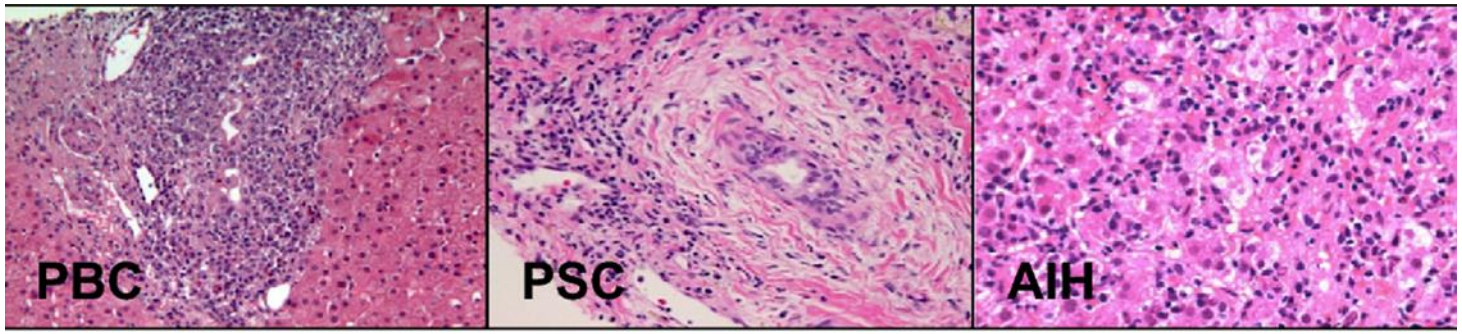
Autoimmune Liver Diseases

Presenter: Dr G L Gaskin

Facilitator: Dr N Gogela

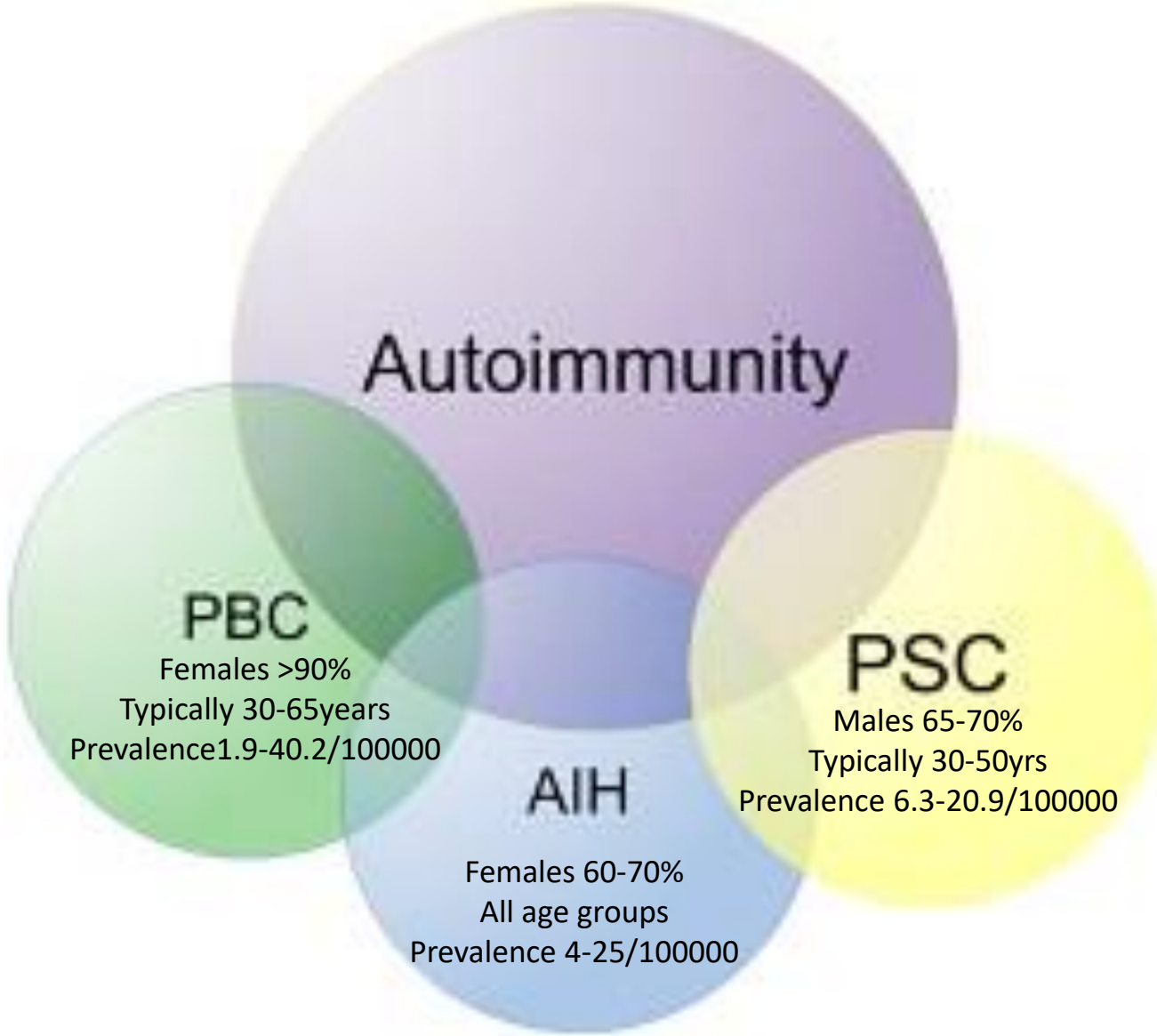
17 March 2025



Outline of the talk

- Introduction to Autoimmune liver diseases
- Practical aspects to diagnosis and management of AIH
- Practical aspects to diagnosis and management of PSC
- Diagnosis and management approach to PBC, including new drugs
- Overlap syndromes
- Conclusion

Autoimmune Liver Diseases

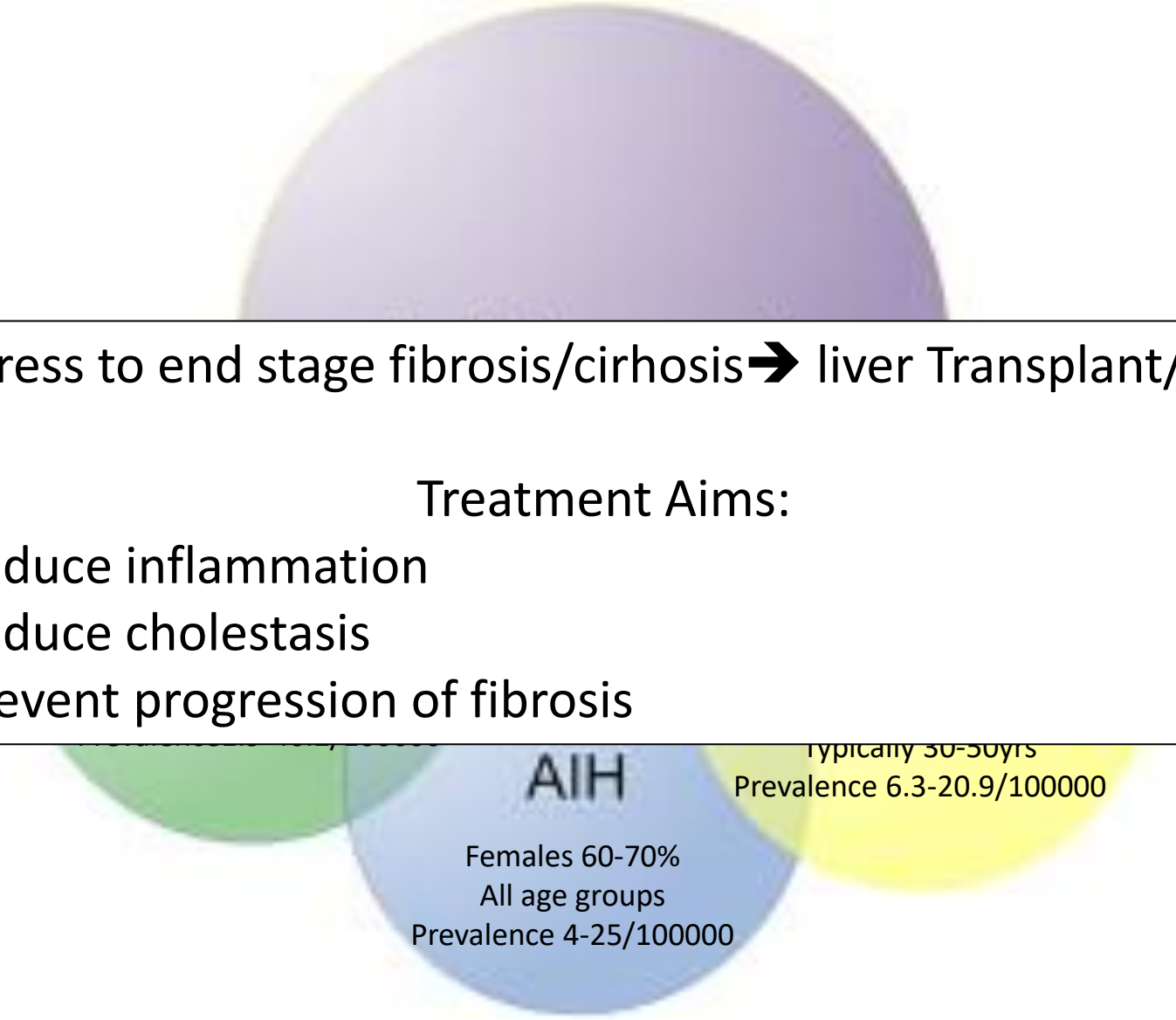


Small/interlobular bile ducts➔ non-suppurative destructive cholangitis

Medium/intra and extrahepatic ducts➔ obliterative fibrosis and multifocal stricturing

Hepatocytes➔ Interface hepatitis

Autoimmune Liver Diseases

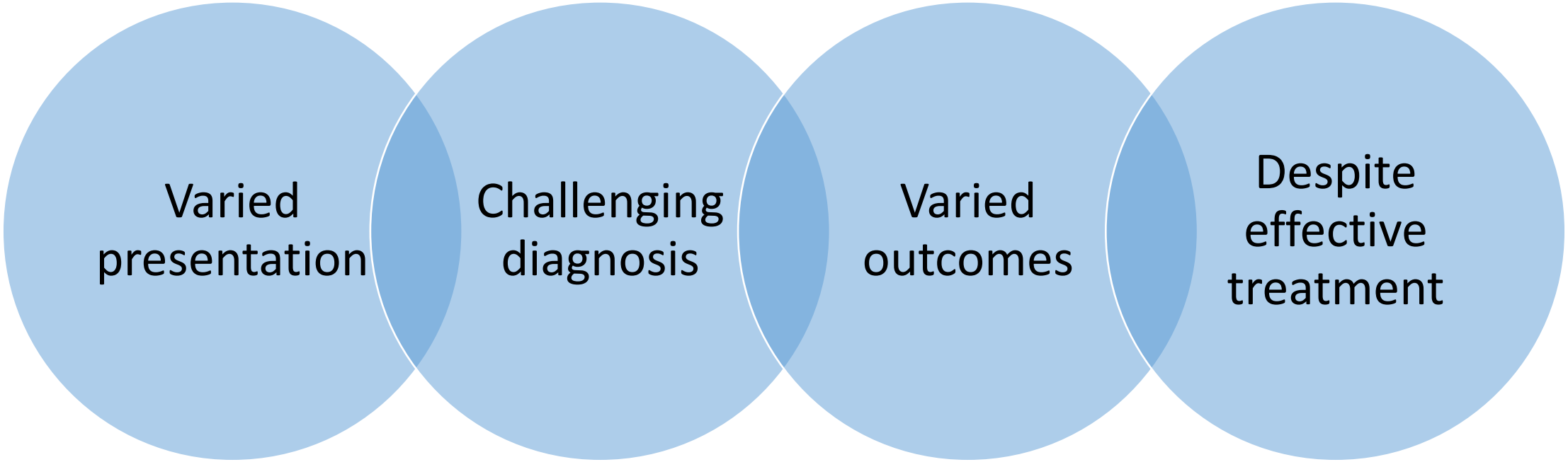


Progress to end stage fibrosis/cirhosis➔ liver Transplant/death

Treatment Aims:

1. Reduce inflammation
2. Reduce cholestasis
3. Prevent progression of fibrosis

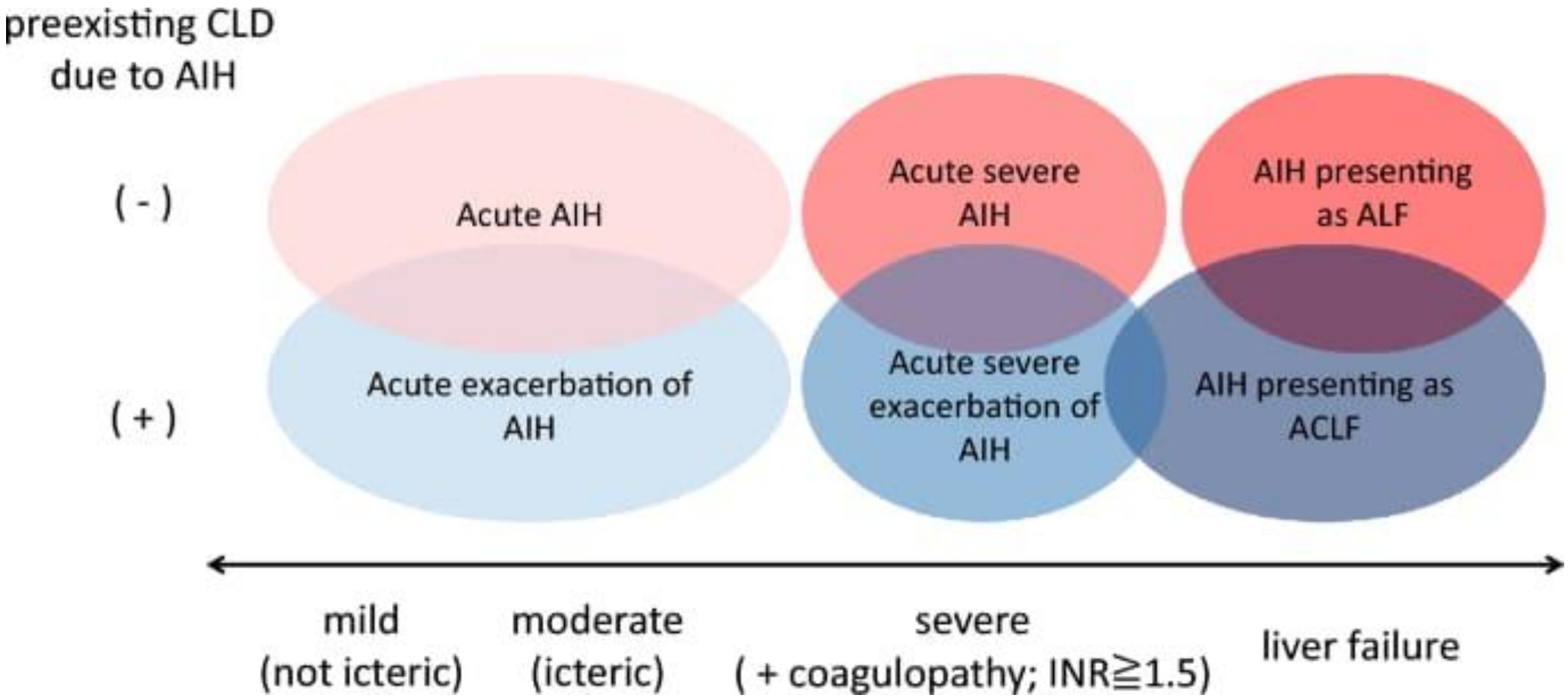
Autoimmune Hepatitis (AIH)



Clinical Presentation

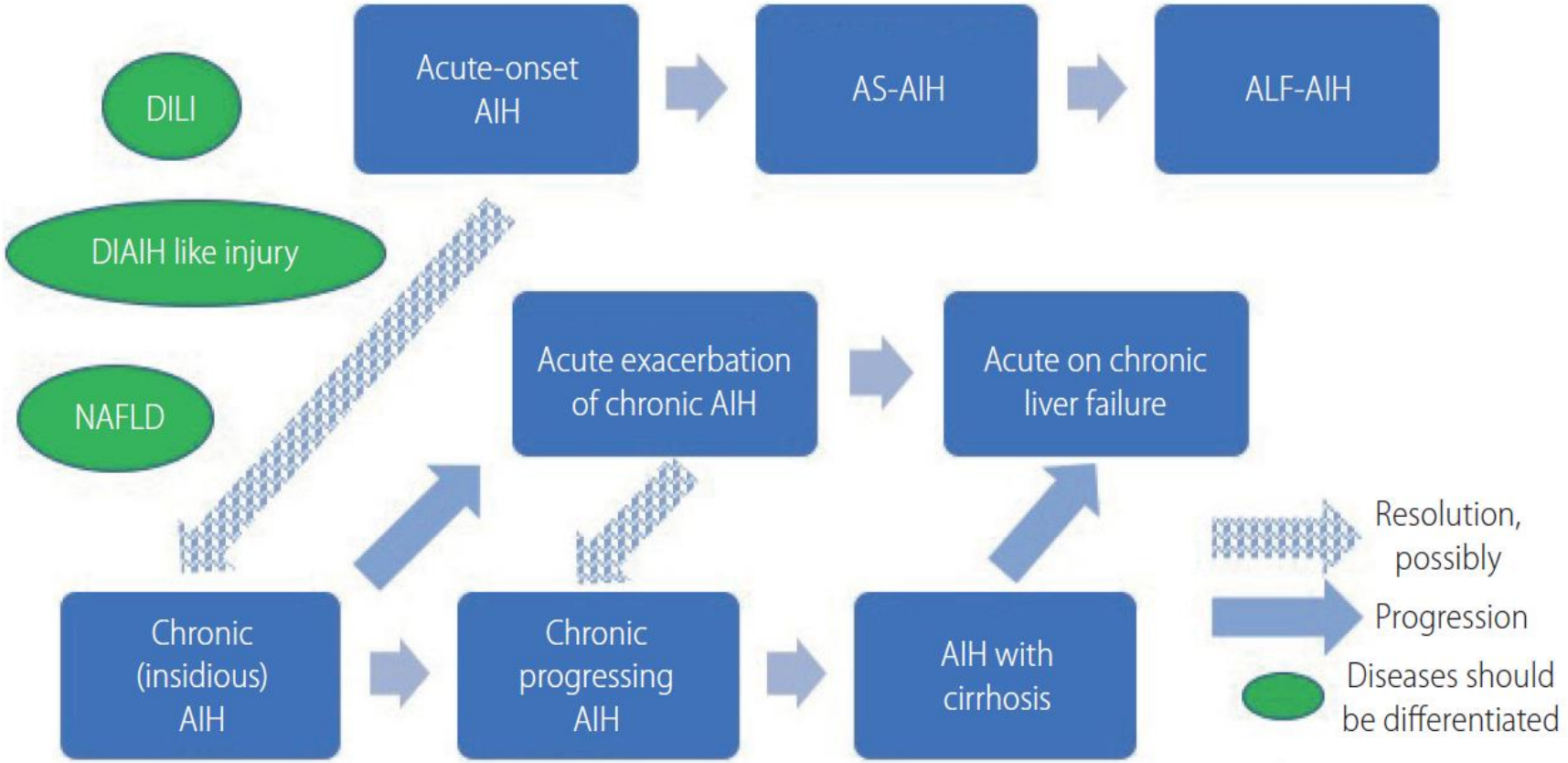
- Typical biochemical profile
  - Aminotransferase elevations +- ↑Bili
  - Normal or moderately elevated ALP and GGT

Clinical Presentation



Tanaka A etal. Hepatol Int.18, 1385-1395(2024)

Clinical Presentation



AS-AIH (Acute severe AIH), ALF-AIH (Acute liver failure from AIH), DILI (Drug induced liver injury), DIAIH- like injury(Drug induced AIH like injury), NAFLD(Non alcoholic fatty liver disease)

Komori A et al. Clinical and Molecular Hepatology 2021; 27:58-69

How To Make A Diagnosis?

