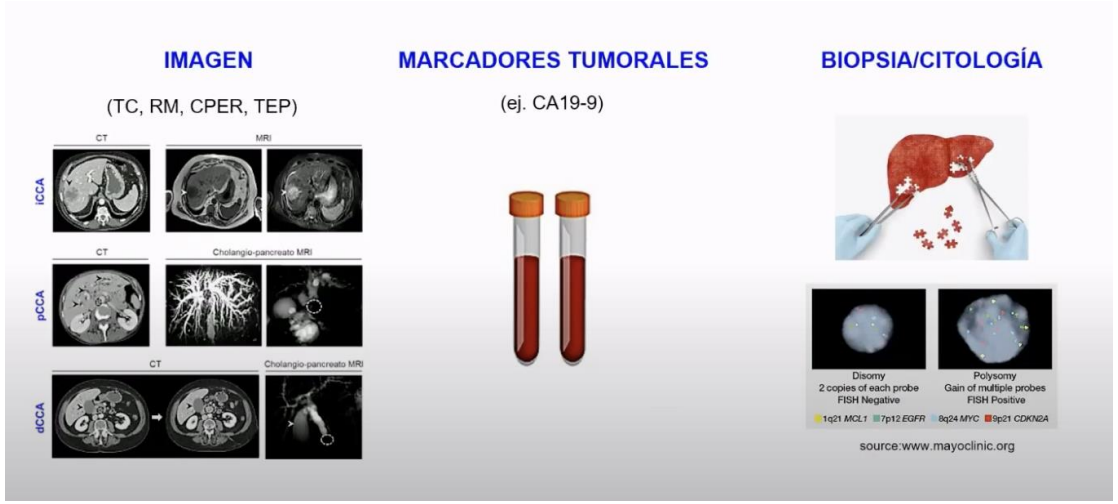
- Grado 0: Sin anomalías
- Grado I: Irregularidades o angulaciones del árbol biliar
- Grado II : Estenosis sin dilatación o indentaciones de la vía biliar
- Grado III: Estenosis con dilatación (Intrahepática > 4 mm; extrahepática > 7 mm)

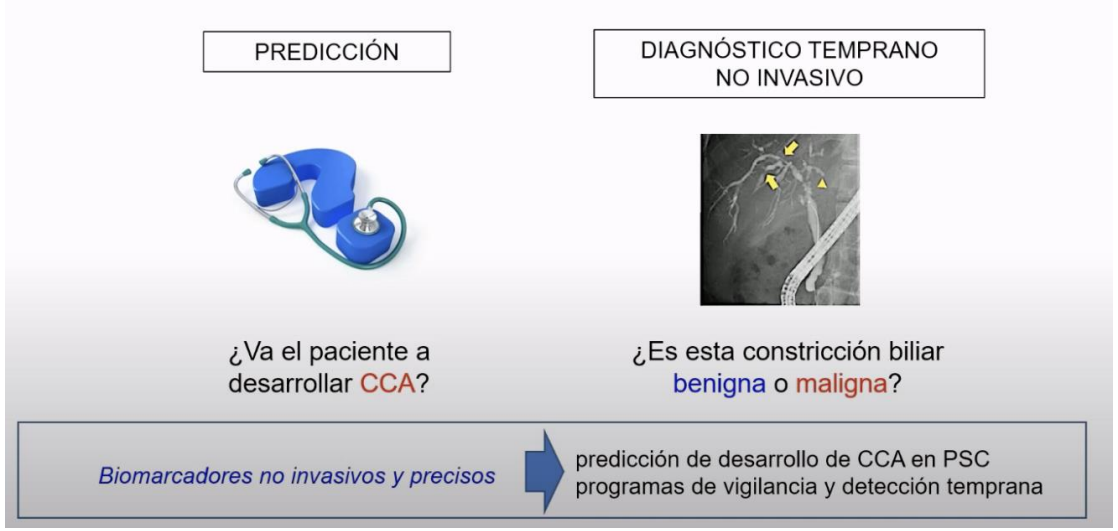


Cortesia Dr. JC García Pagán

Estrategia diagnóstica en la CEP.

CEP como enfermedad preneoplásica. Colangiocarcinoma.

