Clinical Practice Guidelines

Primary biliary cholangitis

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About these slides

- These slides give a comprehensive overview of the EASL clinical practice guidelines on the management of primary biliary cholangitis

- The guidelines were published in full in the July 2017 issue of the Journal of Hepatology
  - The full publication can be downloaded from the Clinical Practice Guidelines section of the EASL website
  - Please cite the published article as: EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol 2017;67:145–72

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About these slides

- Definitions of all abbreviations shown in these slides are provided within the slide notes

- When you see a home symbol like this one:  , you can click on this to return to the outline or topics pages, depending on which section you are in

These slides are intended for use as an educational resource and should not be used in isolation to make patient management decisions. All information included should be verified before treating patients or using any therapies described in these materials

- Please send any feedback to: slidedeck_feedback@easloffice.eu

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Guideline panel

- **Chair**
  - Gideon M Hirschfield
- **Panel members**
  - Ulrich Beuers, Christophe Corpechot, Pietro Invernizzi, David Jones, Marco Marzioni, Christoph Schramm
- **Reviewers**
  - Kirsten M Boberg, Annarosa Floreani, Raoul Poupon

Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis☆

European Association for the Study of the Liver*

Summary

Primary biliary cholangitis (PBC) is a chronic inflammatory autoimmune cholestatic liver disease, which when untreated will culminate in end-stage biliary cirrhosis. Diagnosis is usually based on the presence of serum liver tests indicative of a cholestatic hepatitis in association with circulating antimitochondrial antibodies. Patient presentation and course can be diverse and risk stratification is important to ensure all patients receive a personalised approach to their care. The goals of treatment and management are the prevention of end-stage liver disease, and the amelioration of associated symptoms. Pharmacologic approaches in practice, to reduce the impact of the progressive nature of disease, currently include licensed therapies (ursodeoxycholic acid and obeticholic acid) and off-label therapies (fibric acid derivatives, budesonide). These clinical practice guidelines summarise the evidence for the importance of a structured, life-long and individualised, approach to the care of patients with PBC, providing a framework to help clinicians diagnose and effectively manage patients.

Introduction

Primary biliary cholangitis (PBC; formerly known as primary biliary cirrhosis [1]) is an important but uncommon disease that predominantly affects women. It is a globally recognised autoimmune cholestatic liver disease [2–5] with several characteristics, including: cholestasis, serologic reactivity to antimitochondrial antibodies (AMA) or specific antinuclear antibody (ANA) reactivity, with accompanying histologic evidence of chronic non-suppurative, granulomatous, lymphocytic small bile duct cholangitis. The disease is chronic and often progressive, resulting in end-stage liver disease and its associated complications [6–8]. The youngest reported age of confirmed disease onset is 15 in a post-menarche young adult; true paediatric disease is not classically encountered [9,10]. The goal of life-long therapy is to prevent progressive liver disease, and ameliorate disease-associated symptoms that reduce patient quality of life (QoL).

The factors leading up to disease initiation are not well understood. Environmental influences are likely to play a significant role in driving PBC, interacting with immunogenetic and epigenetic risk, favouring chronic immune mediated biliary epithelial injury with subsequent cholestasis, ductopenia, and progressive biliary fibrosis [11–13]. Data from multiple studies indicate that globally, an estimated 1 in 1,000 women over the age of 40 live with PBC [14]. Epidemiologic studies are continuing to improve our understanding of the international burden of PBC, and in European populations, the estimated incidence is between 1–2 per 100,000 population per year; commonly cited ranges for incidence and prevalence per 100,000 are 0.3–5.8 and 1.9–40.2, respectively [15–17]. The disease is female predominant (as confirmed by large registry efforts), although some recent data suggest an increasing male prevalence [18]; the female predominance of PBC continues to be unexplained [19].

Understanding the biology of PBC is important for providing effective care for patients, enabling therapeutic options to increase and to become more targeted [4,20–22]. PBC pathogenesis occurs through the interaction of immune and biliary pathways, progressing to injury – driving an inter-dependent and chronic cycle of cholestasis and liver fibrosis (Fig. 1). Animal models can recreate a variety of relevant immunologic features of the disease and highlight the importance of interferon (IFN) signalling. Inflammatory responses, mediated by type 1 T helper cells, play a critical role in the loss of immunological tolerance to biliary epithelial cells (as shown in part by the association between disease and AMA). This parallels the understanding of the genetic risks for PBC that span key immune-regulatory pathways, including interleukin (IL)-12 and Janus kinase/signal transducer and activator of transcription (JAK-STAT) signalling, as well as the human leukocyte antigen (HLA) locus [23,24]. Immune injury and cholestasis interact; the Cl^-/HCO_3^- exchanger (AE2; anion exchanger 2) and an intact biliary glycocalyx are important in maintaining a protective biliary 'umbrella' against invasion of hydrophobic bile acid monomers. In patients with PBC, downregulation of AE2 can sensitize cholangiocytes to apoptotic insults by activating adenylyl cyclase. In addition, hydrophobic bile acids (glycochenodeoxycholic acid) suppress AE2 expression in biliary epithelial cells by inducing reactive oxygen species and biliary epithelial cell senescence, leading to bile duct inflammation