IAIHG Simplified Scoring system(2008)

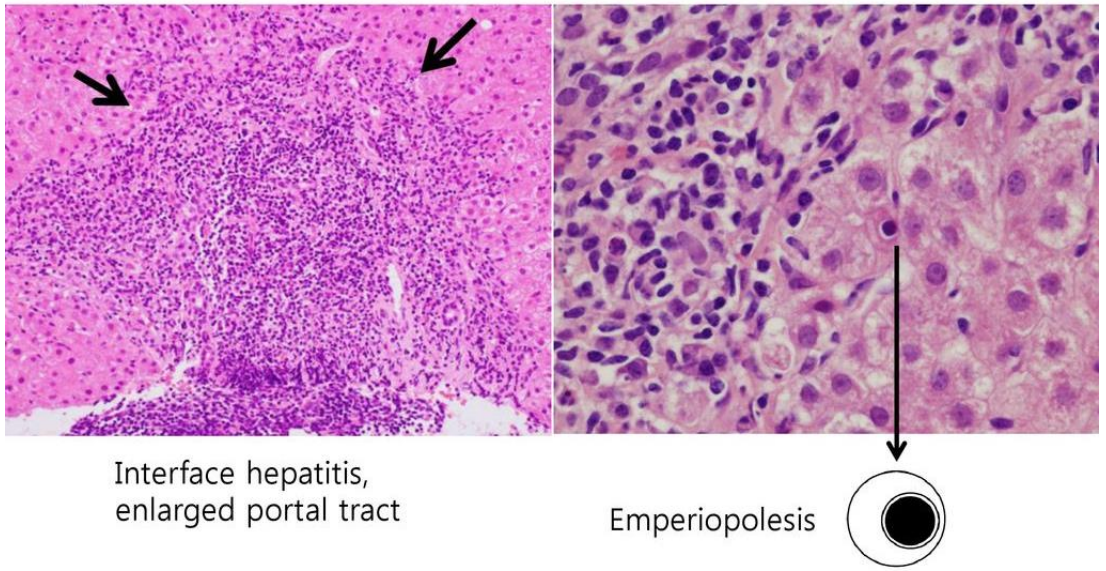
Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1*
ANA or SMA+	≥1:80	+2*
or LKM+	≥1:40	+2*
or SLA/LP+	Any titer	+2*
IgG or γ-globulins level	>upper limit of normal >1.1x upper limit	+1 +2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH Typical of AIH Atypical	+1 +2 0
Absence of viral hepatitis	No Yes	0 +2

Score >/= 7: Definite AIH
Score >/=6: Probable AIH

Autoimmune hepatitis.Journal of Hepatology 2015 vol. 63 j 971–100

Diagnosis: Liver Biopsy

- Liver biopsy prerequisite to diagnosis of AIH
  - Make a diagnosis
  - Assess degree of inflammation
  - Assess degree of fibrosis
  - Exclude alternate diagnosis
- Patient with cirrhosis:
  - Biopsy should be performed irrespective of transaminase levels
- If no evidence of fibrosis
  - Defer biopsy if transaminases are normal



IAHG simplified score- 2 out of 3

- Interface lymphocytic hepatitis
- Emperipolesis
- Hepatocellular rosettes

Diagnosis: Liver Biopsy

- Liver biopsy prerequisite to diagnosis of AIH
  - Make a diagnosis
  - Assess degree of inflammation
  - Assess degree of fibrosis
  - Exclude alternate diagnosis
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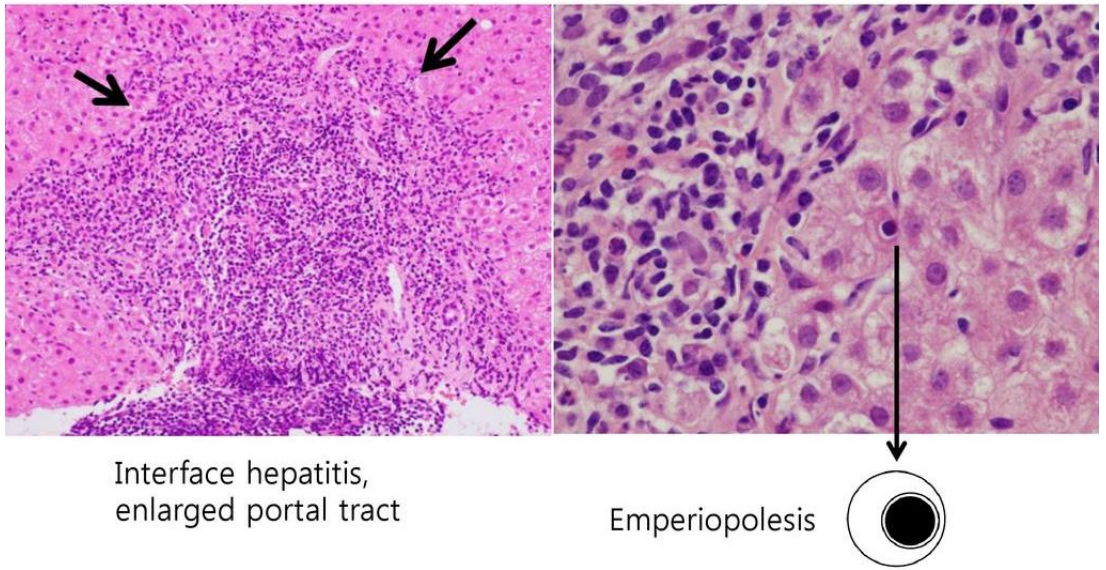

IAHG simplified score [illegible] of 3

- Interface lym[illegible]tic hepatitis
- Emper[illegible]sis
- H[illegible]tocellular rosettes

UPDATED 2022

Diagnosis: Updated Histological Features

The International Autoimmune Hepatitis Group (IAIHG)

TABLE 5 Diagnostic criteria for autoimmune hepatitis in the settings of both portal lobular hepatitis

	Portal hepatitis	Lobular hepatitis
Likely AIH	Portal lymphoplasmacytic infiltrate PLUS one or both of the following features 1. more than mild interface hepatitis 2. more than mild lobular inflammation • in the absence of histological features suggestive of another liver disease	More than mild lobular hepatitis (+/− centrilobular necroinflammation) PLUS at least one of the following features 1. lymphoplasmacytic infiltrates 2. interface hepatitis 3. portal-based fibrosis • in the absence of histological features suggestive of another liver disease
Possible AIH	Portal lymphoplasmacytic infiltrate • without either of the likely features 1 or 2 above • in the absence of histological features suggestive of another liver disease OR • with one or both of likely features above • in the presence of histological features suggestive of another liver disease	Any lobular hepatitis (+/− centrilobular necroinflammation) • without any of the likely features 1–3 above • in the absence of histological features suggestive of another liver disease OR • with any of the likely features above • in the presence of histological features suggestive of another liver disease
Unlikely AIH	Portal hepatitis • without either of the likely features above • in the presence of histological features suggestive of another liver disease	Any lobular hepatitis • without any of the likely features above • in the presence of histological features suggestive of another liver disease

Ansgar W. Lohse et al. Liver International. 2022;42:1058–1069

Diagnosis: Updated Histological Features

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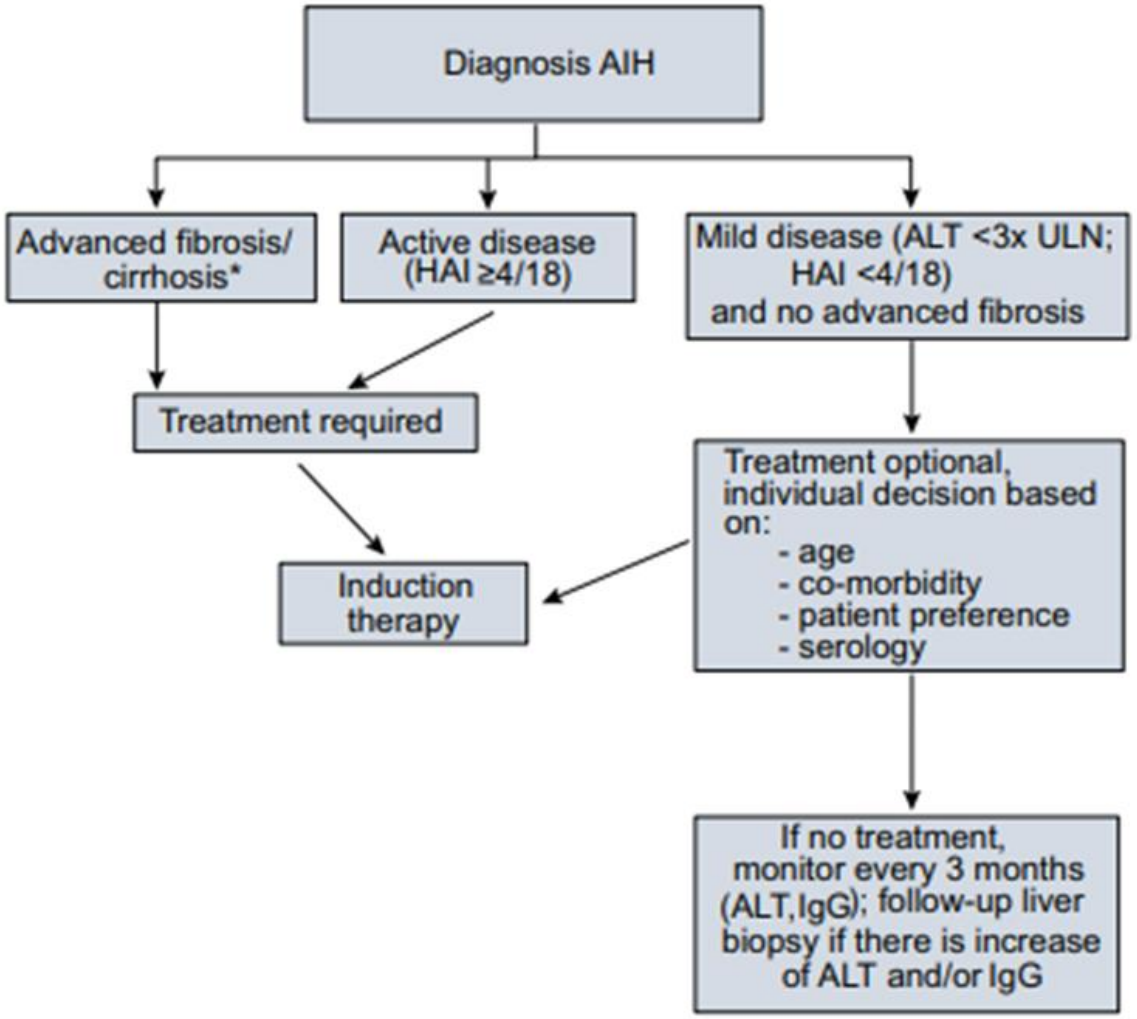
Ansgar W. Lohse et al. Liver International. 2022;42:1058–1069

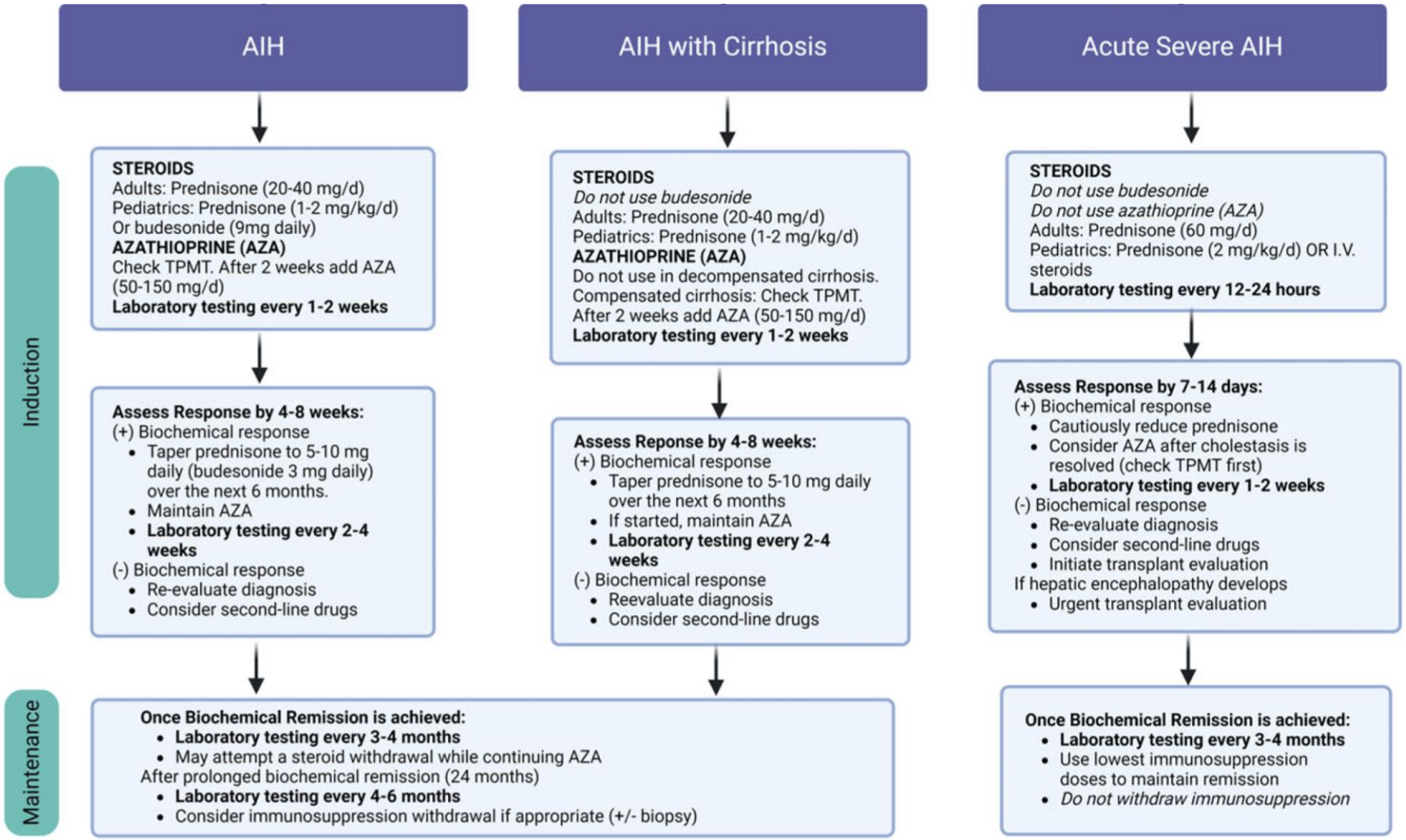
Treatment of AIH

- The aims of treatment:
  - Obtain complete remission
  - Prevent progression
- All patients with active AIH should be treated
  - Induction
  - Maintenance
- Small subset (spontaneous remission) no treatment but close monitoring
- Pretreatment:
  - Screening TPMT activity/ Vaccination status/ Bone density assessments by DEXA/ Pregnancy counselling