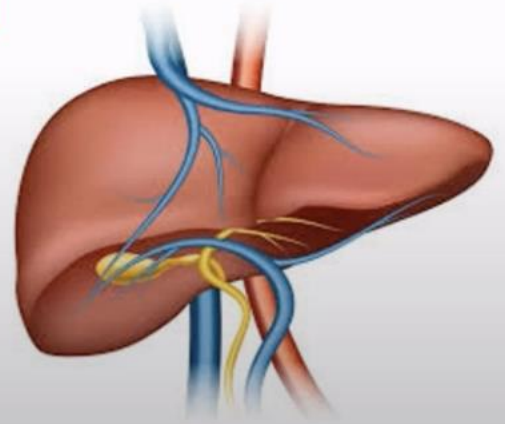




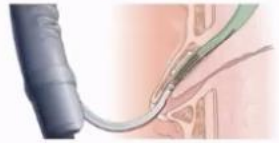
Modalidades diagnósticas del CCA en fase de experimentación

Diagnóstico molecular en Sangre/Bilis/Orina

- Células tumorales circulantes (**CTC**)
- **Mutaciones** (ADN tumoral)
- **Metilación** del ADN
- Vesículas extracelulares (**EVs**)
- **miRNAs**
- **Metabolómica**



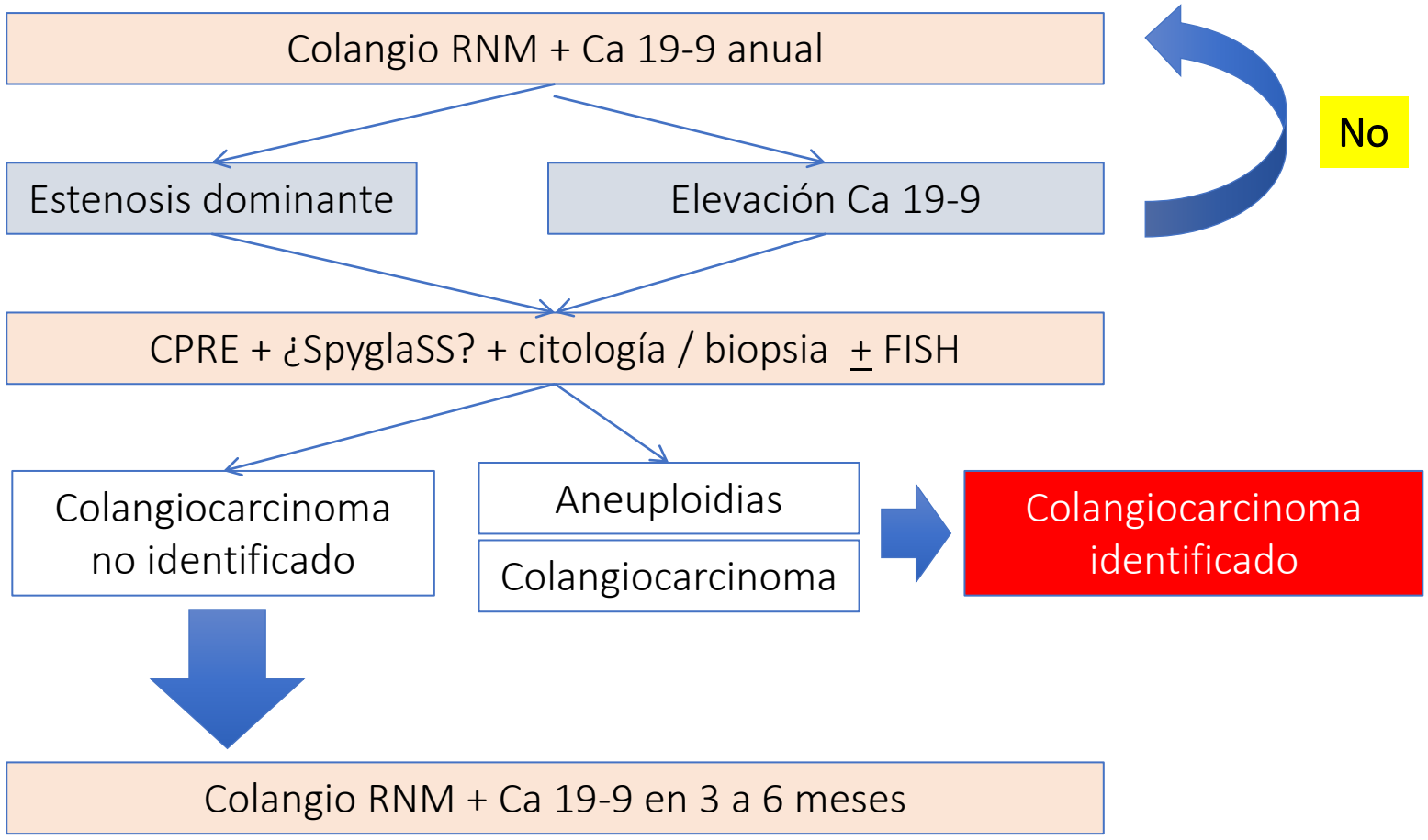
Cepillado biliar



- **Citología convencional**
- **FISH** (*fluorescence in situ hybridation*)
- **NGS** (*next generation sequencing*)

Estrategia diagnóstica en la CEP.

CEP como enfermedad preneoplásica. Colangiocarcinoma.



Eaton et al. Gastroenterology 2013