Keywords: Cholestasis; Guidelines; Care pathway; Liver.
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Outline

Methods	• Grading evidence and recommendations
Background	• Epidemiology of PBC • PBC pathogenesis • Impact of PBC
Guidelines	• Key recommendations

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Methods

Grading evidence and recommendations

Grading evidence and recommendations

- Grading is adapted from the GRADE system[1]

Grade of evidence	
I	Randomized, controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytical studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology
Grade of recommendation	
1	Strong recommendation: Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
2	Weaker recommendation: Variability in preferences and values, or more uncertainty; more likely a weak recommendation is warranted Recommendation is made with less certainty: higher cost or resource consumption

1. Shaneyfelt TM, et al. JAMA 1999;281:1900–5;
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Background

Epidemiology of PBC

PBC pathogenesis

Epidemiology of PBC

- Remains a female predominant disease
  - Mainly >40 years
  - Does not present in childhood

- **Global:** Estimated 1 in 1,000 women over the age of 40 years old living with PBC

- **Europe:** Estimated incidence 1–2 per 100,000 population per year
  - Incidence range: 0.3–5.8 per 100,000
  - Prevalence range: 1.9–40.2 per 100,000

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Pathogenesis of PBC

- Effective biliary secretion is essential for adequate hepatic detoxification and is integral to digestive function

- **PBC** reflects the consequences of immune and cellular injury to biliary epithelial cells, resulting in cholestasis and progressive liver fibrosis

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Impact of PBC

- Patients can progress to **end-stage liver disease**
  - Average survival (historical) among those untreated is 9–10 years
- **Symptoms** associated with PBC **impact on QoL**, and include:
  - Pruritus
  - Sicca complex
  - Abdominal discomfort
  - Jaundice
  - Fatigue
  - Restless legs
  - Insomnia
  - Depression
  - Cognitive dysfunction

Life-long care that is **structured** and **individualized** is required

Goal is to **prevent end-stage complications** of liver disease and **manage associated symptoms*** that reduce QoL

*Statement 11 (Grade of evidence III, Grade of recommendation 1)
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Guidelines

Key recommendations

Topics

Click on a topic to skip to that section

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Diagnostic approach to cholestasis

- A systematic approach to diagnosis of PBC is recommended

Recommendations*	Grade of evidence	Grade of recommendation
Take detailed **history** and **physical examination** when evaluating patients with biochemical tests that suggest cholestatic liver disease	III	1
Ultrasound should be the first-line non-invasive imaging procedure to differentiate intra- from extrahepatic cholestasis	III	1
Perform serological screening for **AMA** and **PBC-specific ANA** by immunofluorescence in all patients with unexplained cholestasis	III	1
Image using **MRCP** in patients with unexplained cholestasis. **EUS** can be an alternative to MRCP to evaluate distal biliary disease	III	1
Consider **liver biopsy** after serological screening and extended imaging in patients with ongoing unexplained intrahepatic cholestasis	III	1
Consider **genetic tests** for inherited cholestatic syndromes in patients where clinically appropriate	III	1