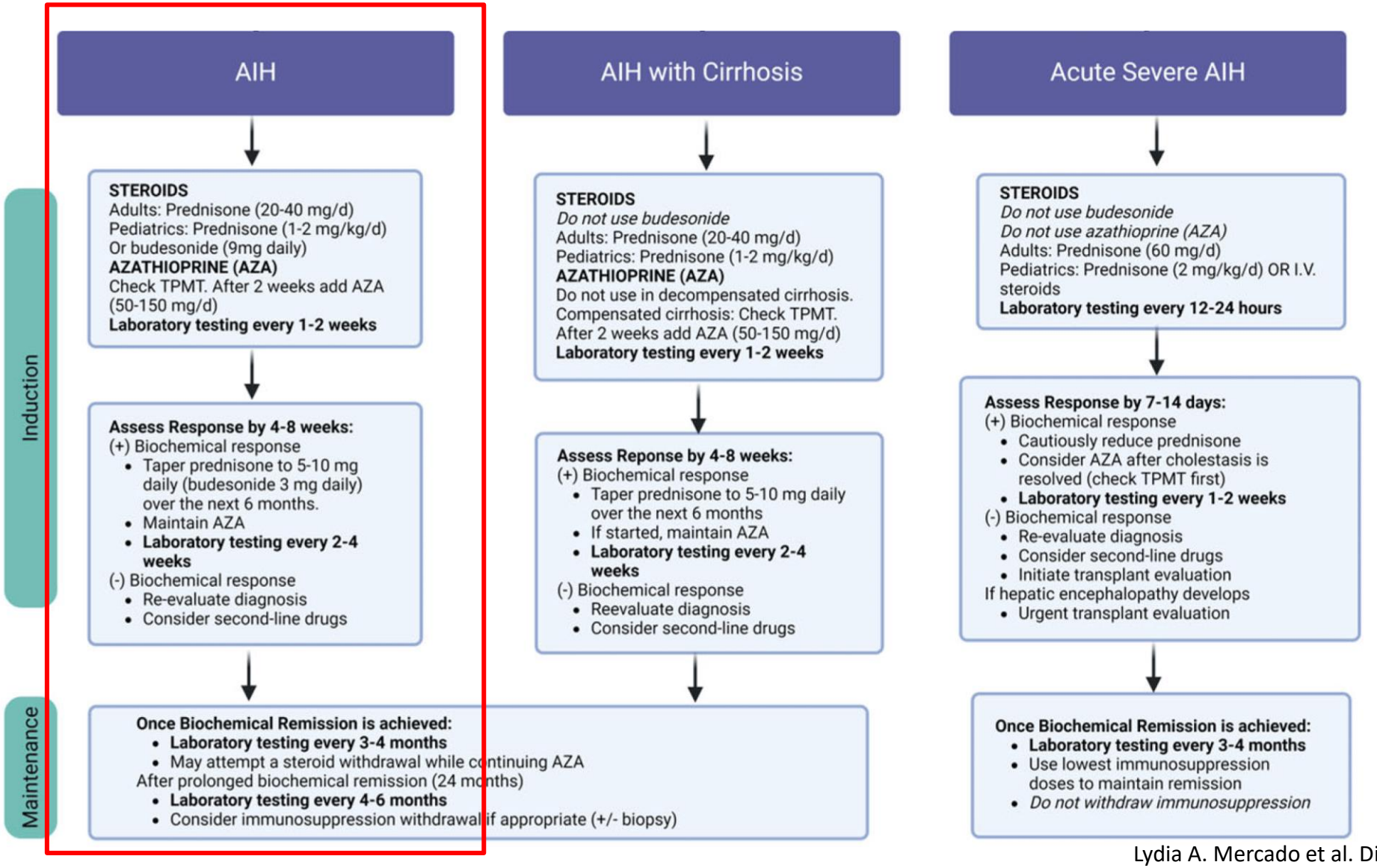
Autoimmune hepatitis. Journal of Hepatology 2015 vol. 63 j 971–100

Treatment: First Line



Lydia A. Mercado et al. Diagnostics 2024, 14, 382

Treatment: First Line



Lydia A. Mercado et al. Diagnostics 2024, 14, 382

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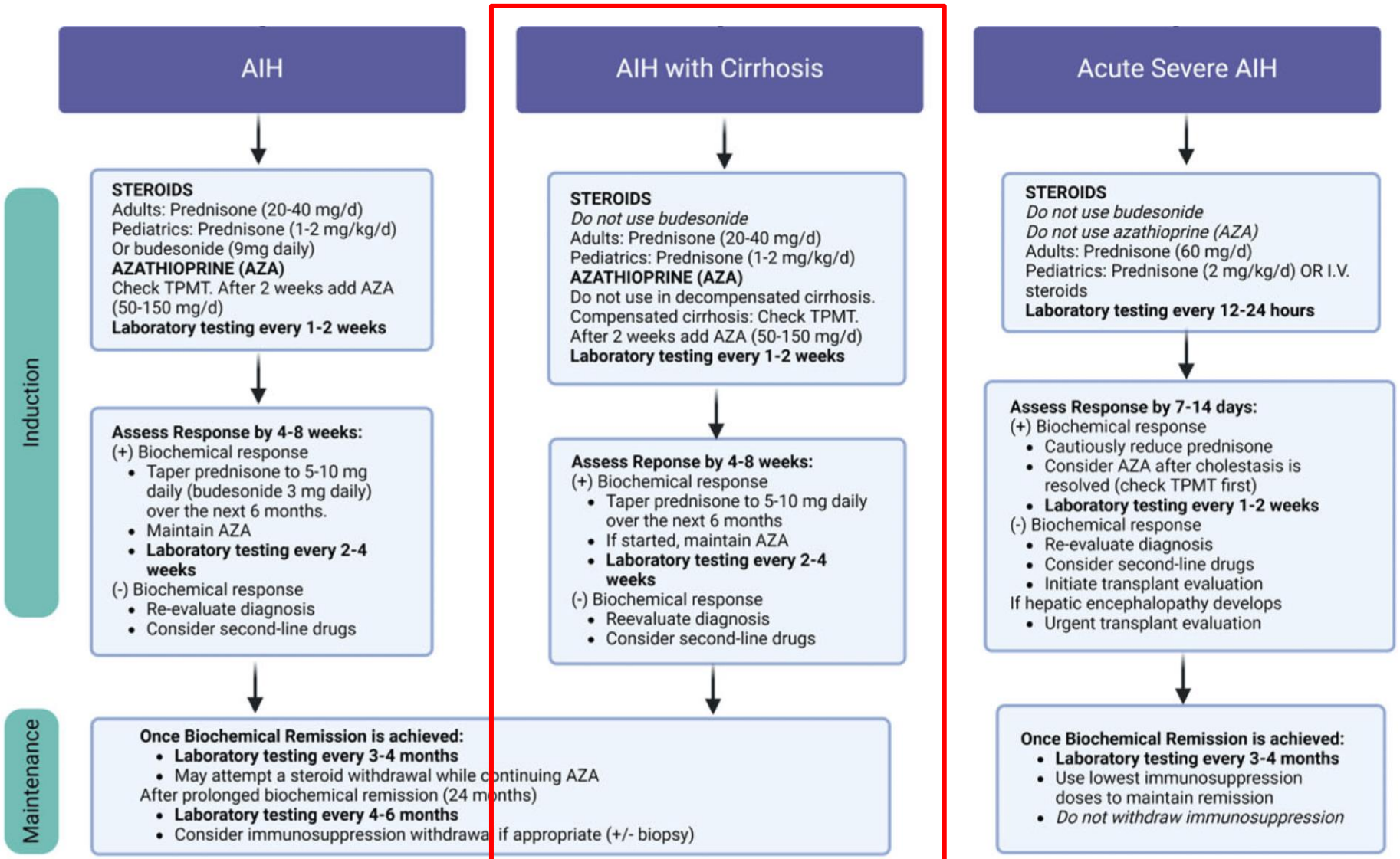
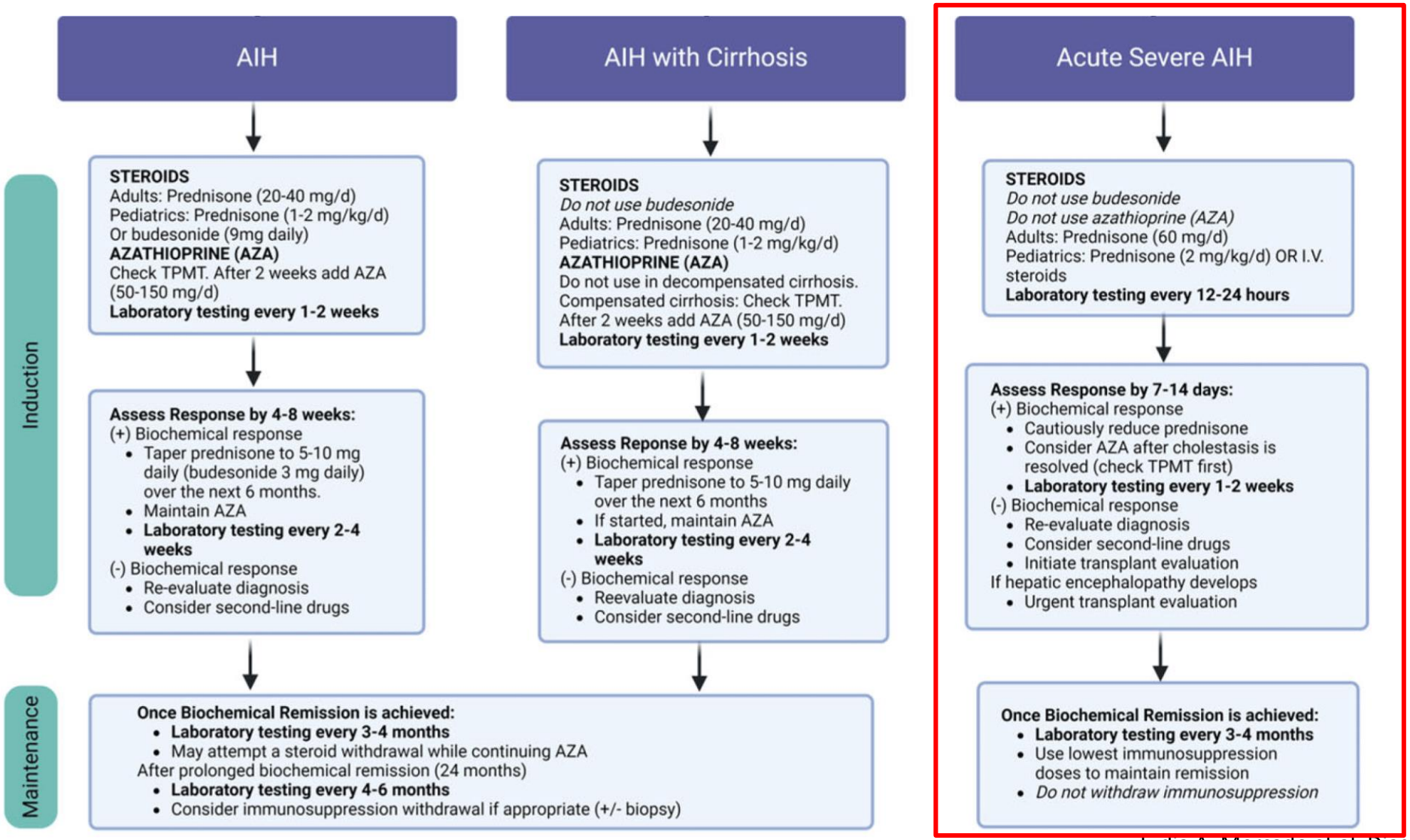


Lydia A. Mercado et al. Diagnostics 2024, 14, 382

Treatment: First Line



Lydia A. Mercado et al. Diagnostics 2024, 14, 382

Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL OF HEPATOLOGY

An open-label randomised-controlled trial of azathioprine *vs.* mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis

Methods

70 patients

Probable or definite diagnosis treatment-naive AIH

Randomised (1:1), open-label, parallel-group, 24-week, multicentre trial

Intervention

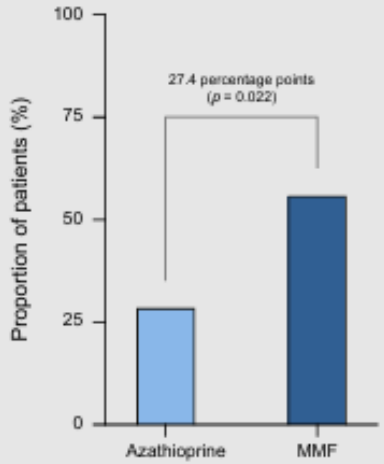
Prednisolone tapering + azathioprine (n = 31)

Prednisolone tapering + MMF (n = 39)

Primary outcome
% patients with normalisation of ALT and IgG after 24 weeks of treatment

Results

Primary outcome
Biochemical remission

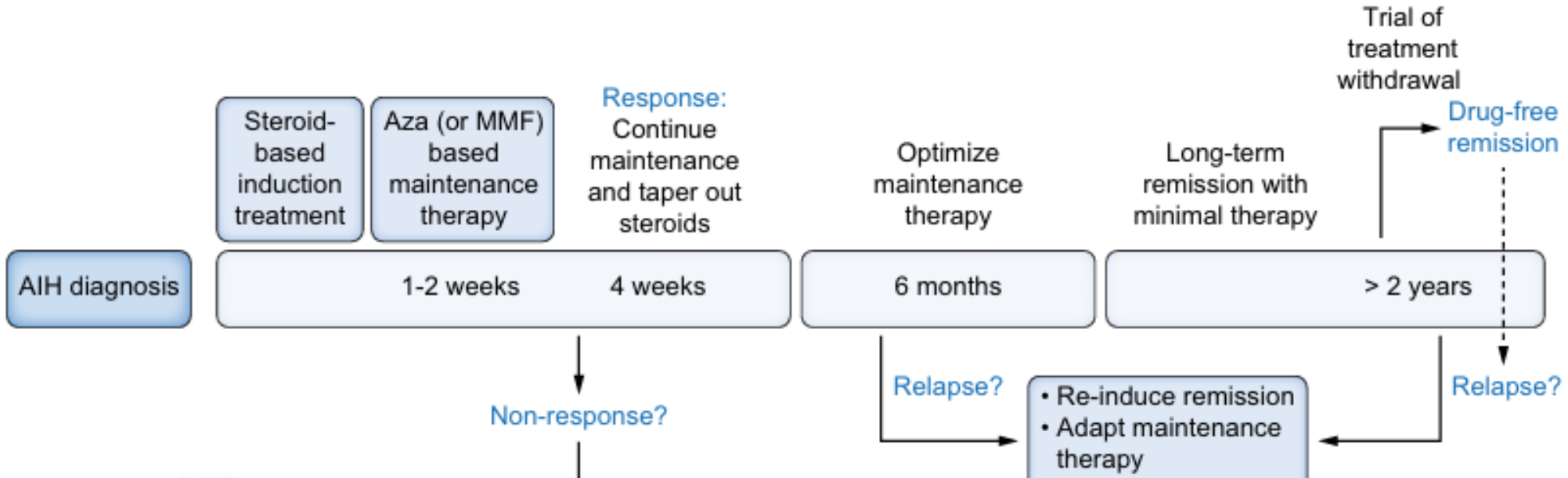


Secondary outcomes
SAEs occured in 4 patients in the azathioprine group and were absent with MMF (12.9% *vs.* 0%, $p = 0.034$)

Cessation of treatment due to (S)AEs occurred more often with azathioprine than MMF (25.8% *vs.* 5.1%, $p = 0.018$)

Romée J.A.L.M. et al. J. Hepatol. 2024, 80, 576–585

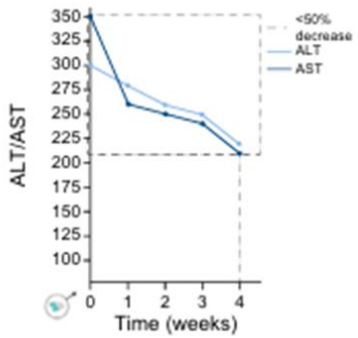
Treatment: Monitoring



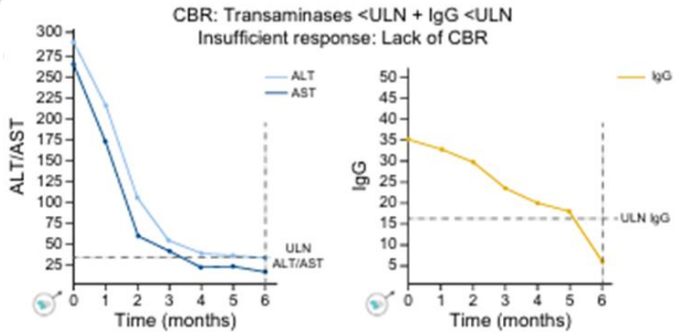
Intolerance to treatment

Any adverse event possibly related to treatment as assessed by the treating physician leading to potential discontinuation of the drug

Diagnosis of AIH and initiation of treatment

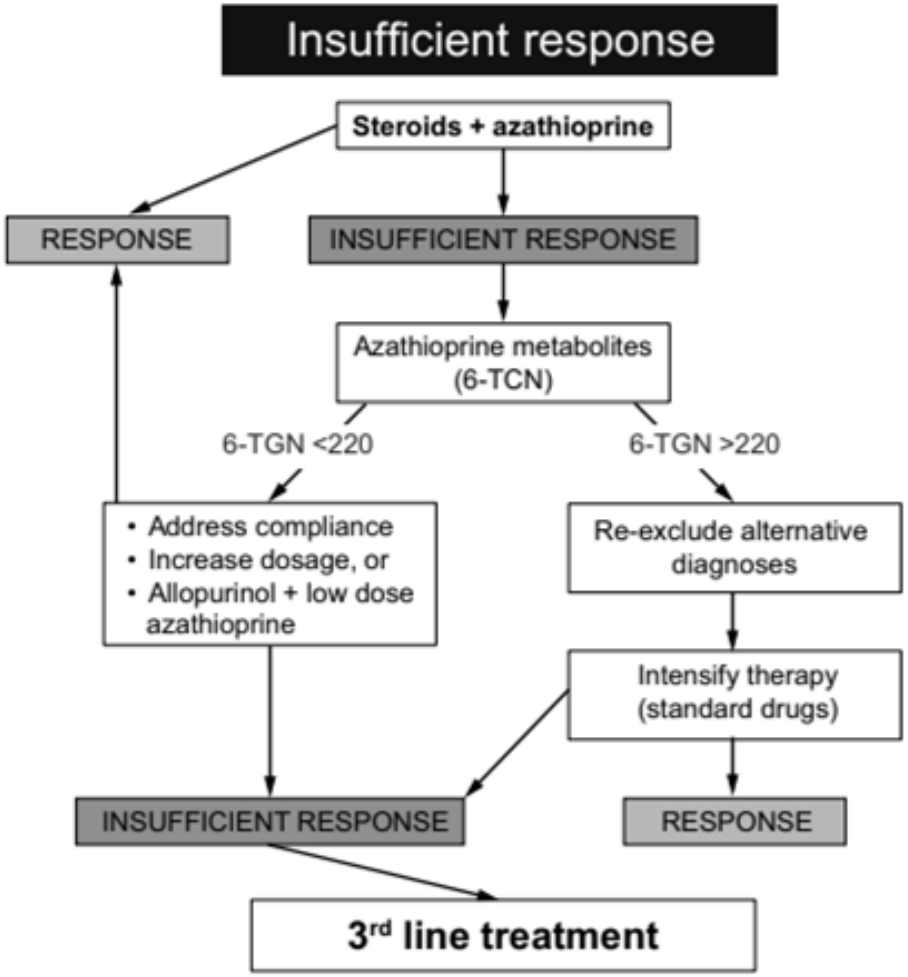


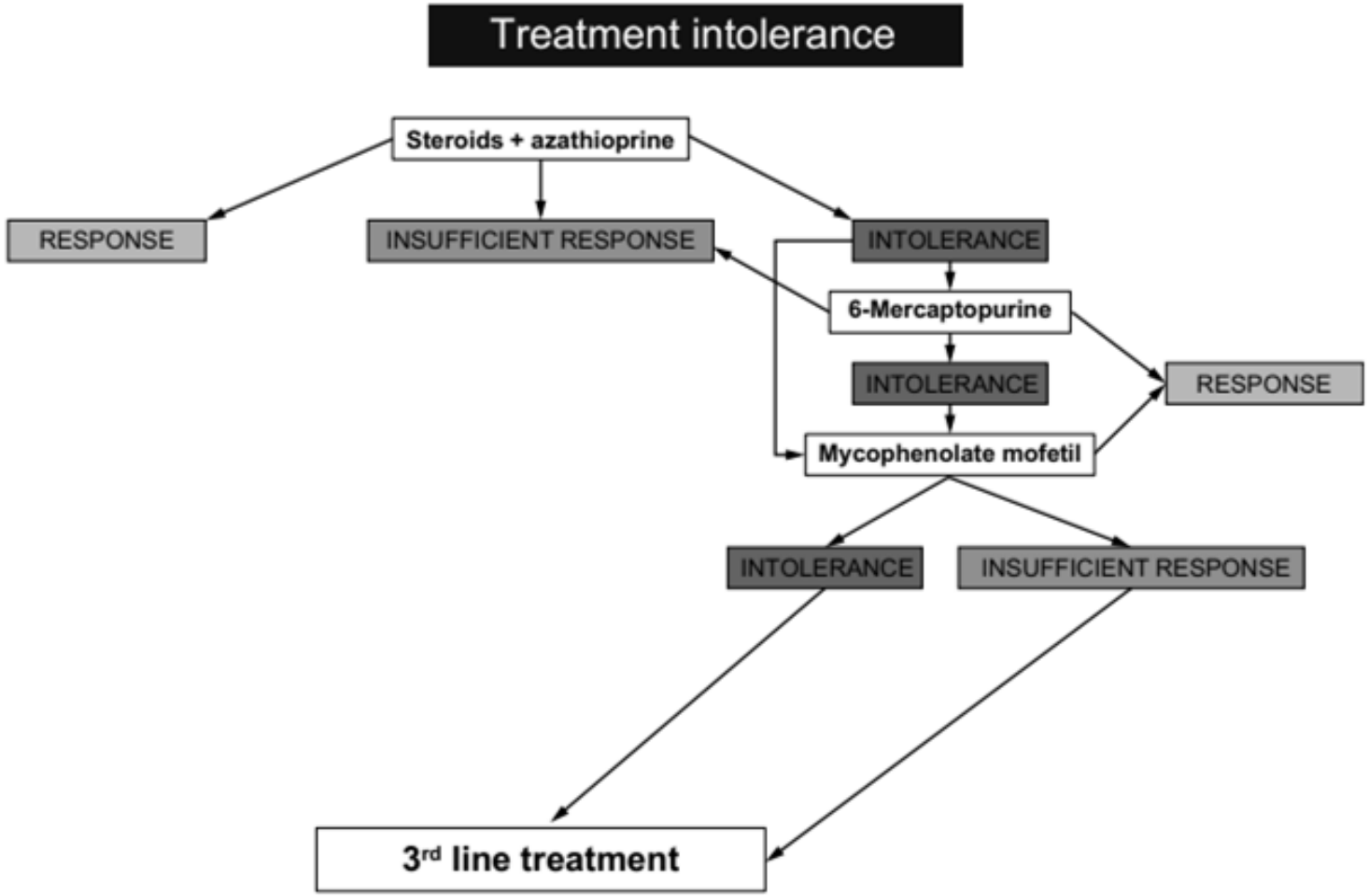
Non-response



Complete biochemical response (CBR)/insufficient response

Treatment: Failure of First Line





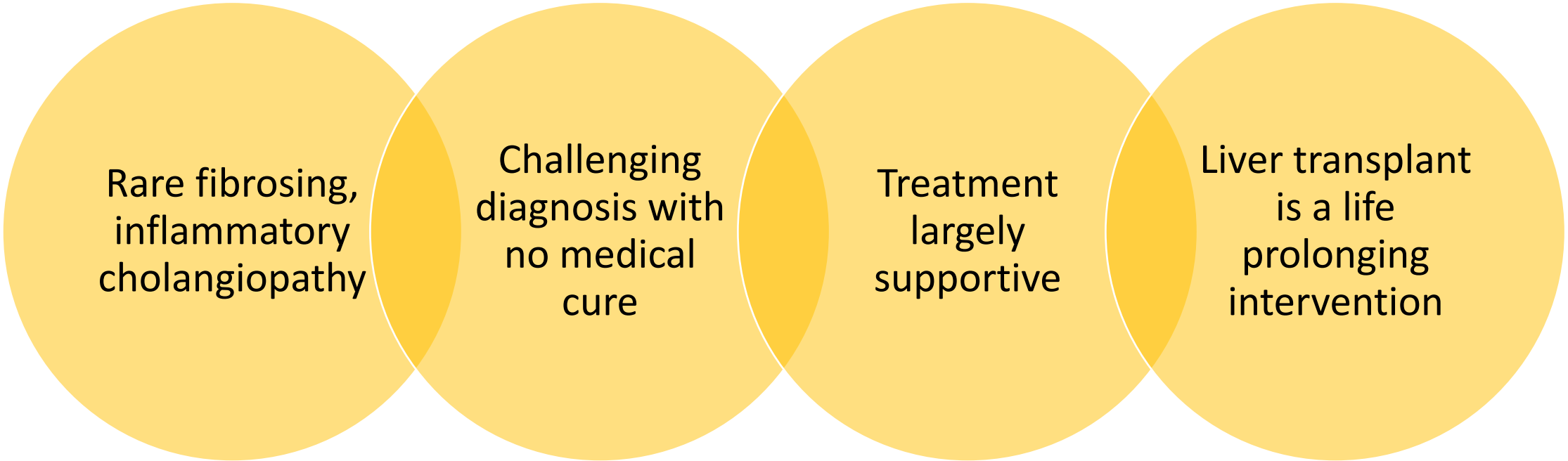
Lohse et al. Journal of Hepatology 2020 vol. 73 j 1496–1506

Treatment: Third line

Therapy	Adult dose	Therapy	Adult dose
Tacrolimus Everolimus	0.1mg/kg bd trough levels 8ng/ml <0.75-1.5mg/day trough level 3-6ng/ml	Infliximab	5mg/kg/day at week 0, 2, 6 and every 4-8 weeks
Ciclosporin	2mg/kg bd serum trough levels <120ng/ml	Methotrexate	7.5-15mg weekly
Rituximab	1000mg at week 0 and 2 and repeated whenever transaminases rise (eg 6-12 months)	Cyclophosphamide	1-1.5mg/kg/day or pulse therapy 1g ivi every 4 weeks

Lohse et al. Journal of Hepatology 2020 vol. 73 j 1496–1506

Primary Sclerosing Cholangitis (PSC)



Clinical Presentation

Assymptomatic

- Elevations in ALP/GGT +- Bili
- Routine IBD care
- Incidental findings on imaging

Symptomatic

- Cholestasis
- Weight loss
- Cholangitis

Complicated

- Cirrhosis
- Portal hypertension
- Malignancy

Clinical Presentation

Assymptomatic

- Elevations in ALP/GGT +- Bili
- Routine IBD care
- Incidental findings on imaging

- Detailed history and physical examination
- Liver US to exclude extra hepatic causes of cholestasis
- Consider PBC- AMA+-liver biopsy

Symptomatic

- Cholestasis
- Weight loss
- Cholangitis

Complicated

- Cirrhosis
- Portal hypertension
- Malignancy

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- Incidental findings on imaging

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- Cirrhosis
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- MRCP: Evidence of biliary strictures

Clinical Presentation

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- Weight loss
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Complicated

- Cirrhosis
- Portal hypertension
- Malignancy

- Detailed history and physical examination
- Liver US to exclude extra hepatic causes of cholestasis
- Consider PBC- AMA+-liver biopsy

- MRCP: Evidence of biliary strictures

- Consider secondary causes of sclerosing cholangitis

Secondary Sclerosing Cholangitis

Ischemia
- Critical illness/ICU
- Post-liver transplant ischemic cholangiopathy*
- Intra-arterial chemotherapy
- Hepatic artery thrombosis
- Hereditary Hemorrhagic Telangiectasia

Infection
- HIV related cholangiopathy
- Parasitic Cholangiopathy
- Pyogenic Cholangitis
- COVID 19 induced cholangiopathy

Malignancy
- Cholangiocarcinoma
- Diffuse intrahepatic metastasis
- Lymphoma
- Langerhans cell histiocytosis

Autoimmune
- IgG-4 associated cholangitis
- Mast cell cholangiopathy
- Sarcoidosis
- Eosinophilic cholangitis
- Inflammatory Pseudotumor

Anatomic
- Choledocholithiasis
- Intrahepatic fibrosis
- Cystic fibrosis liver disease
- Post liver transplant Anastomotic stricture*
- Portal hypertensive biliopathy
- Recurrent pancreatitis
- Sickle cell cholangiopathy
- Choledochal cyst
- Surgery related/vascular trauma

Drug induced
- Immunotherapy associated with check point inhibitor
- Ketamine

https://www.aasld.org/liver-fellow-network/core-series/clinical-pearls/cholestatic-challenge-identifying-secondary

Clinical Presentation

Assymptomatic

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Symptomatic

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Complicated

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- Detailed history and physical examination
- Liver US to exclude extra hepatic causes of cholestasis
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- MRCP: Evidence of biliary strictures

- Consider secondary causes of sclerosing cholangitis

Diagnosis of PSC:
Typical cholangiographic findings in the setting of a consistent clinical/biochemical phenotype after exclusion of secondary causes of sclerosing cholangitis

Clinical Presentation

Assymptomatic

- Elevations in ALP/GGT +- Bili
- Routine IBD care
- Incidental findings on imaging

Symptomatic

- Cholestasis
- Weight loss
- Cholangitis

Complicated

- Cirrhosis
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- Detailed history and physical examination
- Liver US to exclude extra hepatic causes of cholestasis
- Consider PBC- AMA+-liver biopsy

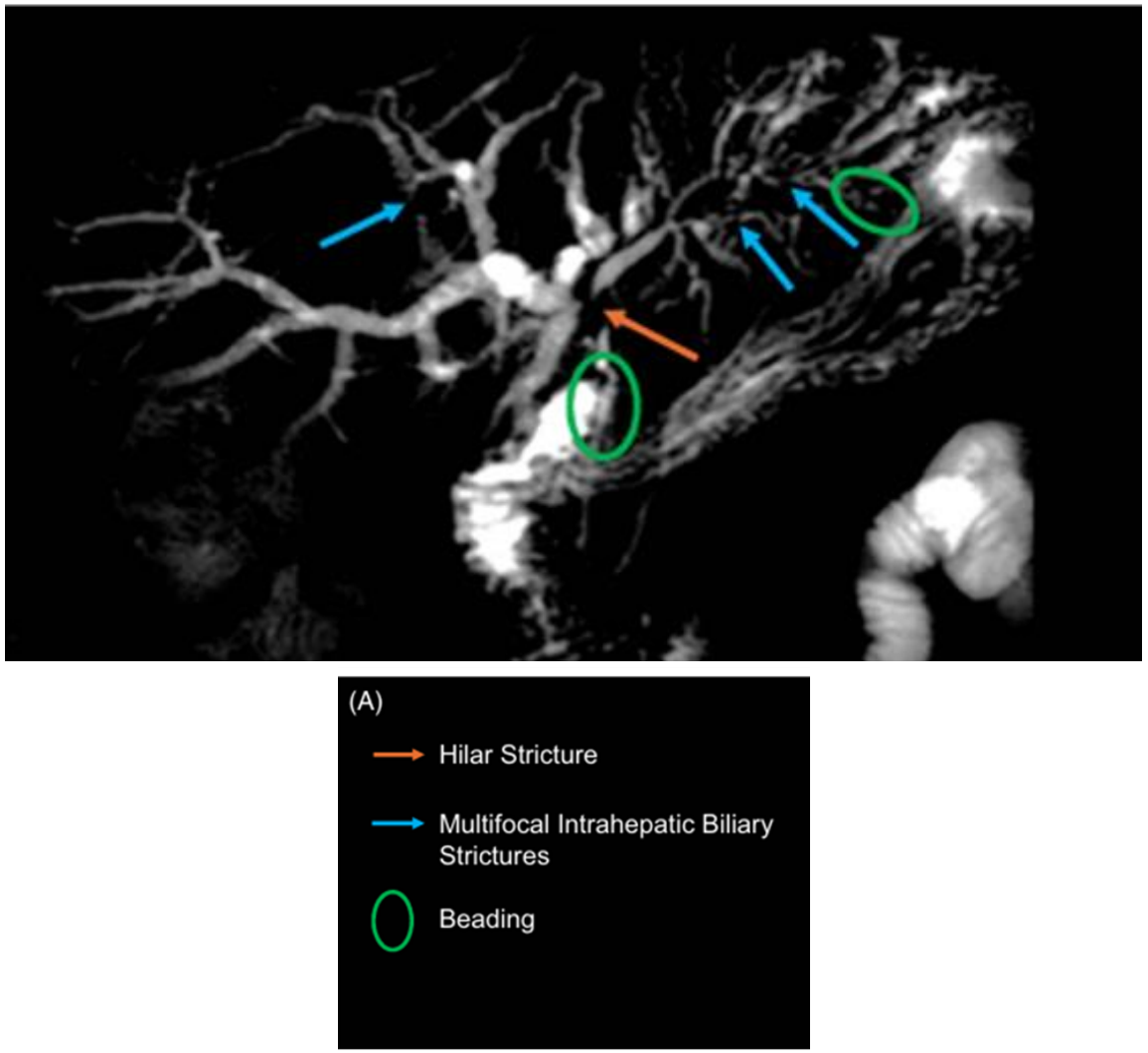
Serology?

- MRCP: Evidence of biliary strictures

- Consider secondary causes of sclerosing cholangitis

Diagnosis of PSC:
Typical cholangiographic findings in the setting of a consistent clinical/biochemical phenotype after exclusion of secondary causes of sclerosing cholangitis

Diagnosis: Imaging

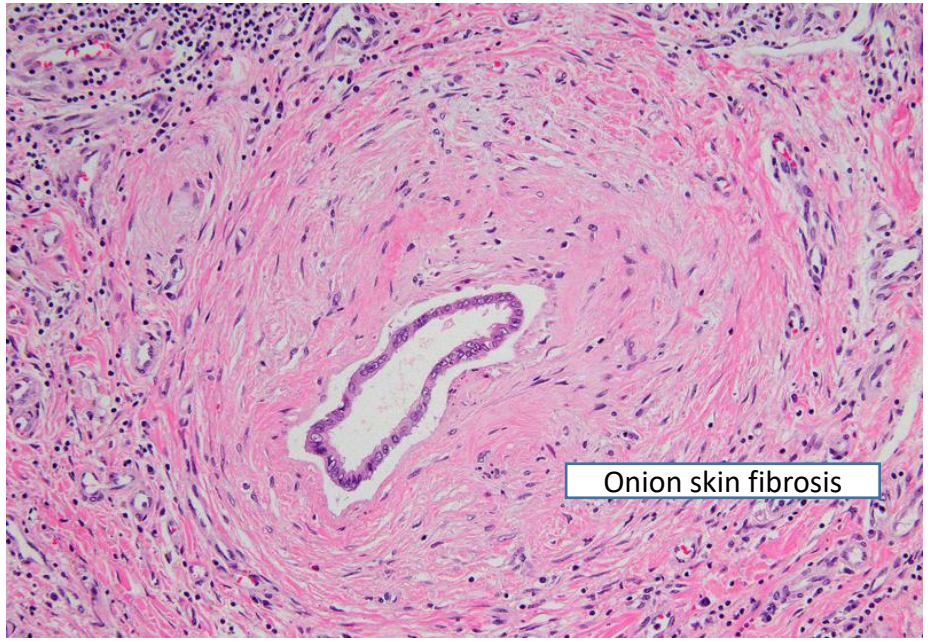


- Main findings MRI/MRCP
  - Multifocal stricturing of intrahepatic and extra hepatic bile ducts
  - Bile ducts with intervening segments that are relatively normal in caliber or mildly dilated (“beaded” appearance)
  - Intra ductal stones can be evident
- Progressive disease
  - Strictures worsen and ducts become obliterated
  - Fibrosis may be demonstrated by focal atrophy and liver dysmorphy

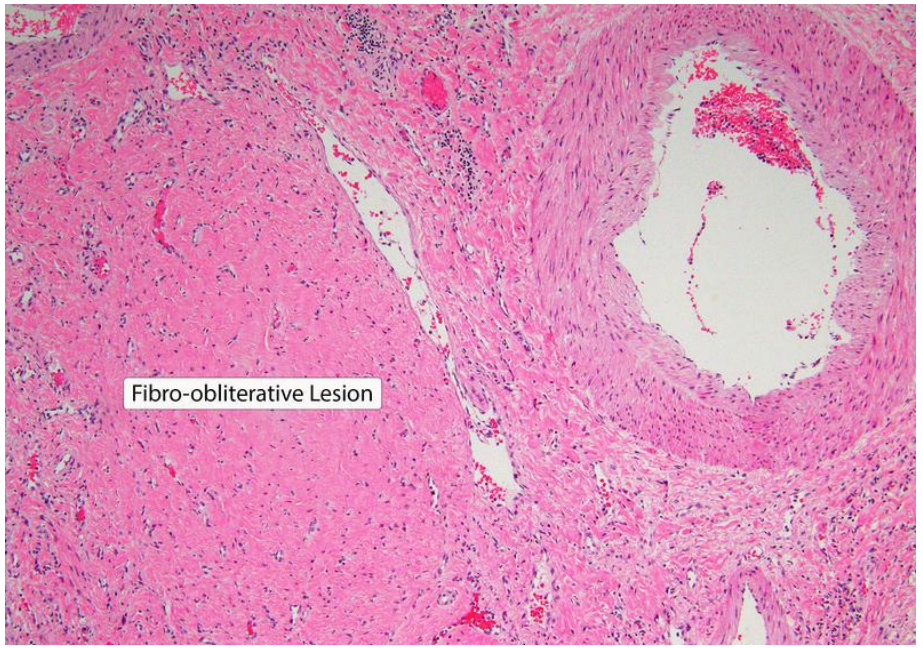
Cançado G et al. Hepatology Communications. 2024;8:e0590