*Statements 1–6

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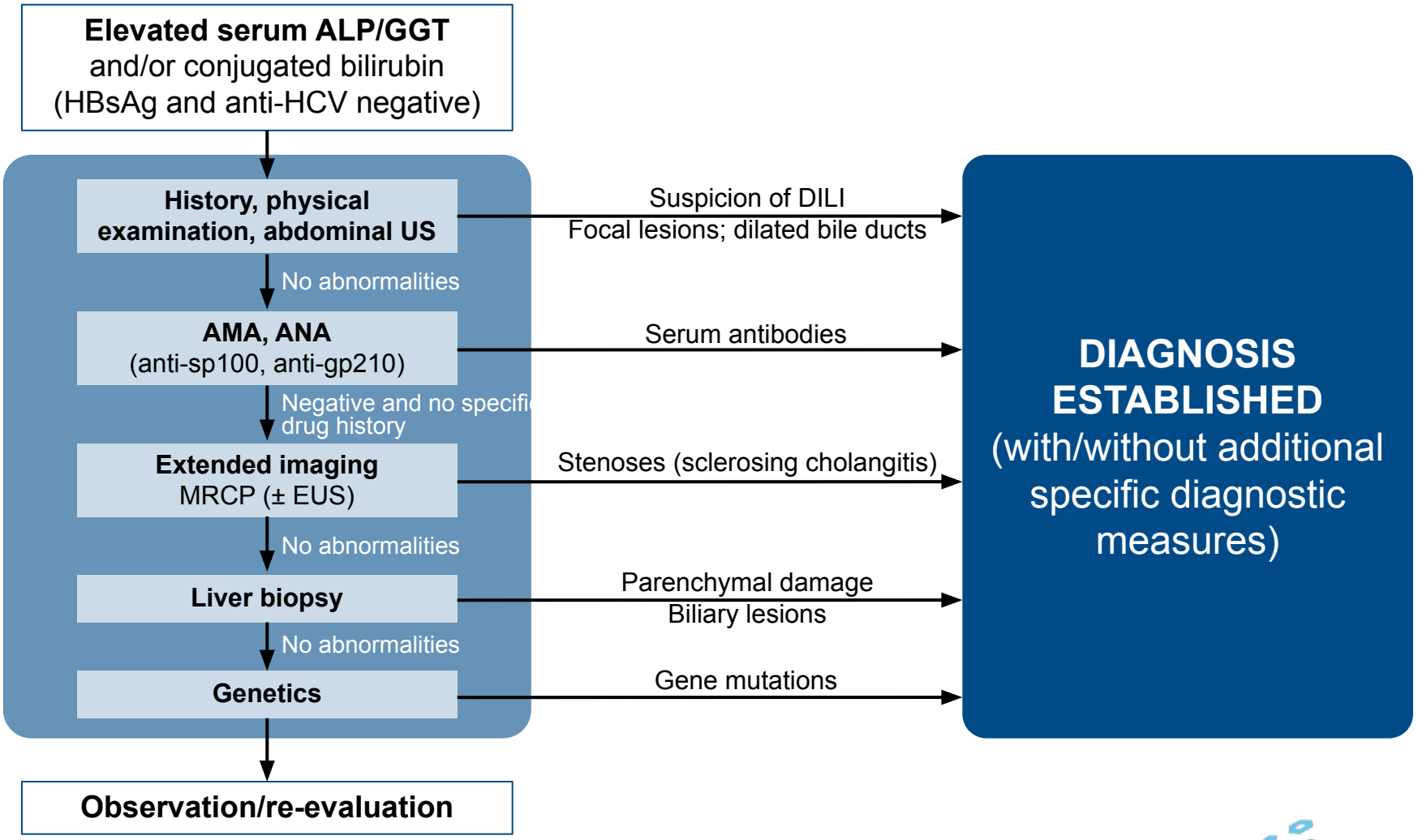
Structured algorithm to diagnose chronic* cholestasis



*Lasting for >6 months

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Initial diagnosis of PBC

- PBC should be suspected in patients with persistent cholestatic serum liver tests or symptoms
  - Including pruritus and fatigue

Recommendations*	Grade of evidence	Grade of recommendation
In adults with cholestasis and no likelihood of systemic disease, an **elevated ALP** plus **AMA at a titre >1:40** is diagnostic	III	1
In the correct context, a diagnosis of AMA-negative PBC can be made in patients with cholestasis and **specific ANA immunofluorescence** (nuclear dots or perinuclear rims) or ELISA results (sp100, gp210)	III	1
Liver biopsy not required for diagnosis of PBC, unless PBC-specific antibodies absent, coexistent AIH or NASH suspected, or other (usually systemic) comorbidities are present	III	1
AMA reactivity alone is not sufficient to diagnose PBC. Follow up patients with normal serum liver tests who are AMA positive with annual biochemical reassessment for the presence of liver disease	III	1

*Statements 7–10

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Overview of utility of investigations in PBC

- Elevated ALP is typical of PBC

Test	Finding	Suspicion	Diagnosis	Prognosis
ALP	☐	✔	✔	✔
AST/ALT	☐	✔		✔
GGT	☐	✔		
IgM	☐	✔		
AMA (>1/40)	+		✔	
Specific ANA	+		✔	
Anti-gp210	+		✔	✔
Anti-sp100	+		✔	
Anti-centromere	+			✔
Bilirubin	☐			✔
Platelets	☐			✔
INR	☐			✔
Albumin	☐			✔

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Overview of utility of investigations in PBC

- Elevated ALP is typical of PBC

Test	Finding	Notes
ALP	□	Values associated with disease progression
AST/ALT	□	□□ May be suggestive of PBC with features of AIH
GGT	□	Reflects cholestatic liver injury
IgM	□	Elevated values associated with disease
AMA (>1/40)	+	Diagnostic in >90% of cases in correct clinical context
Specific ANA	+	Specific immunofluorescence patterns* present in 30%
Anti-gp210	+	Specific immunoassays available
Anti-sp100	+	Specific immunoassays available
Anti-centromere	+	Associated with portal hypertensive phenotype
Bilirubin	□	Elevation at late stages frequently indicative of cirrhosis†
Platelets	□	Indicative of cirrhosis
INR	□	Indicative of cirrhosis
Albumin	□	Indicative of cirrhosis