Role of liver Biopsy

- The histological hallmark of PSC is concentric “onion skin” periductal fibrosis
- Small duct PSC- less common variant



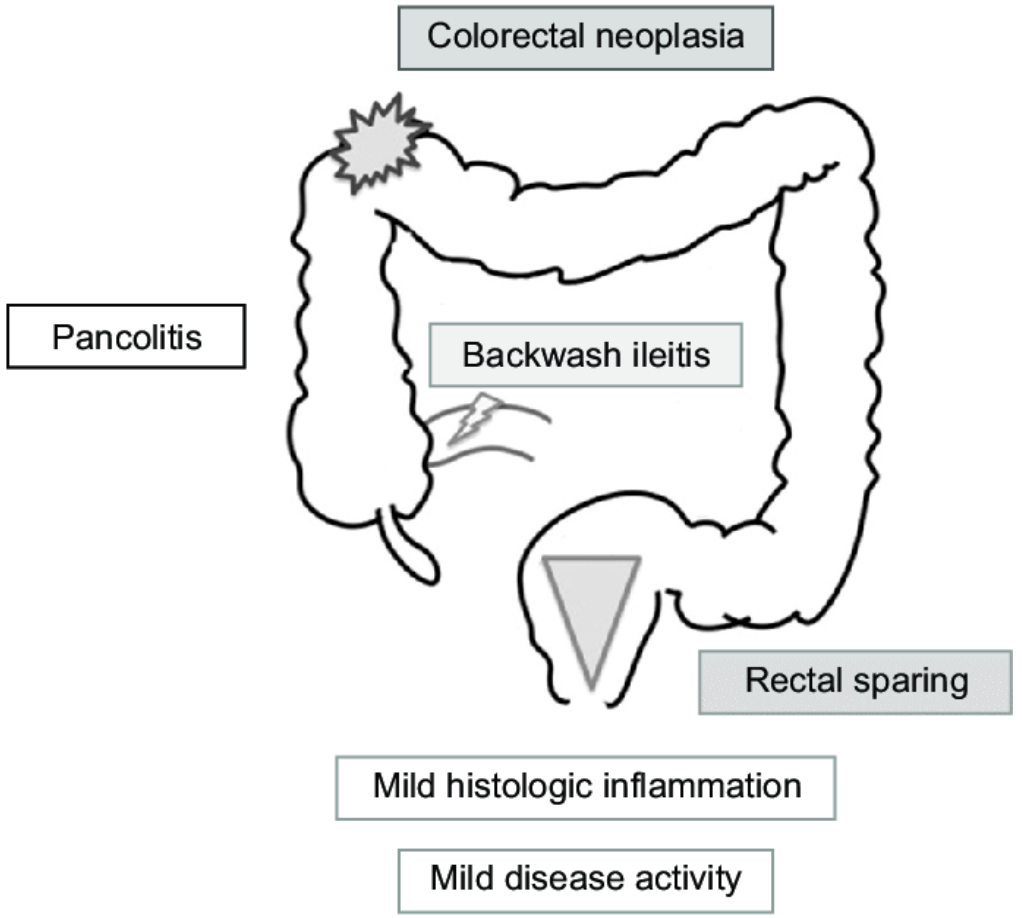
- Bile duct loss (ductopenia)
- Fibrotic scar that replaces the bile ducts (fibro-obliterative lesion)
- Progressive fibrosis



https://www.aasld.org/liver-fellow-network/core-series/pathology-pearls/-8-primary-sclerosing

Inflammatory bowel disease (IBD) and PSC

- Over 70% of patients with PSC have IBD
- Ileocolonoscopy **with biopsies** at PSC diagnosis- if normal repeat at 5-year intervals
- IBD phenotype is different compared to classic UC or CD colitis- often milder
- IBD and PSC is associated with a higher risk of colorectal cancer
- Aim for close disease control and annual surveillance for dysplasia
- Surveillance to continue post transplant



Palmela et al. Gut and liver. 12. 10.5009
Cançado G et al. Hepatology Communications. 2024;8:e0590

Medical Management

Ursodeoxycholic Acid (UDCA): Secondary hydrophilic bile acid

- Meta-analyses UDCA for PSC: [1]
  - No beneficial effect on survival, liver histology, prevention of CCA, or improvement of clinical symptoms
- UDCA treatment has been associated with improved cholestatic enzymes
- Insufficient evidence for a beneficial effect of UDCA in reducing the risk of CCA and CRC

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

PRACTICE GUIDANCE

Guidance statements

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.

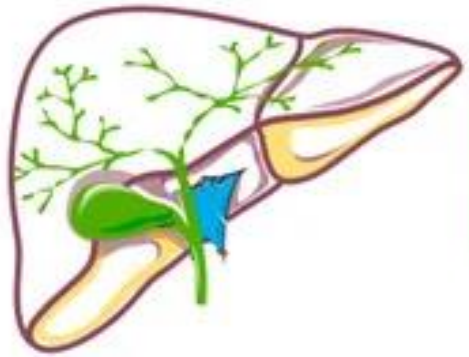
1. Triantos CK et al. Aliment Pharmacol Ther. 2011 Oct;34(8):901-10
2. Bowlus CL et al. Hepatology. 2022;00:1–44

Further Therapeutic Targets

PSC

Targeting bile acid metabolism in hepatocytes and cholangiocytes
UDCA
Nor-UDCA
FXR agonists: obeticholic acid, cilofexor, tropifexor
FGF19 analogues
GPBAR1
PPARs

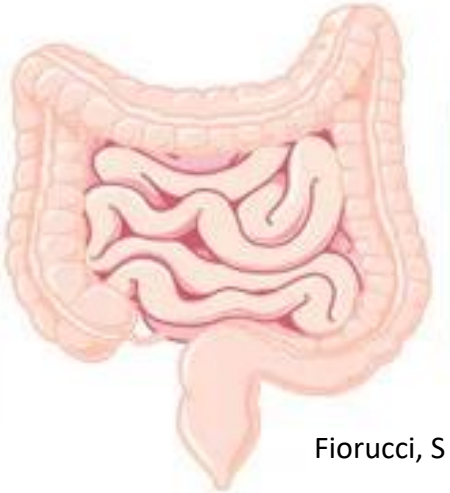
Immune-mediated therapies
Vidofludimus calcium



Antifibrotic agents
Anti-Integrin αVβ6 and αVβ1
simtuzumab

Targeting intestinal bile acid metabolism
FGF19 analogues
GPBAR1

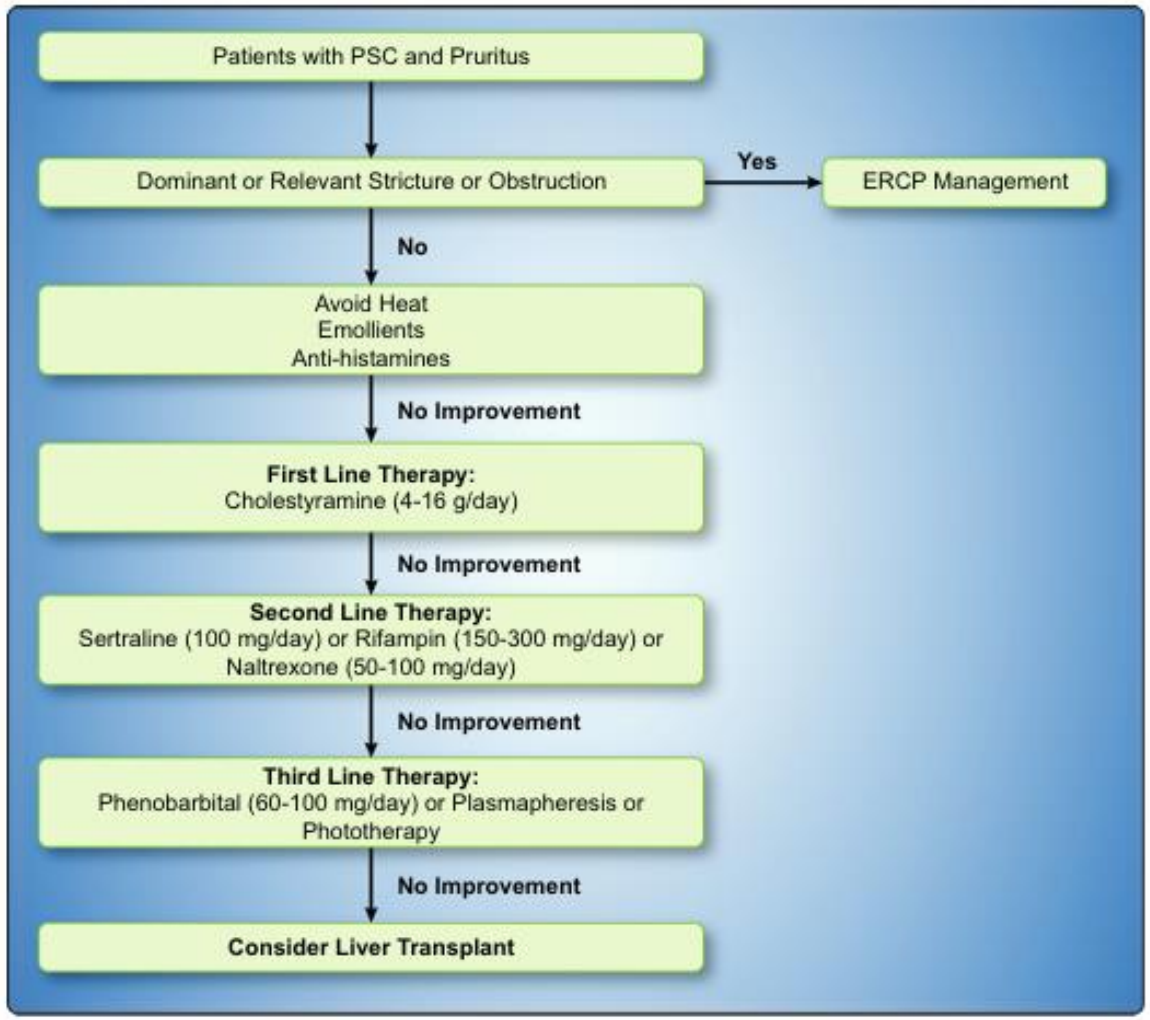
IBAT (SLC10A2) inhibitor
Volixibat,, odevixibat, maralixibat
(approved cholestatic pruritus



Microbiota based therapies
Antibiotics: vancomicyn
Fecal microbiota transplantation

Fiorucci, S et al. Current Landscape and Future Developments. Cells 2024, 13, 1650

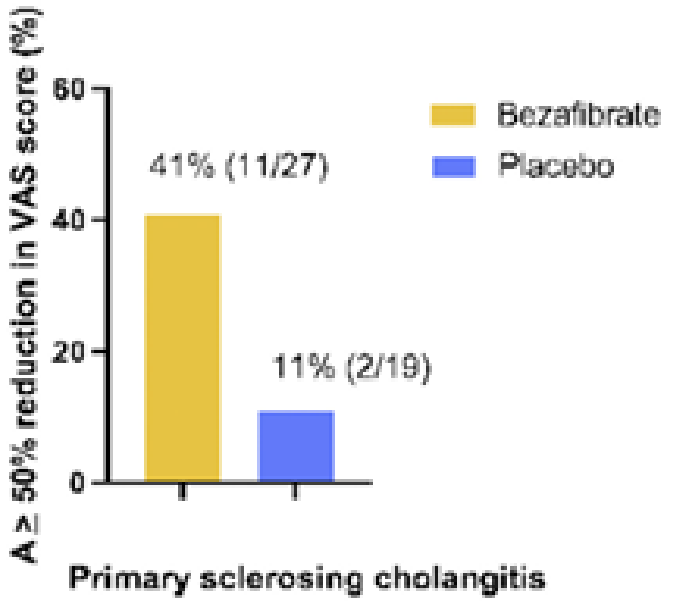
Medical Management of Symptoms



Gastroenterology 2021;160:734–743

CLINICAL—LIVER

Fibrates for Itch (FITCH) in Fibrosing Cholangiopathies: A Double-Blind, Randomized, Placebo-Controlled Trial



De Vries E et al. Gastroenterology 2021;160:734–743
Bowlus CL et al. Hepatology. 2022;00:1–44

Role of ERCP in PSC Management

Indications:

- Diagnosis of PSC: High index of suspicion but inconclusive or contraindicated MRCP
- Cholangitis: Inadequate response to antibiotics
- Assessment of a dominant, clinically relevant stricture confirmed at MRCP- exclude CCA
- Provide therapeutic options for stricture mx, stone removal

Concerns:

- Post ERCP Cholangitis (risk 2-8%)- prophylactic antibiotics
- Risks with sphincterotomy (portal hypertension/coagulopathy)
- Balloon dilation vs stenting
- Pancreatitis- Prophylactic measures
- Likelihood of repeated procedures

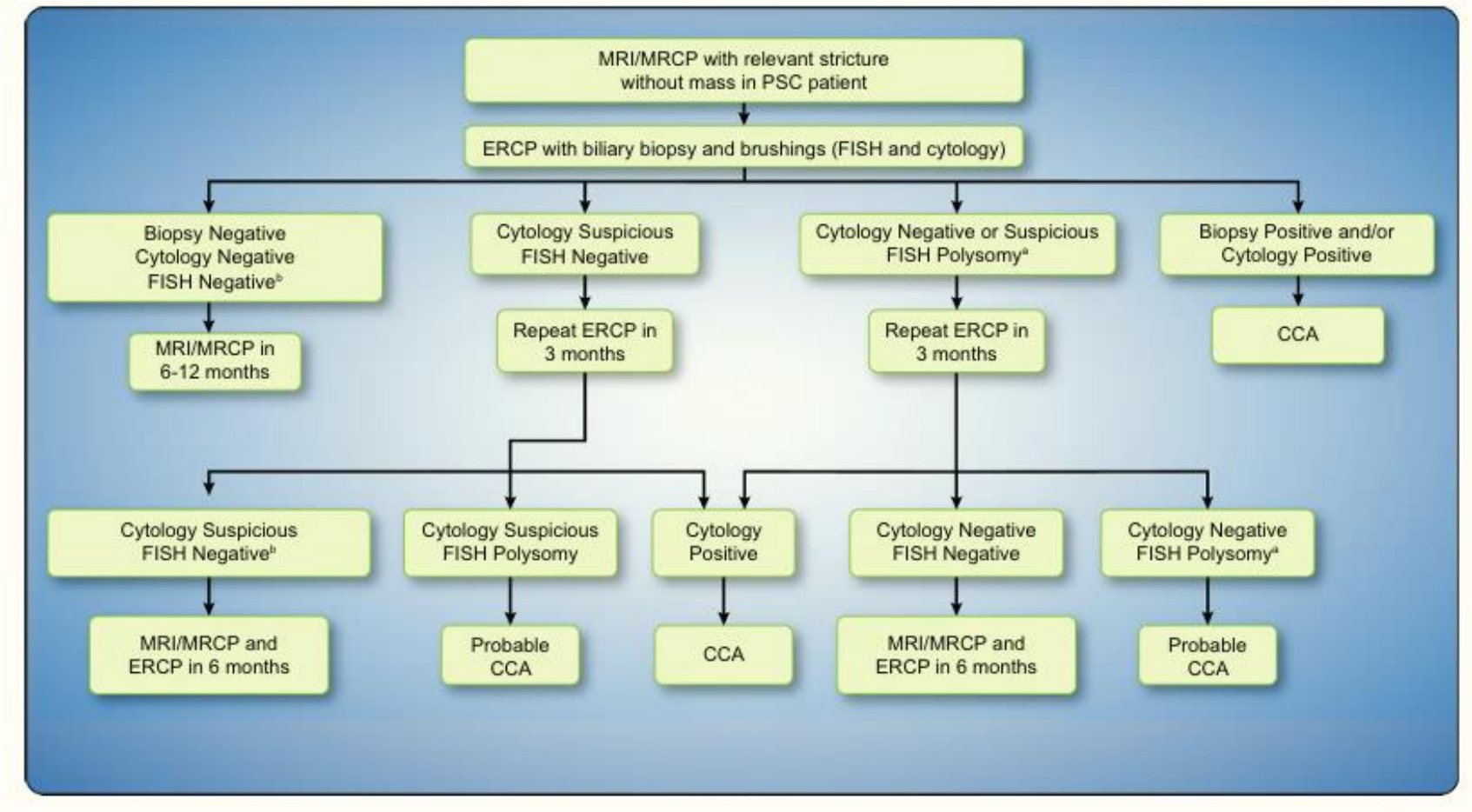
Bowlus CL et al. Hepatology. 2022;00:1–44

Management of a Relevant Stricture

Dominant stricture:
A biliary stricture on ERCP with a diameter of ≤1.5mm in the CBD or of ≤1 mm in the hepatic duct within

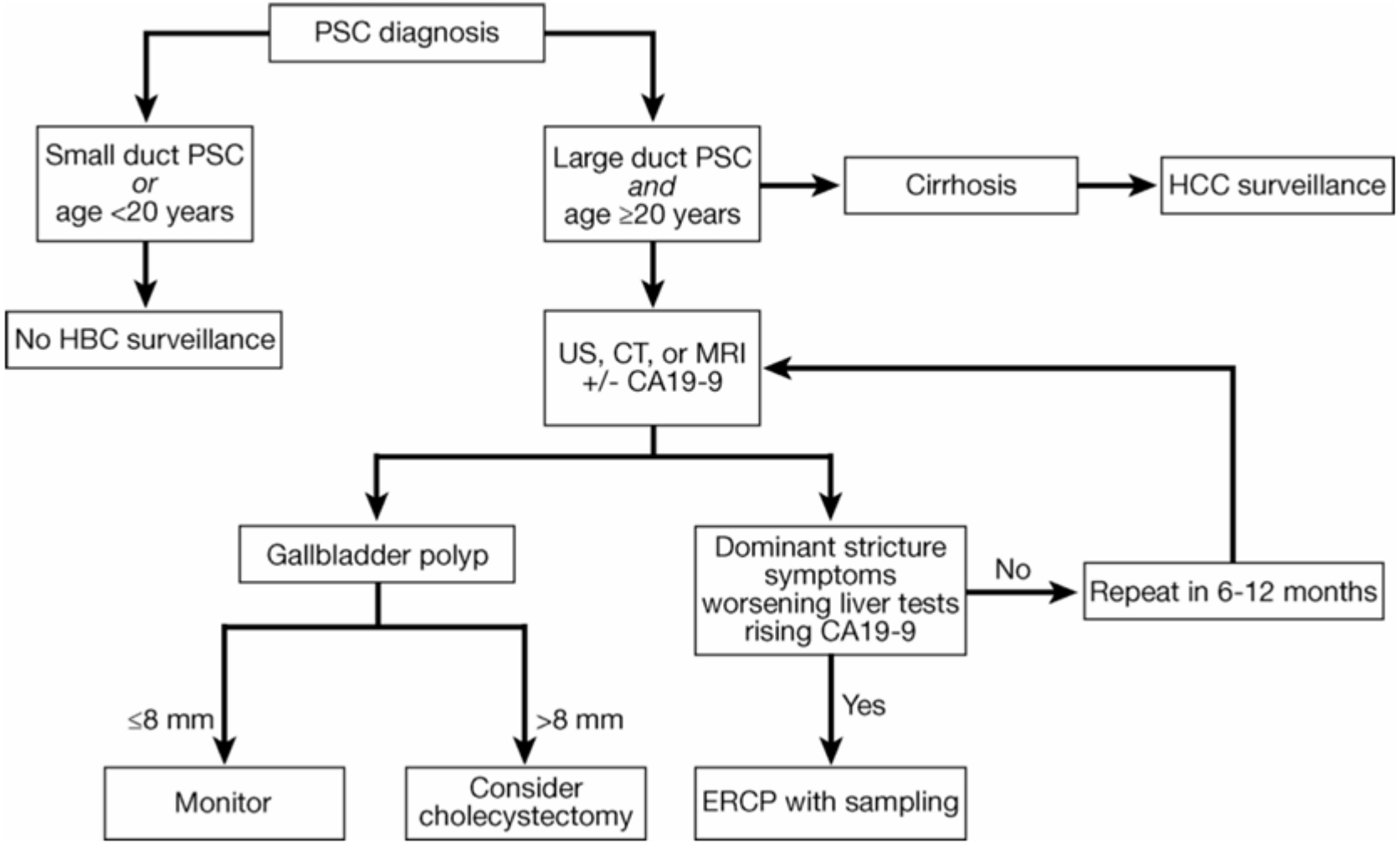
High-grade Stricture:
A biliary stricture on MRCP with >75% reduction in the CBD or hepatic ducts

Relevant stricture:
Any biliary stricture of the CBD or hepatic ducts associated with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis



Bowlus CL et al. Hepatology. 2022;00:1–44

Malignancy Surveillance



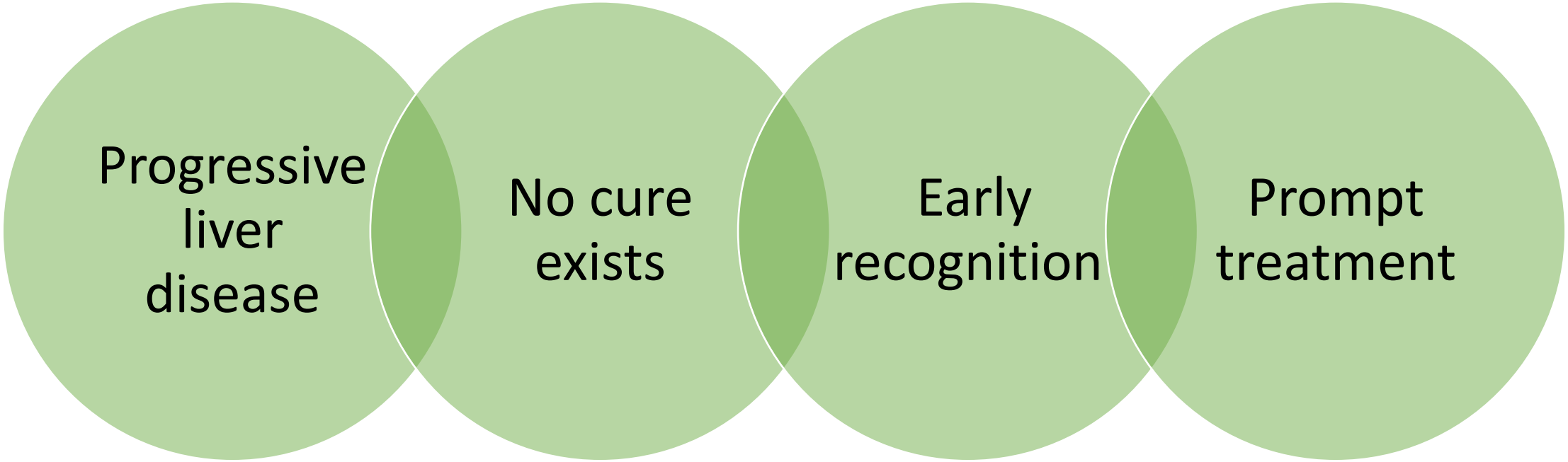
Bowlus CL Clinical Gastroenterology and Hepatology 2019;17:2416–2422

Liver Transplant

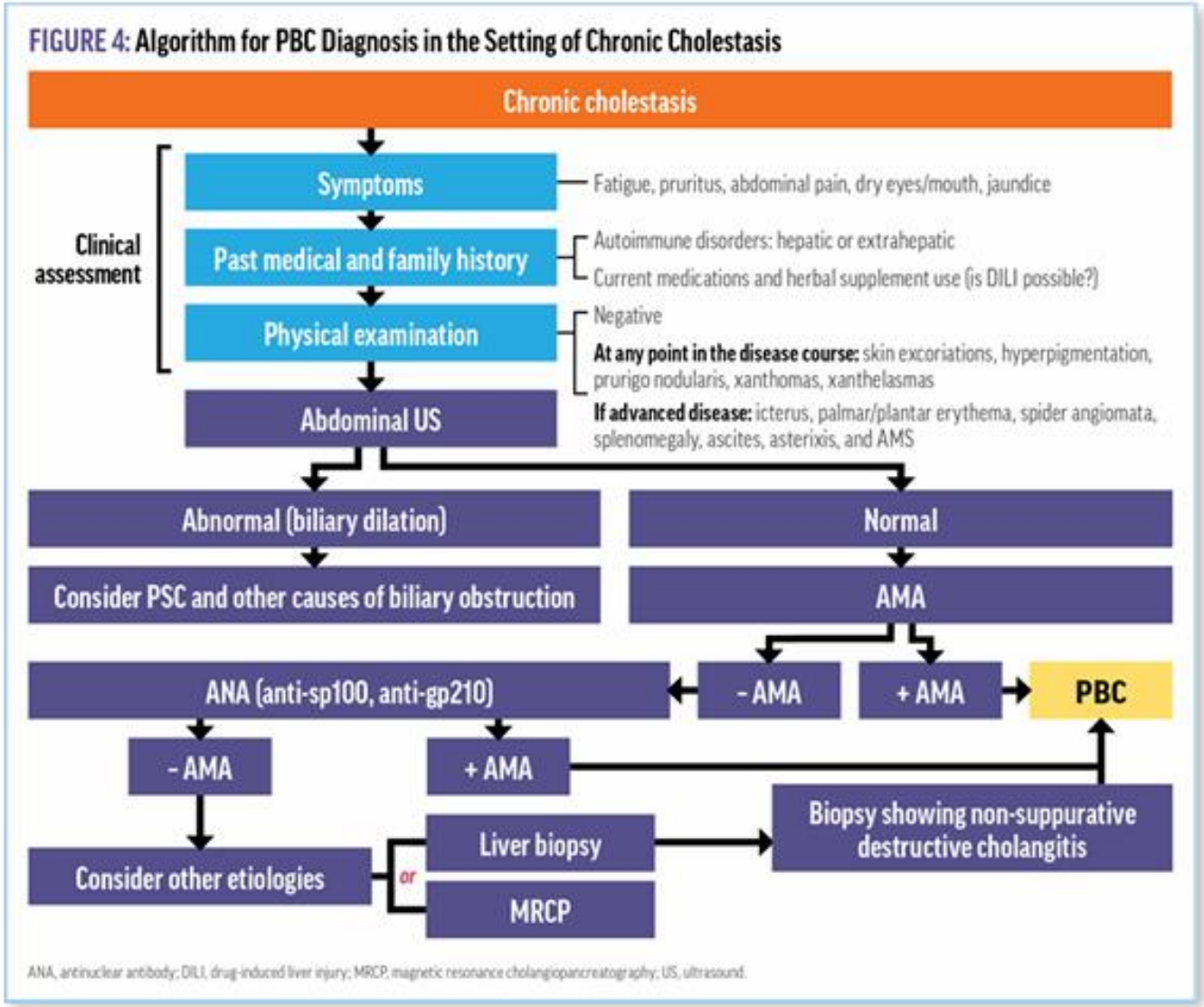
- PSC accounts for approximately 5% of LTs annually in the US
- Wits Transplant unit annual report: The most common indication for liver transplant (2018-2022) was cholestatic liver diseases (PSC/PBC)
- Indications for transplant in PSC:
  - Complications of cirrhosis/portal hypertension
  - Intractable pruritus
  - Recurrent bacterial cholangitis
  - Early-stage CCA
- Patient and graft survival in PSC are comparable with transplant for other liver diseases
- Recurrence of PSC occurs in 10%–37%, at a mean of 0.5–5 years post-LT

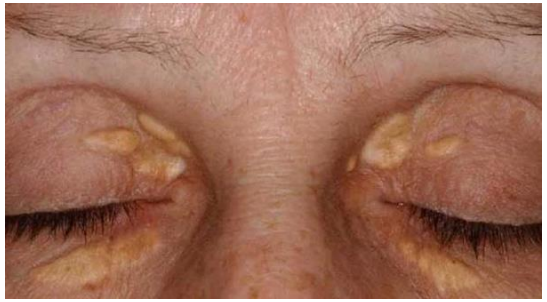
Bowlus CL et al. Hepatology. 2022;00:1–44
E U Wessels, K Kinandu et al. Afr Med J 2024;114(3b):e1365

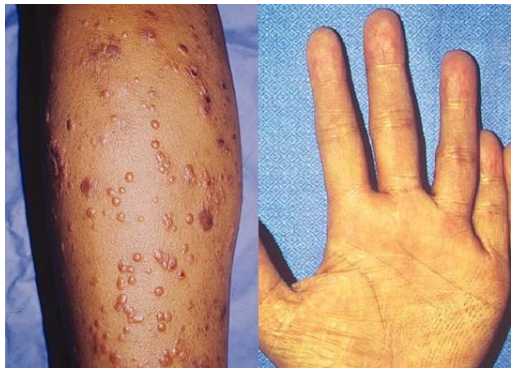
Primary Biliary Cholangitis (PBC)



Clinical Evaluation &Diagnosis

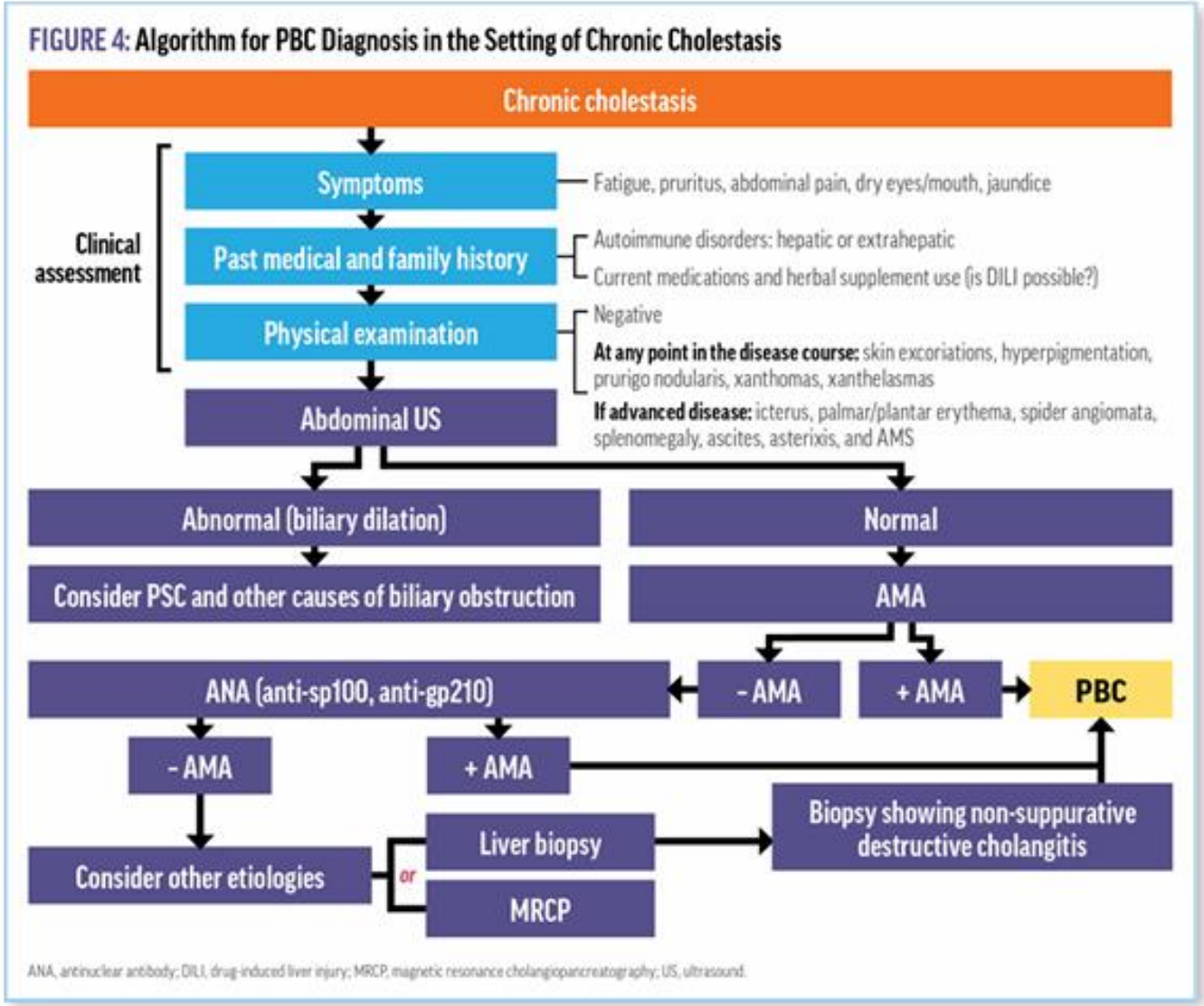






Trivella J et al. Hepatol Commun. 2023;7(6):e0179

Clinical Evaluation &Diagnosis



Conditions associated with PBC

Common (up to 80%)

- Sicca syndrome

Less common (about 20%)

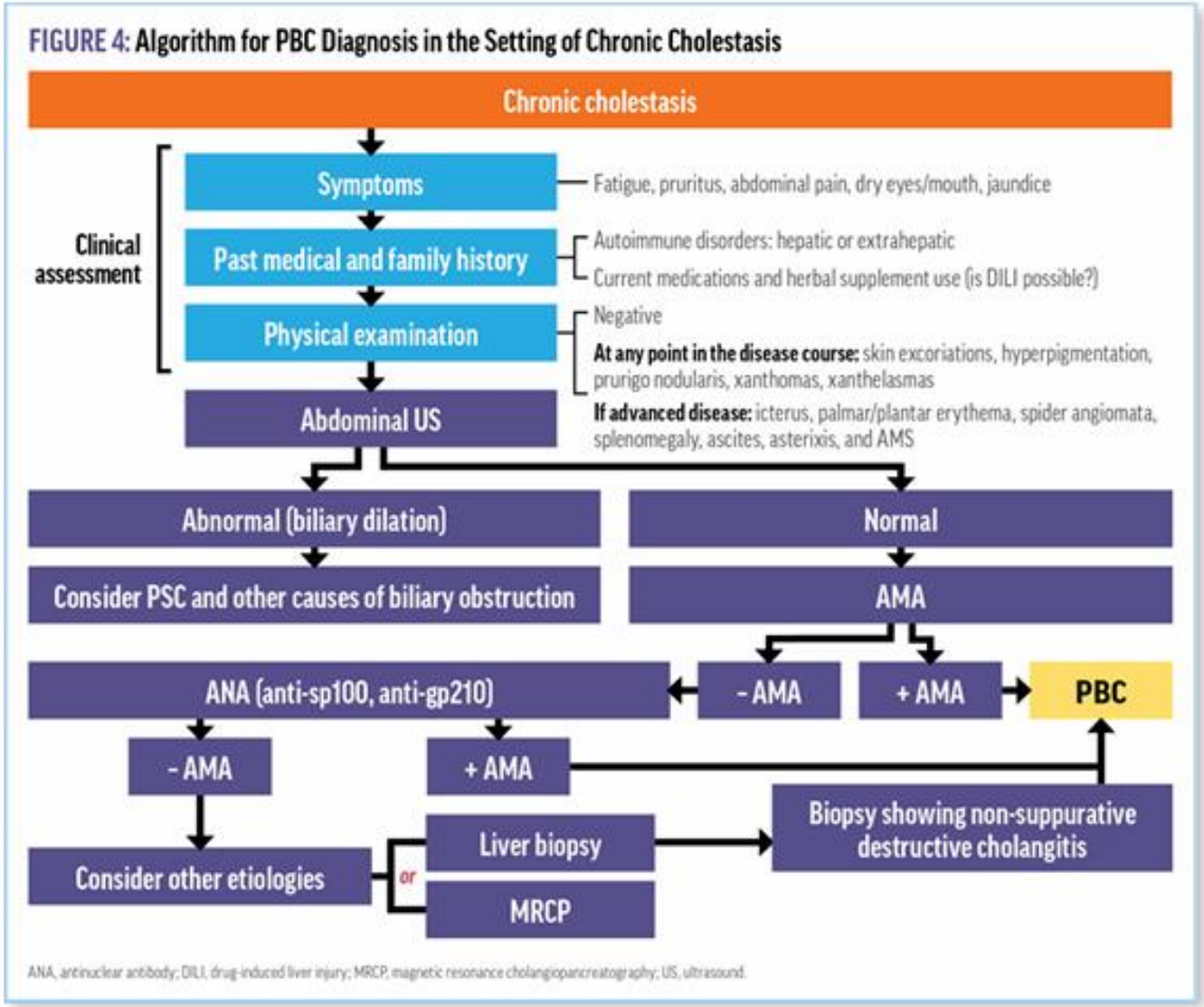
- Thyroid disease
- Arthralgia
- Raynaud's syndrome
- Sclerodactyly
- Fibrosing alveolitis

Uncommon (less than 5%)