*Perinuclear rims, nuclear dot, centromere;
† Except in patients with ductopenic non-cirrhotic variant
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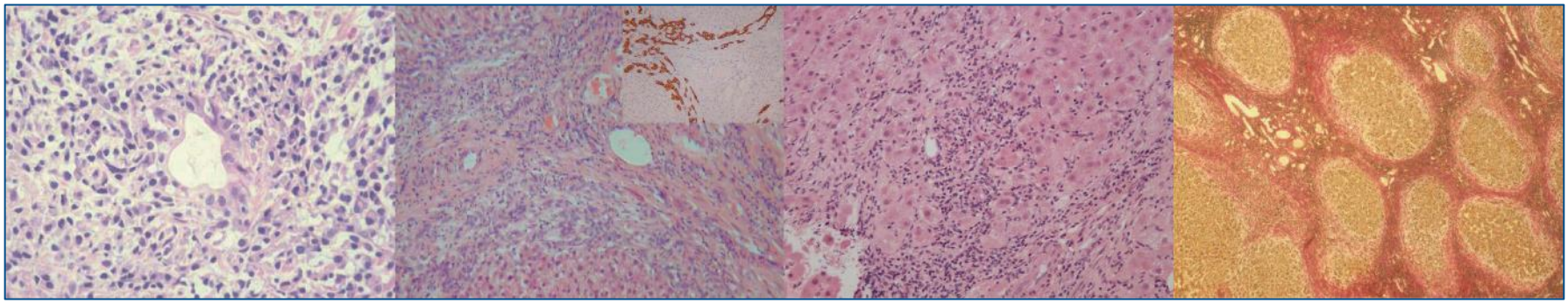
Histopathological features of PBC

- Liver biopsy is not generally required to diagnose PBC
  - Essential when:
    - PBC-specific antibodies are absent
    - Co-existent AIH or NASH is suspected
    - With other systemic/extrahepatic co-morbidities



Lymphocytic cholangitis	Bile duct loss and ductular reaction	Interface hepatitis	Cirrhosis

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Histopathological features of PBC

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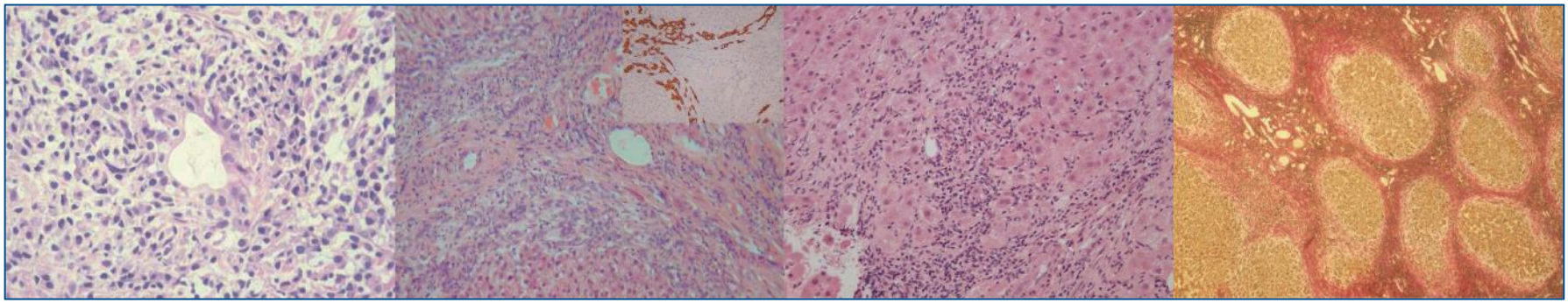

Bile duct loss and ductular reaction | Interface hepatitis | Cirrhosis

Florid duct lesion showing a dense periductal inflammatory infiltrate associated with disruption of bile duct epithelium*

*Haematoxylin and eosin stain

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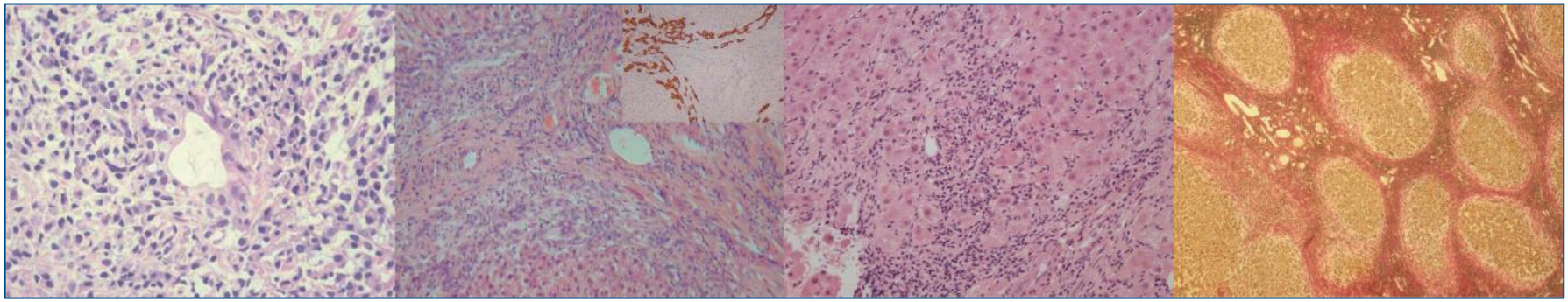

Lymphocytic cholangitis | Interface hepatitis | Cirrhosis

Expanded portal tract contains arterial branches without accompanying bile ducts
Marginal ductular reaction associated with loose fibrosis (biliary interface activity)*
Absence of properly formed bile ducts/presence of prominent marginal ductular reaction†

*Haematoxylin and eosin stain; †Immunostaining for keratin 7 with immunoperoxidase

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Histopathological features of PBC

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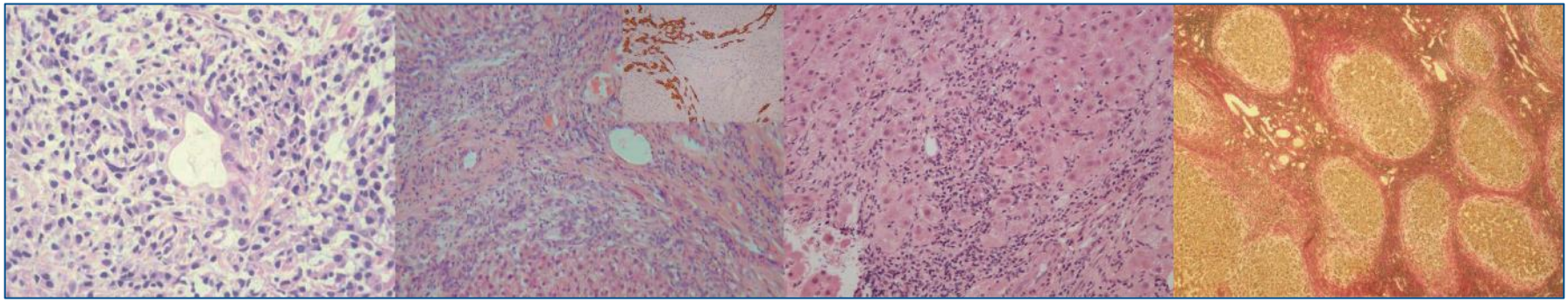

Lymphocytic cholangitis	Bile duct loss and ductular reaction	Cirrhosis

In the presence of prominent interface hepatitis associated with ballooning, rosetting and entrapment of periportal hepatocytes, additional autoimmune hepatitis should be considered. Focal lymphocyte emperipolesis is also present*

*Haematoxylin and eosin stain

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Histopathological features of PBC

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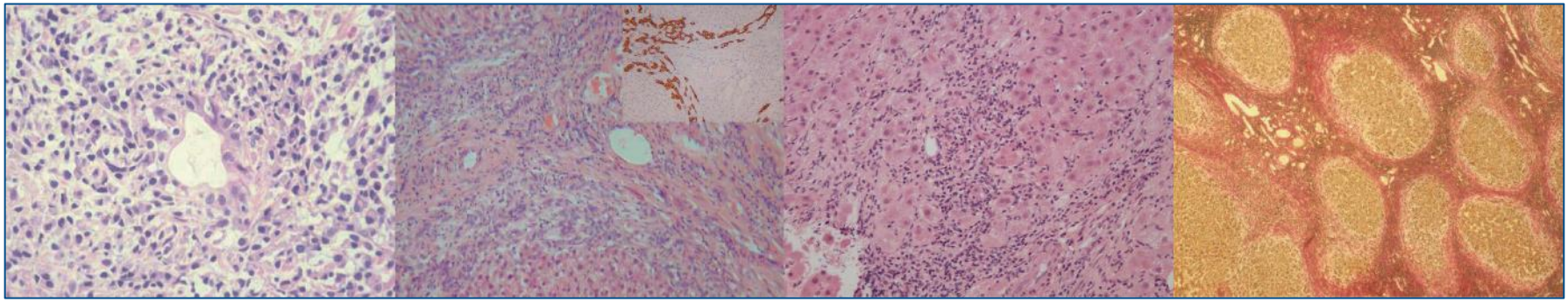

Lymphocytic cholangitis	Bile duct loss and ductular reaction	Interface hepatitis

Established cirrhosis with broad fibrous septa surrounding small hepatocyte nodules
Septa have narrow peripheral ‘halo zones’ of loose fibrosis characteristic of chronic biliary disease*

*Haematoxylin Van Gieson

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Stratification of risk in PBC

- Even when treated, PBC can remain a progressive disease
  - Risk of liver-related complications
  - Risk of death
- All patients should be evaluated for their **risk of developing progressive PBC***
  - Consequently, their potential need for additional treatments