- CREST (calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, telangiectasia) syndrome
- Addison's disease
- Celiac disease
- Glomerulonephritis
- Vitiligo
- Renal tubular acidosis
- Myasthenia gravis
- Hypertrophic pulmonary osteoarthropathy

Trivella J et al. Hepatol Commun. 2023;7(6):e0179

Clinical Evaluation &Diagnosis



The diagnosis of PBC is established when 2 out of 3 of the following criteria are met:

LAB TEST RESULTS

Chronic cholestasis
ALP ≥1.5 times the ULN

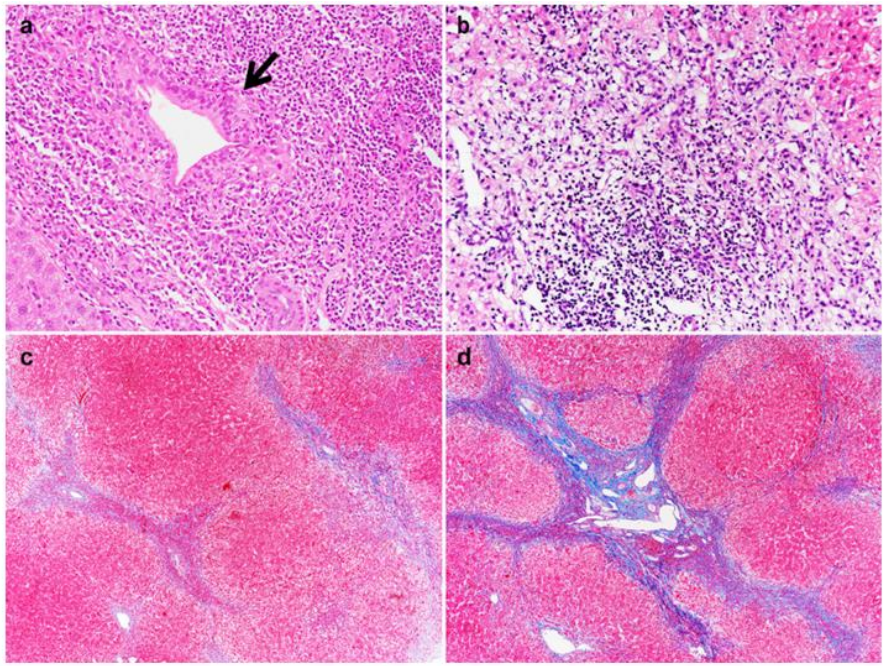
ANTIBODIES

Elevated AMA
(≥1:40)
Or
PBC specific ANA
(anti-gp210 or anti-sp100)

Liver histology consistent with PBC

Trivella J et al. Hepatol Commun. 2023;7(6):e0179

Diagnosis: Histology



Histology

- "The florid duct lesion"- Pathognomonic of PBC
  - Chronic non-suppurative destructive cholangitis with epithelioid cell granulomas adjacent to damaged bile ducts
- Progressive necroinflammatory bile duct destruction and ductopaenia

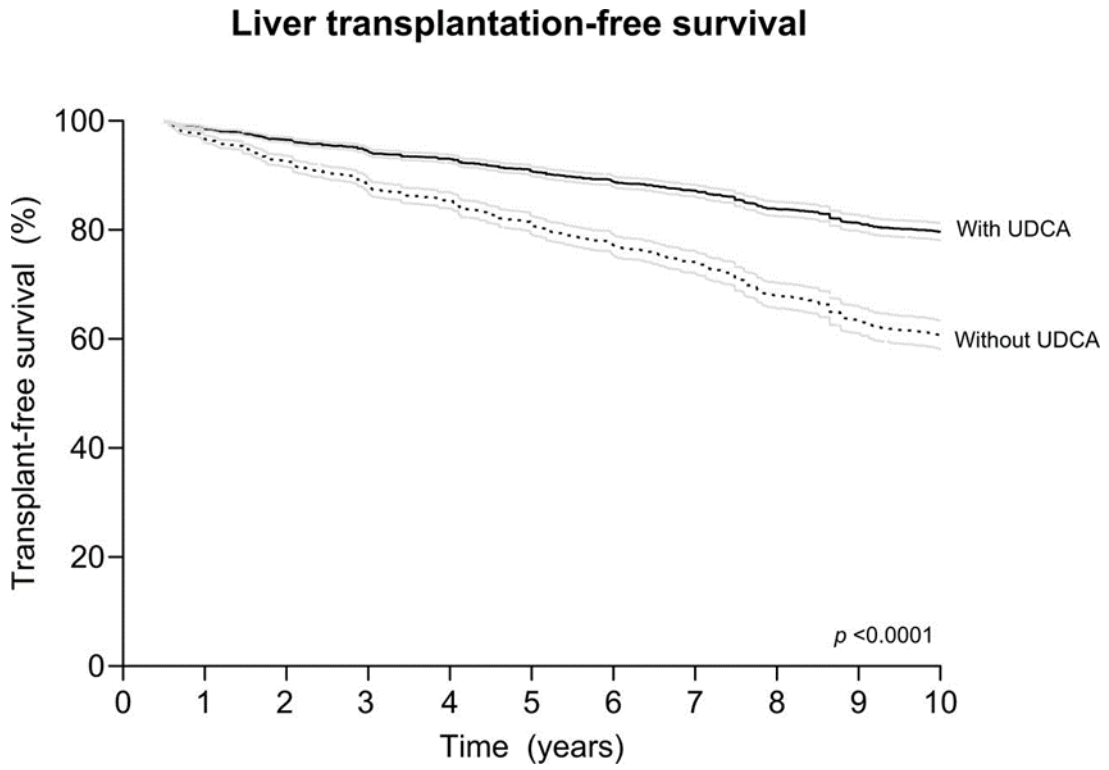
Histological Stages

Stage I: chronic non-suppurative destructive cholangitis
Stage II: ductular reaction/peri-portal necroinflammatory activity
Stage III: multiple portal-portal bridging fibrosis
Stage IV: biliary cirrhosis with nodule formation

Hong You et al. Hepatology International (2022) 16:1–23

Treatment: First Line
Ursodeoxycholic acid (UDCA)

- UDCA is a hydrophilic bile acid
- Recommended standard of care
- Most cost-effective dose 13 to 15 mg/kg/day, given in divided doses with meals
- UDCA is safe and well-tolerated
- ALP above 1.67xULN at 1 year of UDCA is predicted of histological progression
- Non responders: 40%



Harms M et al. Journal of hepatology.71(2) August 2019,357-365

Risk Factors for Poor Prognosis

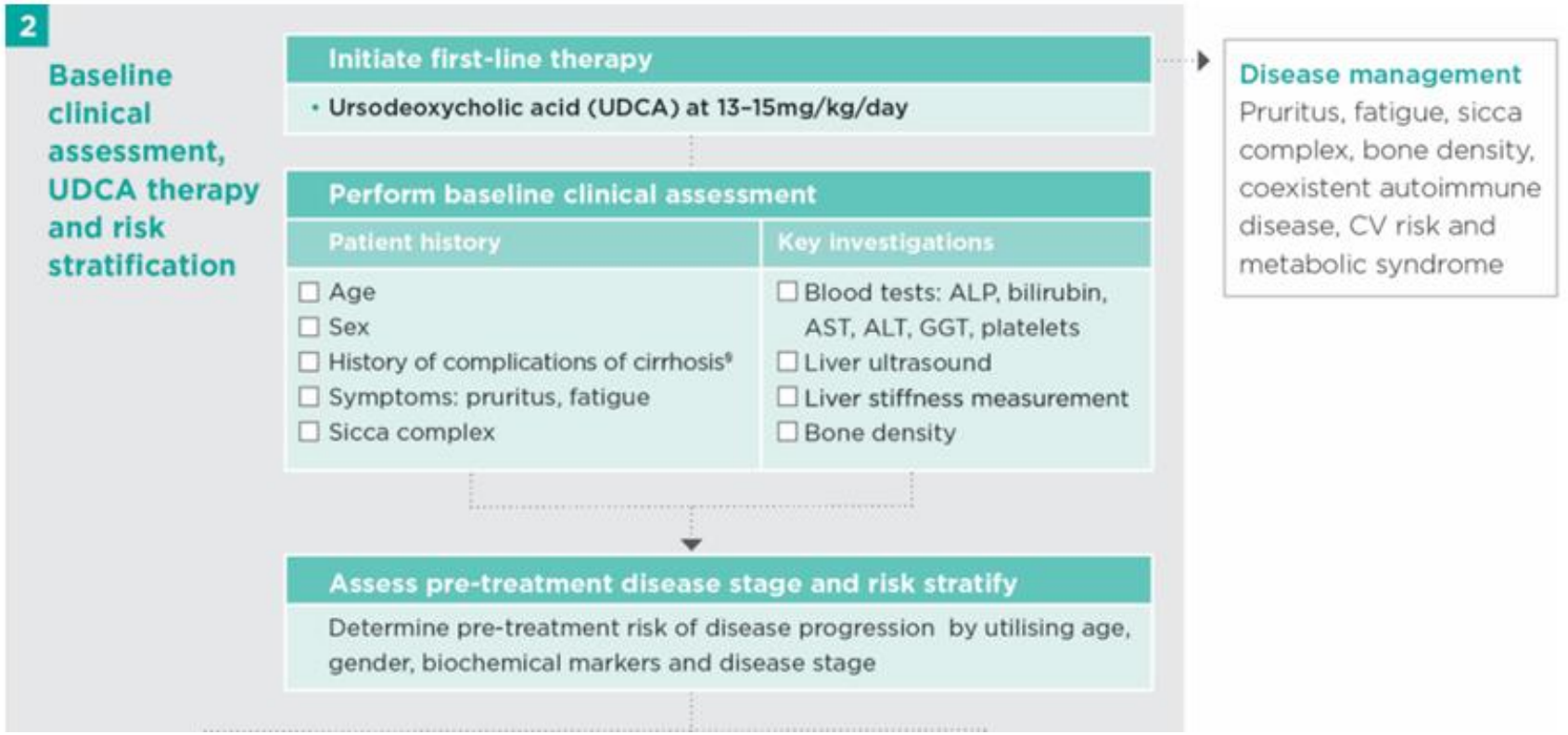
- Age at diagnosis <45 years
- Male sex
- ALP >1.5x ULN; or
- Abnormal bilirubin; or
- Low albumin
- Advanced fibrosis/Cirrhosis

Inadequate response to UDCA

Paris II criteria:

- ALP >1.5x ULN; or
- AST >1.5x ULN; or
- Bilirubin >17.1umol/l

Pre-treatment assessment

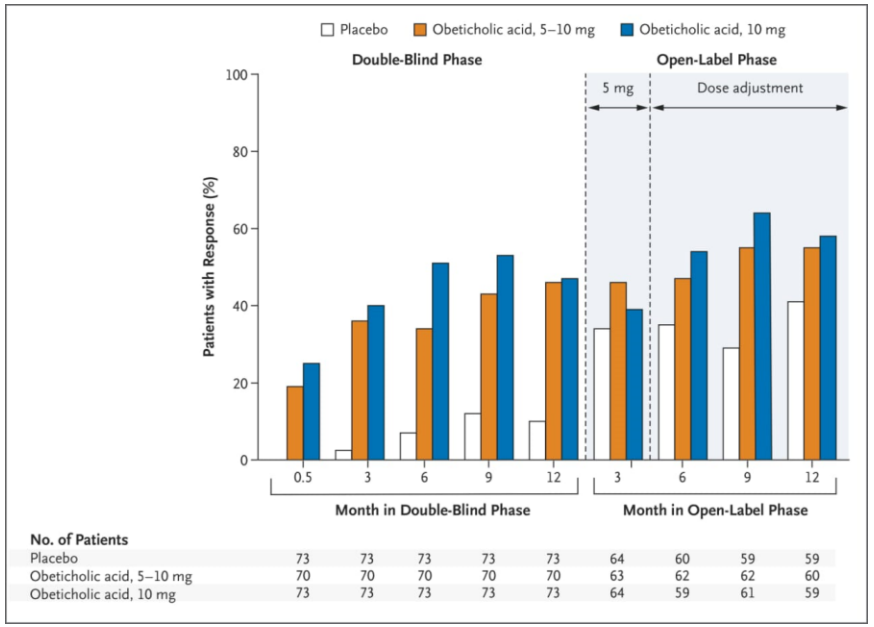


On-treatment assessment

Hirschfield G M et al. Expert Review of Gastroenterology & Hepatology, 15:8, 929-939

Treatment: Traditional Second line Obeticholic Acid(OCA)

- OCA: Agonist of the intranuclear bile acid farnesoid X receptor (FXR)
- FDA approved
- Successfully met primary composite endpoints (Phase 3 POISE Trial)

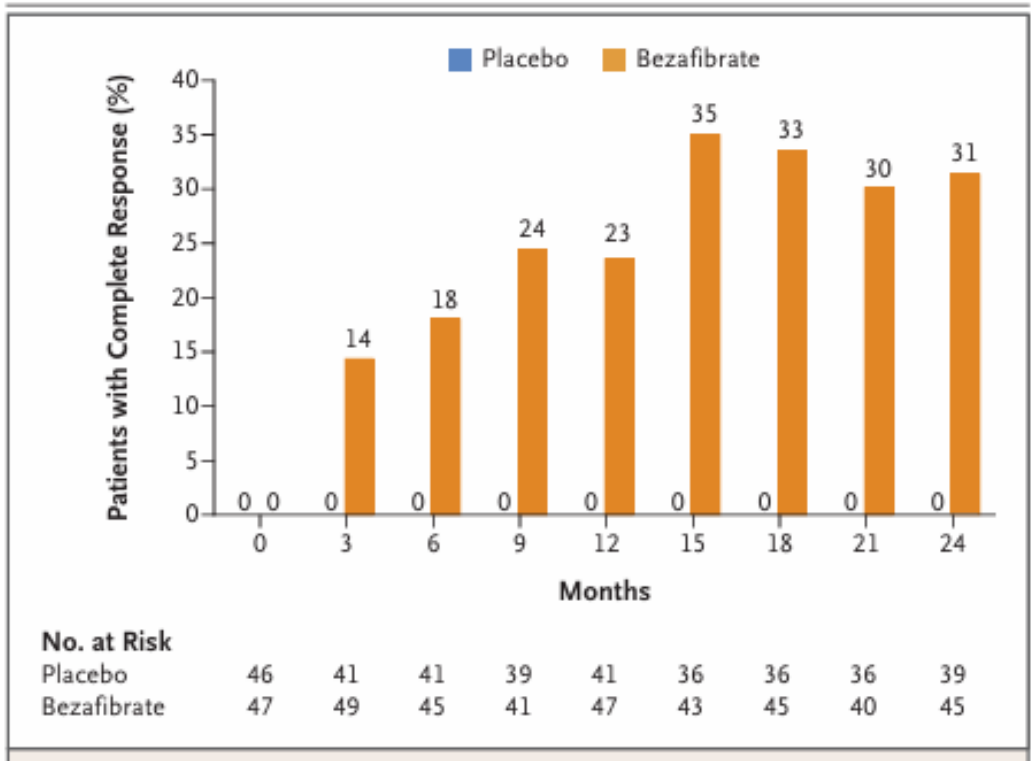


- Safety Concerns:
  - Exacerbation of pruritus
  - 2021 FDA black box warning- Avoid in advanced cirrhosis
- Required post marketing study (Phase 4 COBOLT trial)
  - Hampered by poor enrollment
  - lack of demonstrated improved outcome
- November 2024, the FDA declined to grant full approval of OCA due to the drug's less than-favorable benefit-risk profile

Nezens F et al. N Engl J med 2016;375:631-643
Heyes CM et al. Hepatology Communications 2025;9:e0612

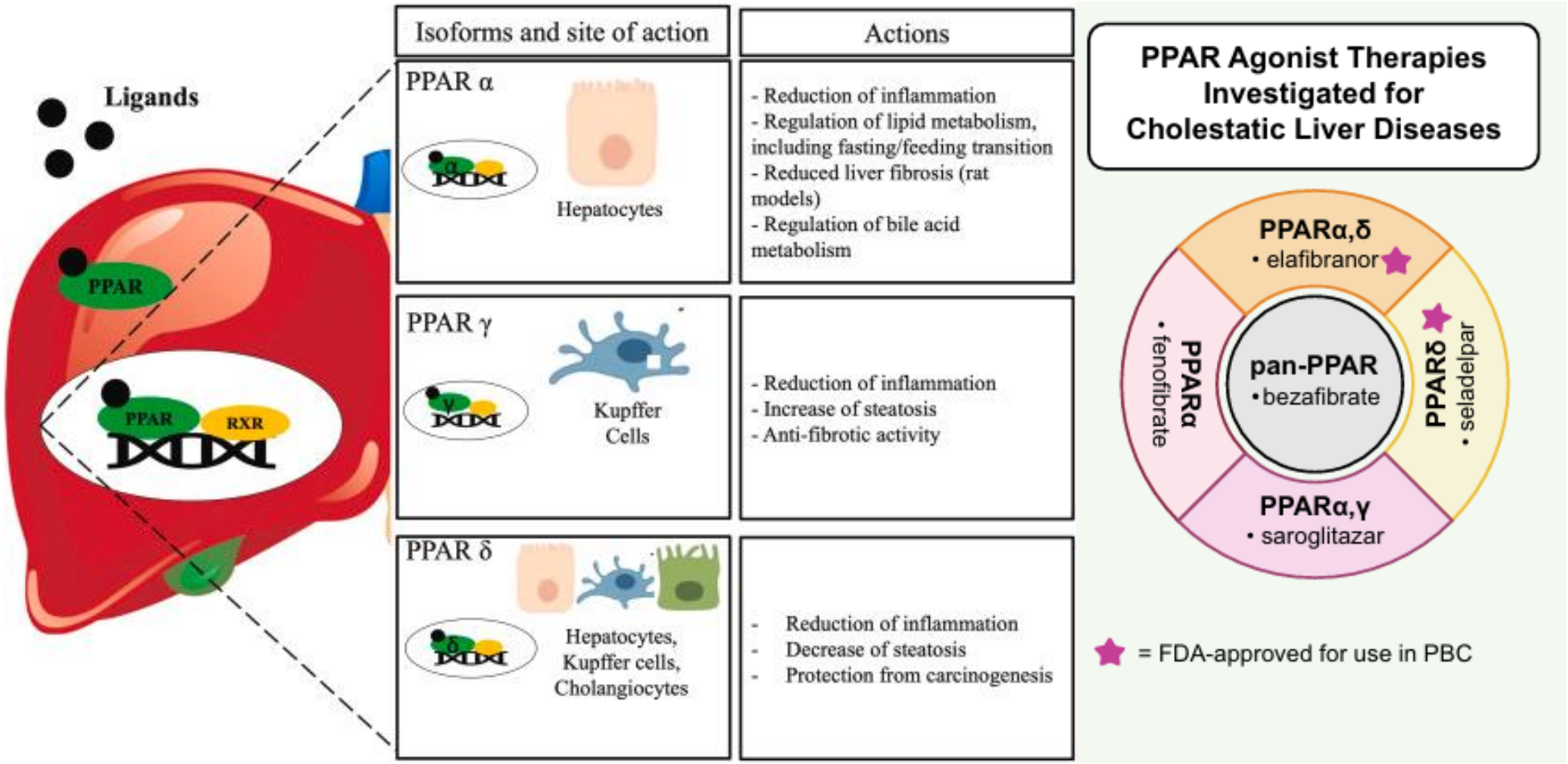
Treatment: off label Bezafibrates

- Bezafibrates- Pan PPAR agonists
- Used off label as Second line treatment together with UDCA
- Phase 3 study- demonstrated effectiveness
- Safety concerns:
  - Increase ALT, AST
  - Increase CK, rhabdomyolysis, myopathy
- Effective treatment for pruritus:
  - FITCH trial