High- and low-risk disease defined by:

- Evaluation of response to first-line agent UDCA

Greatest **risk of disease complications** identified by:

- **Age** at onset
- **Sex** (male)
- **Stage** at presentation
- Selected **biochemical/ serological indices** pre- and post-therapy with UDCA

*Statement 12 (Grade of evidence III, Grade of recommendation 1)
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Stratification of risk in PBC

Recommendations*	Grade of evidence	Grade of recommendation
Recognize that patients at greatest risk of complications from PBC have **inadequate biochemical response to therapy**, and **cirrhosis**	II-2	1
Actively recognize that the strongest risk factors for inadequate biochemical response to therapy are **early age at diagnosis** (e.g. <45), and **advanced stage at presentation**	III	1
Evaluate all patients for **stage of disease** using a combination of non-invasive tests (bilirubin, alkaline phosphatase, AST, albumin, platelet count and elastography) at baseline, and during follow-up	III	1
Elevated serum bilirubin and ALP can be used as **surrogate markers of outcome** for patients with PBC • Routine biochemistry and haematology indices should underpin clinical approaches to stratify individual risk of disease progression	II-2	1
Recognize that **transplant-free survival** for early-stage patients with ALP <1.5x ULN and a normal bilirubin after 1 year of therapy with UDCA, is not significantly different to a control healthy population	II-2	1
Use **elastography** and **risk scores** (eg, GLOBE and UK-PBC score) for patients with PBC, to help better define individual risk of developing **complications** of advanced liver disease in the future	III	1

*Statements 13–18

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Three pillars of PBC management

Primary biliary cholangitis
Prevent end-stage liver disease and manage associated symptoms

1. Stratify risk and treat

UDCA
For all (13–15 mg/kg/day)

Assess biochemical response at 1 year
goal: identification of low- and high-risk patients

- UDCA responder (low-risk disease) → **Individualized follow-up**
  According to symptom burden and disease stage
- Inadequate UDCA responder → ? Features of AIH → **Add 2nd-line therapy**
  Obeticholic acid
  Off-label*
  Clinical trials

Monitoring based on
Bilirubin, ALP, AST, albumin, platelet count, and elastography

2. Stage and survey

Disease staging
Serum liver tests, US, elastography

Cirrhosis

- □ bilirubin and/or decompensated disease → **Refer to expert centre/transplant centre**
- **HCC + varices screening**

3. Manage actively

Symptom evaluation/ active management

- Pruritus
- Fatigue
- Sicca complex
- Bone density
- Co-existent autoimmune disease

Actively manage as per guidelines
Offer information about patient support groups

Intractable symptoms

Refer to expert centre

Clinical audit standards
Reference network consultation

*E.g. Fibrates, budesonide

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Defining inadequate response to treatment

- Treatment failure must be defined on validated surrogate endpoints
  - To account for the slow progression of disease
- Qualitative biochemical response to UDCA assessed using binary definitions or continuous scoring

Binary definitions	Time (months)	Treatment failure
Rochester[1]	6	ALP ≥2 ULN or Mayo score ≥4.5
Barcelona[2]	12	Decrease in ALP ≤40% and ALP ≥1x ULN
Paris-I[3]	12	ALP ≥3x ULN or AST ≥2x ULN or bilirubin >1 mg/dl
Rotterdam[4]	12	Bilirubin ≥1x ULN and/or albumin <1x ULN
Toronto[5]	24	ALP >1.67x ULN
Paris-II[6]	12	ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin >1 mg/dl
Ehime[7]	6	Decrease in GGT ≤70% and GGT ≥1 ULN
Continuous scoring	**Time (months)**	**Scoring parameters**
UK-PBC[8]	12	**12 months:** bilirubin, ALP and AST (or ALT); **Baseline:** albumin and platelets
GLOBE[9]	12	**12 months:** bilirubin, ALP, albumin, and platelet count; **Baseline:** age

See notes for full reference list
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Prognostic tools for PBC in practice: guidance

- Prognostic tools allow:
  - Selection of patients for second-line therapies
  - Risk stratification in clinical trials to account for prognostic disparity

Rational approaches to risk stratification in PBC	
Level of applicability	**Prognostic tools**
High (High applicability, robust validation)	• On-treatment ALP and bilirubin-based assessment of response to UDCA • Baseline disease stage* as defined by elastography, serum levels of bilirubin and albumin, or histology
Moderate (High applicability, further validation pending)	• LSM by elastography • APRI • ELF test
Indeterminate (Limited applicability and/or validation)	• Age, gender and symptom profile • PBC-specific ANA • Degree of interface hepatitis and ductopenia • Novel histological scoring systems • Direct measurement of portal pressure

*Early vs. advanced (histology on biopsy, absent or mild vs. bridging fibrosis or cirrhosis; Elastography, LSM ≤9.6 kPa vs. >9.6 kPa; Serum bilirubin and albumin, both normal vs. ≥1 elevated)

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Treatment: therapies to slow disease progression

- **Ursodeoxycholic acid** (UDCA) and **obeticholic acid** (OCA) approved in PBC
- **Heterogeneity of treatment efficacy** in clinical trials may be due to:
  - Variable inclusion criteria without reference to disease risk or stage

Recommendations*	Grade of evidence	Grade of recommendation
Oral UDCA: 13–15 mg/kg/day as the first-line pharmacotherapy for all patients with PBC. UDCA is usually continued for life	I	1
Oral OCA: Biochemical efficacy in patients with ALP >1.67x ULN and/or bilirubin elevated <2x ULN demonstrated in a Phase 3 study • Conditionally approved for patients with PBC in **combination with UDCA** for those with an inadequate response to UDCA, or as monotherapy in those intolerant to UDCA • Consider use in such patients (initial dose 5 mg; dose titration to 10 mg according to tolerability at 6 months)	I	2
Data from Phase 3 randomized trials for **budesonide** (in non-cirrhotic patients), and **bezafibrate**, both in **combination with UDCA**, not yet published; currently, a recommendation for therapy cannot be made	II-2	2

*Statements 19–21

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Special settings: pregnancy

- A minority of women diagnosed with PBC are of reproductive age
- UDCA is safe during conception, pregnancy and post-partum according to expert clinical opinion

Recommendations*	Grade of evidence	Grade of recommendation
Expert consultation is required for all pregnant patients to guide therapy. **Pregnancy is typically well tolerated in non-cirrhotic patients with PBC** • Continue **UDCA** in pregnancy, even though data are limited • Pruritus management is important and may require specialist advice; **rifampicin** has been used by experts during third trimester	III	1
Pregnancy in patients with **cirrhosis carries a higher risk of maternal and foetal complications** • Offer pre-conception counselling and relevant specialist monitoring	III	1

*Statements 22, 23

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PBC with features of autoimmune hepatitis

- ~8–10% of patients with PBC have features characteristic of AIH
  - ‘AIH−PBC overlap syndrome’, ‘hepatitic form of PBC’, or ‘PBC with secondary AIH’
- With non-response to UDCA after 6−12 months additional AIH features should be investigated
  - Paris criteria used most commonly†

Recommendations*	Grade of evidence	Grade of recommendation
Liver biopsy is mandatory in confirming the features of AIH, and should be considered in patients with disproportionate elevations in ALT and/or IgG	III	1
Patients with PBC and typical features of AIH may benefit from **immunosuppressive treatment** in addition to **UDCA** • Use immunosuppressive treatment in patients with **severe interface hepatitis**, and consider in patients with moderate interface hepatitis • Counsel patients about immunosuppressive treatment side effects	III	2

*Statements 24, 25;
†According to these criteria, a diagnosis can be made in a patient with PBC with at least two of the following: 1. ALP >2x ULN or GGT >5x ULN. 2. AMA >1:40. 3. Florid bile duct lesion on histology **AND** two of the following three features:1. ALT >5x ULN. 2. IgG serum levels >2x ULN or smooth muscle autoantibody positive. 3. Moderate or severe interface hepatitis on histology
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Management of symptoms

- Symptoms associated with PBC have a significant impact on QoL

Recommendations*	Grade of evidence	Grade of recommendation
Screening: Evaluate all patients for presence of symptoms, particularly pruritus, sicca complex and fatigue. Severity of symptoms not necessarily correlated with stage of disease in PBC	III	1
Pruritus		
• Treat using a step-wise approach. Severe pruritus may indicate an aggressively ductopenic variant of PBC. These patients have a poor prognosis and should be referred to an expert centre	III	1
• First-line: cholestyramine as first-line therapy. Avoid interaction with other medications	II-2	1
• Second-line: rifampicin†	II-2	1
Fatigue		
• Seek and treat associated and alternate causes of fatigue	III	1
• Advise patients with fatigue on developing coping strategies	III	2
Sicca complex: where appropriate consider expert referral	III	1
Miscellaneous: Refer patients with symptoms resistant to medical therapy for specialist management, regardless of disease severity	III	1

*Statements 26–33;
†150–300 mg daily. Monitor serum liver tests after initial use (after 6 and 12 weeks) and after dose increase. Stop if hepatotoxicity observed
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Management of complications of liver disease

- **Osteoporosis** is a common complication in PBC

Recommendations*	Grade of evidence	Grade of recommendation
Consider the **risk of osteoporosis** in all patients with PBC	III	1
To assess risk, consider use of **DEXA** to assess **bone mineral density** at presentation and at follow-up where Indicated	III	1
Supplement patients with PBC with **calcium** and **vitamin D**, according to local practice	III	2
Bisphosphonates are safe and effective treatments for patients with PBC and significantly elevated fracture risk from osteoporosis. Use with caution in patients with varices. Initiate therapy according to specific osteoporosis guidelines	II-2	1