Corpechot C. et al. N Engl J Med 2018;378:2171-81

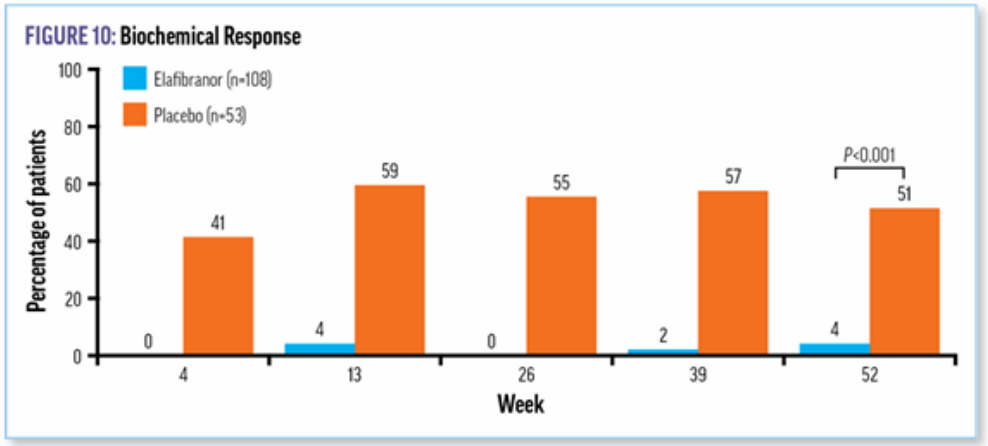
New treatment Paradigm: PPAR agonism

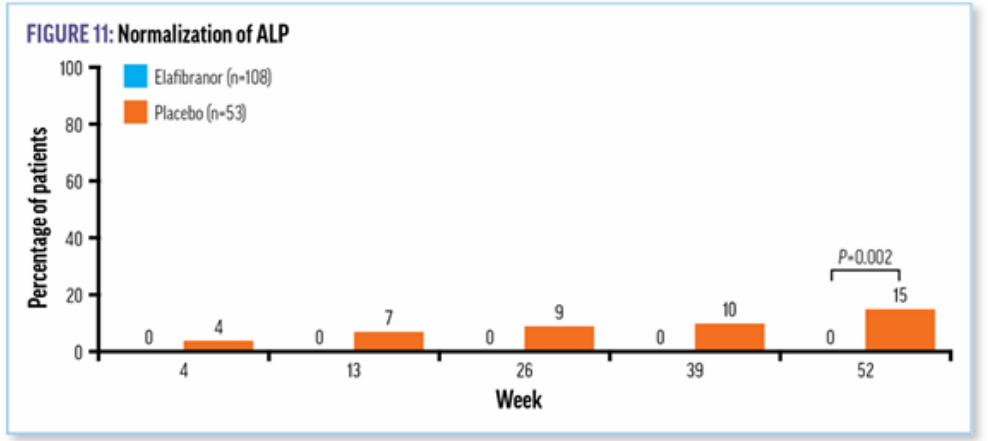


Colapietro F et al. Journal of Translational Autoimmunity 6 (2023) 100188
Heyes CM et al. Hepatology Communications 2025;9:e0612

Treatment: Elafibranor

- Elafibranor- Dual PPARα/δ agonist
- ELATIVE trial
  - N-161 2:1 Elafibranor 80mg or Placebo
  - 95% receiving UDCA
  - Biochemical response: 51% vs 4% in placebo at Week 52
  - Pruritis improvement not met
  - Increased CK, when combined with statin
- Avoid in decompensated cirrhosis, pregnancy and breastfeeding
- Drug interactions:
  - Oestrogen/progesterone
  - Rifampicin/statins

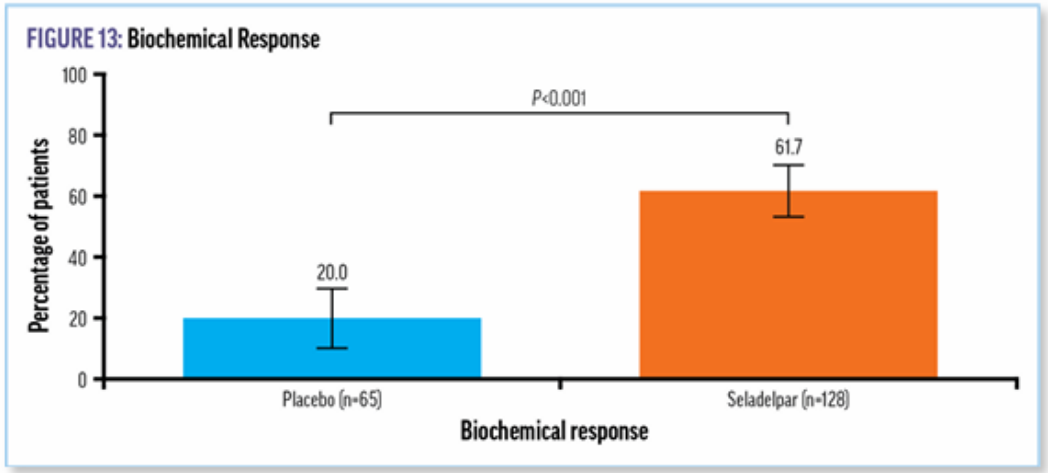


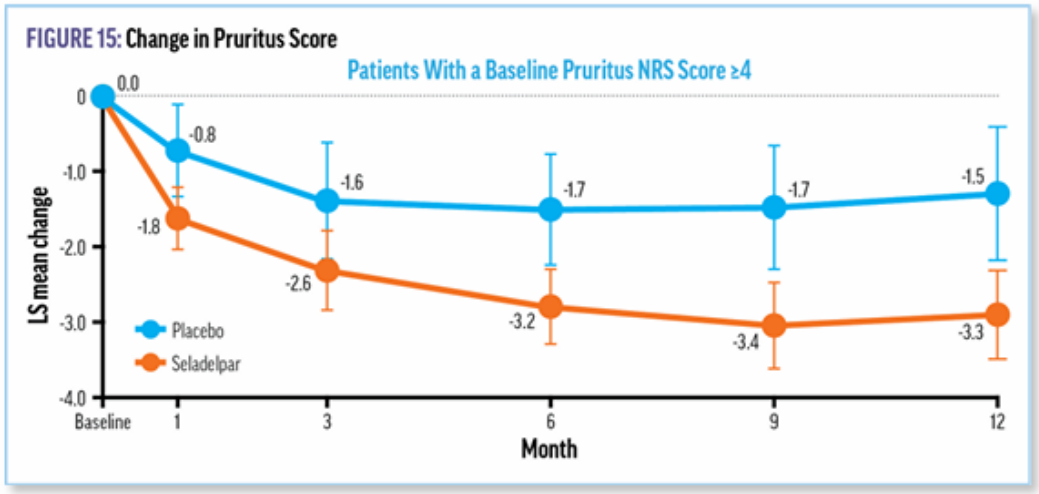


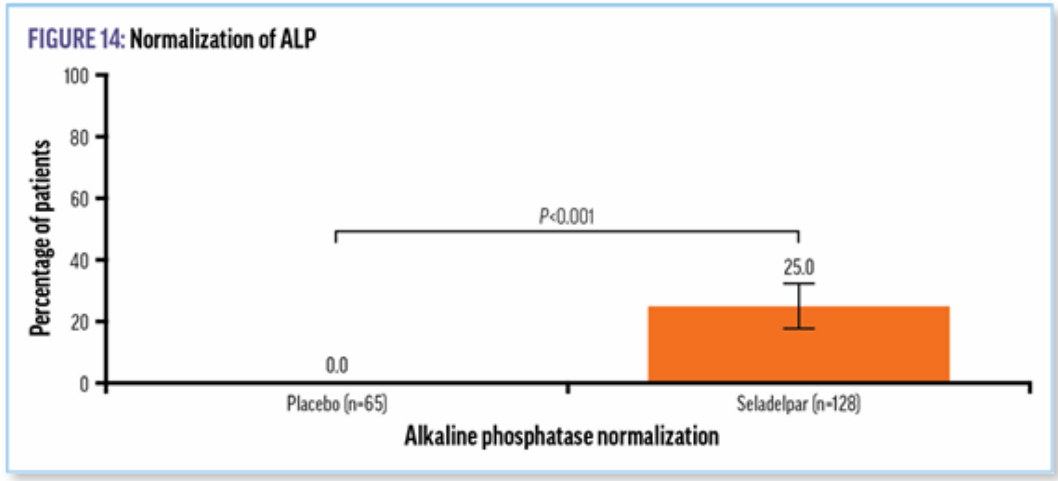
Kris V. Kowdley et al. N Engl J Med 2024;390:795-805

Treatment: Seladelpar

- Seladelpar: a PPARδ agonist
- RESPONSE trial
  - N193 2:1 Seladelpar 10 mg or placebo
  - 93.8% receiving UDCA
  - Biochemical response 61.7% vs 20% in placebo at week 52





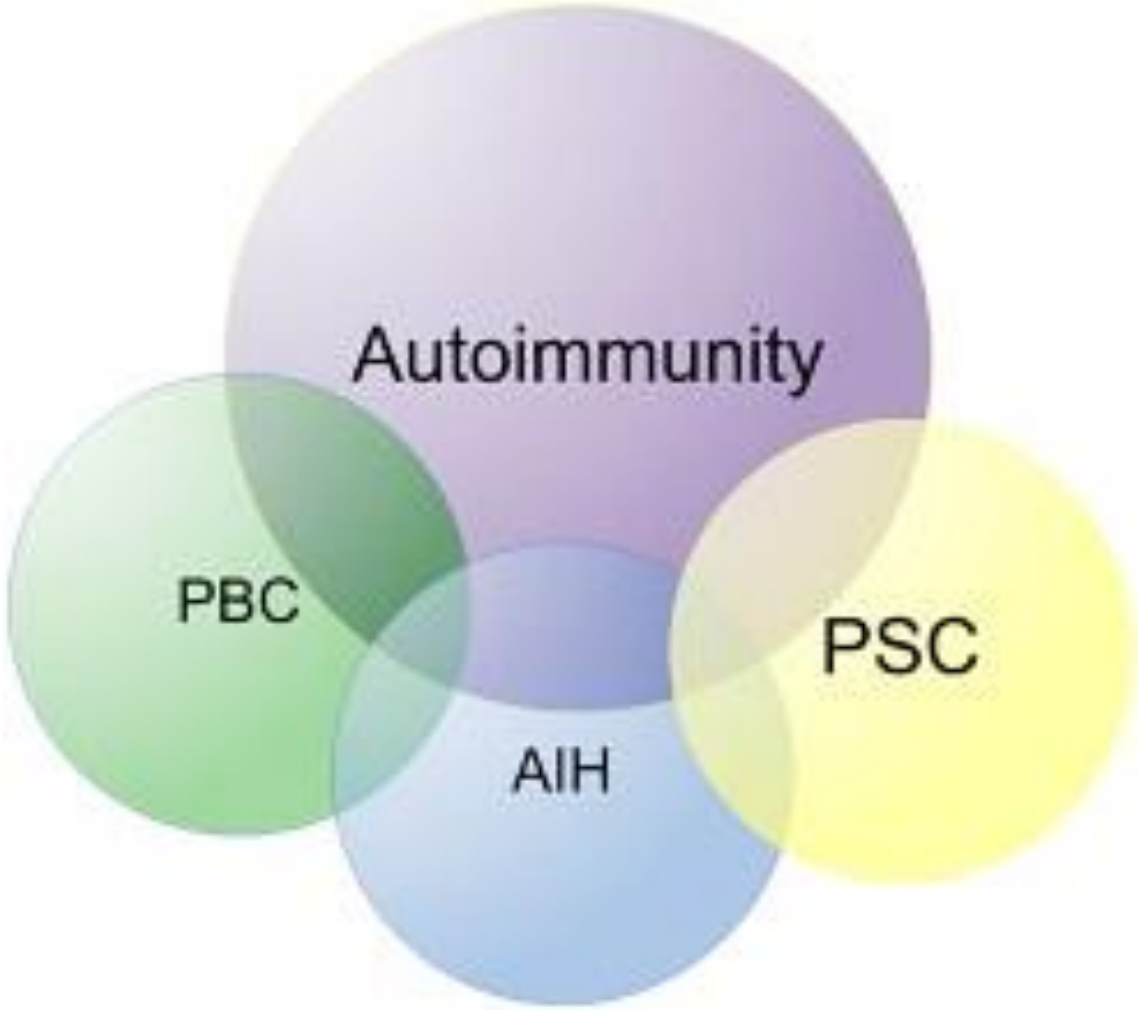


Hirschfield G et al. N Engl J Med 2024;390:783-794

Overlap syndromes

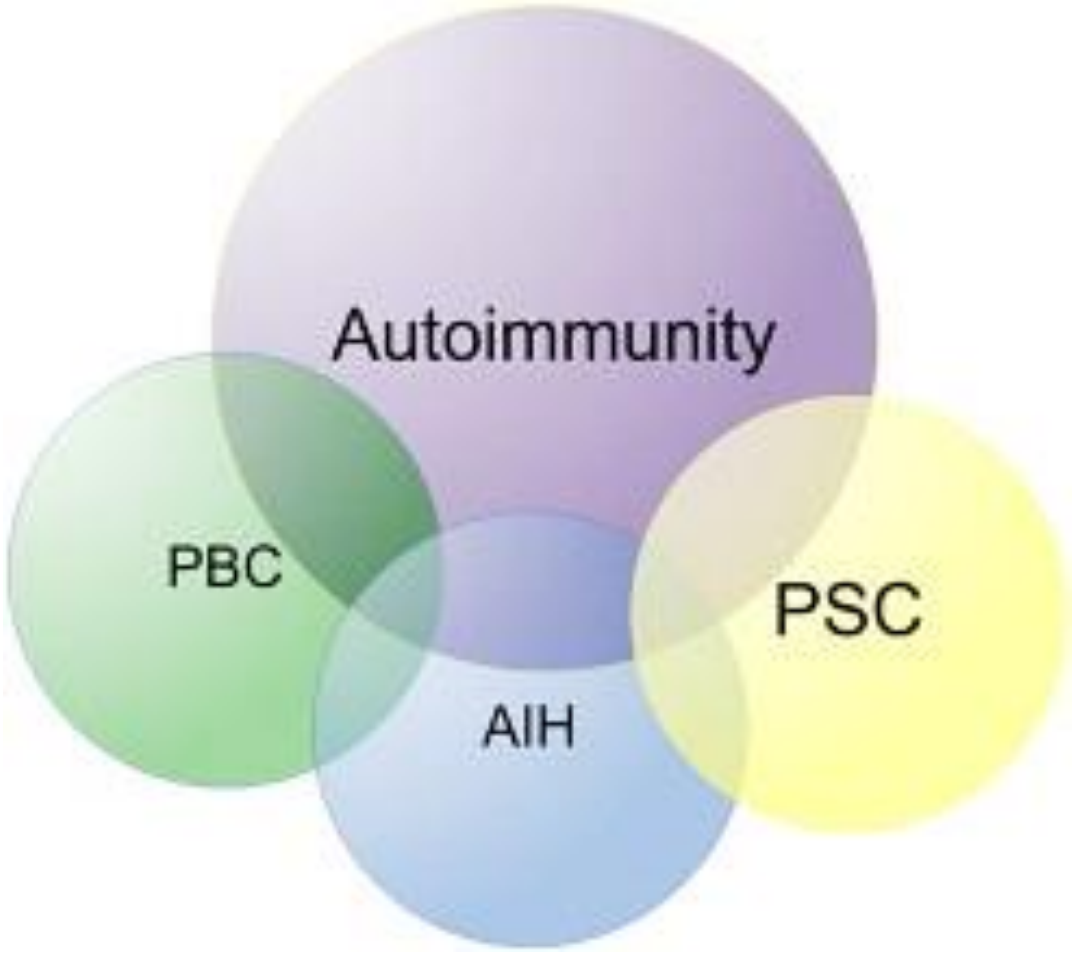
PBC-AIH Overlap

- Prevalence of AIH features is around in 8–10% in PBC patients
- Liver histology is mandatory to confirm diagnosis
- The Paris criteria biochemical and histological features of both disorders (92% sensitivity and 97% specificity)
- Increased risk of early development to fibrosis/cirrhosis, therefore should be promptly treated



D D'Amato and M. Carbone et al.Best Practice & Research Clinical Gastroenterology 67 (2023) 101878

Overlap syndromes



AIH-PSC Overlap

- The prevalence of this condition is around 25%
- Most commonly seen in children
- Phenotype can evolve over time
- No validated diagnostic criteria- characteristic features of both
- Transplant-free survival is similar to classical PSC but lower AIH

D D'Amato and M. Carbone et al.Best Practice & Research Clinical Gastroenterology 67 (2023) 101878

Conclusion

- Autoimmune liver diseases are complex diseases with obscure aetiology
- Phenotypes and risk of progression are very heterogeneous
- Natural history progress to liver cirrhosis and liver-related death
- Lack of curative treatments- “control without curing”
- Continued collaborative research is needed to refine treatment strategies and improve patient quality of life