*Statements 34–37

EASL CPG PBC. J Hepatol 2017;67:145–72

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Management of complications of liver disease

- Fat soluble vitamin malabsorption can occur in PBC

Recommendations*	Grade of evidence	Grade of recommendation
Fat-soluble vitamin malabsorption: Can occur in PBC, particularly with prolonged jaundice. Supplementation should be considered on an individual basis	III	2

- Serum lipids can be elevated in up to 80% of patients with PBC
  - Underlying mechanism is different to that of other conditions
  - No substantial evidence to support an elevated CV risk

Recommendations†	Grade of evidence	Grade of recommendation
Hyperlipidaemia: In patients with PBC and metabolic syndrome (high cholesterol, low HDL-C cholesterol, high LDL-C, consider cholesterol-lowering agents on a case-by-case basis; treatment is not contraindicated	III	2

*Statement 38; †Statement 39
EASL CPG PBC. J Hepatol 2017;67:145–72

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Management of complications of liver disease

- Patients with PBC may develop portal hypertension as a result of biliary cirrhosis
  - Associated with a poor prognosis

Recommendations*	Grade of evidence	Grade of recommendation
Varices: Baveno-VI guidelines for screening and management of varices apply equally to patients with PBC	III	2

- HCC is one of the most serious complications of PBC
  - Incidence of HCC in those with diagnosed PBC is 0.36 per 100 person years

Recommendations†	Grade of evidence	Grade of recommendation
Hepatocellular carcinoma: In patients with suspected cirrhosis, HCC surveillance according to EASL guidelines is indicated	III	2

*Statement 40; †Statement 41

EASL CPG PBC. J Hepatol 2017;67:145–72

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Management of complications of liver disease

- PBC as an indication for liver transplant is declining
  - Despite increasing prevalence of PBC
- Outcome post-liver transplant is usually favourable and better for most other liver transplant indications
  - 5-year survival of 80−85%

Recommendations*	Grade of evidence	Grade of recommendation
Liver transplantation		
• Consider patients for transplant assessment when presenting with complications of cirrhosis, markers of disease severity (e.g. persistent elevated bilirubin values [50 µmol/l or 3 mg/dl] or MELD >15), or severe medically resistant pruritus. Follow local (usually national) guidelines	II-2	1
• In patients with proven or likely recurrent PBC post-liver transplant, use of UDCA is safe and can improve liver biochemistry	II-2	2

*Statements 42, 43

EASL CPG PBC. J Hepatol 2017;67:145–72

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Organisation of clinical care delivery

- Advent of stratified therapy has increased the complexity of managing patients with PBC
- Optimal care models must be flexible
  - Effectively manage high-risk patients/those with a high symptom burden
  - Avoid over-management of low-risk asymptomatic patients

Recommendations*	Grade of evidence	Grade of recommendation
Care pathways:		
• All patients with PBC should have **structured life-long follow-up**	III	1
• Develop care pathway for PBC based on these guidelines	III	2
Clinical care standards: Use standardized clinical audit tools to document and improve the quality of care delivered to patients	III	2
Patient support: Inform patients of support available from patient support groups, including access to patient education material	III	2

*Statements 44–47

EASL CPG PBC. J Hepatol 2017;67:145–72

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Proposed clinical care standards for PBC

Exclude alternate aetiologies for cholestasis: Undertake abdominal US in all patients with suspected PBC as part of baseline assessment	•**Standard 90%**
1st line treatment: UDCA at 13–15 mg/kg/day in all patients with PBC	•**Standard 90%** of patients receiving therapy at adequate dose or documented to be intolerant
Identify patients at risk of progressive disease: Document risk using biochemical response indices after 1 year of UDCA therapy	•**Standard 80%** of patients receiving UDCA to have response status and criteria used recorded
Recognize impact on QoL: Ensure appropriate investigation and treatment of symptoms (particularly pruritus, sicca complex, fatigue)	•**Standard 90%** of patients have the presence/ absence of pruritus, sicca complex and fatigue recorded in notes in the last year
Maximise opportunity for timely LTx: Discuss all established patients with bilirubin >50 µmol/L (3 mg/dl) or evidence of decompensated liver disease* with a hepatologist linked to a transplant programme	•**Standard 90%** documentation that discussion has taken place within 3 months of relevant clinical event and the actions taken recorded
Optimize prevention of osteoporotic bone fractures: Assess risk of osteoporosis in all patients. Treat/follow-up in line with national guidelines	•**Standard 80%** assessment within the last 5 years
Diagnose and treat of PBC with features of AIH promptly: Recognize as rare and when suspected, perform liver biopsy with expert clinicopathological assessment	•**Standard 90%** of patients with diagnosis of PBC with features of AIH have liver biopsy confirmation and clinicopathological discussion noted

*Variceal bleed, ascites, encephalopathy

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