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EASL Clinical Practice Guidelines

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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.
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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

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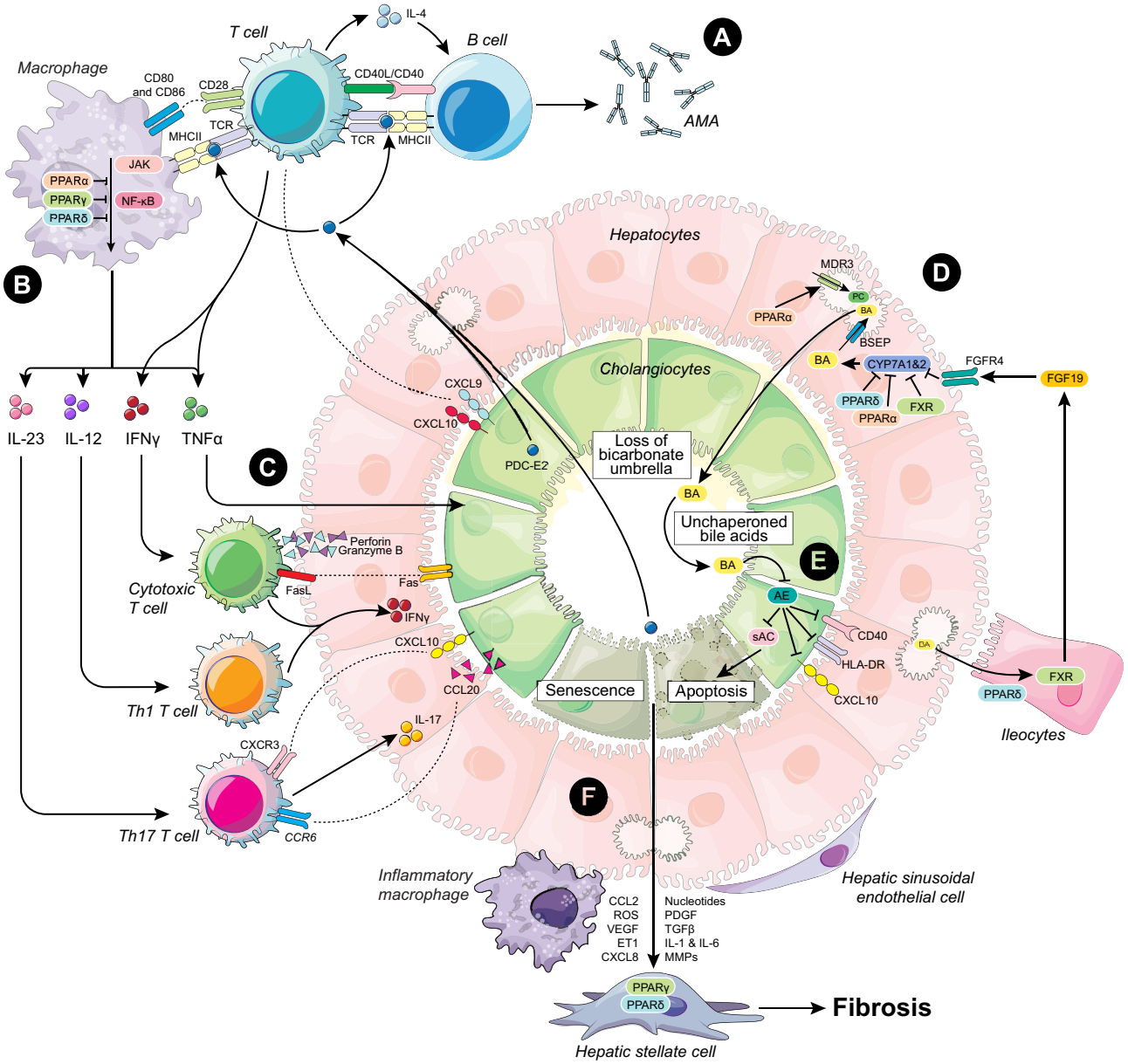


Fig. 1. PBC causes a cycle of immune injury to biliary epithelial cells, resulting in cholestasis and fibrosis. Important, interacting themes in the cycle of disease and its course include: (A) Antimitochondrial antibodies production specific to PDC-E2 through interactions of T and B cells; B cell activation is promoted by costimulatory molecules including CD40/CD40L. (B) Immune cell (including macrophage) activation, is part mediated by JAK-STAT and NFκB signalling; PPAR ligation may reduce NFκB activation. (C) Activated T cells (initially positioned by interactions with CXCL9 and CXCL10) produce cytokines including IFNγ (promoting cytotoxic T cell activity), TNFα (inducing BEC apoptosis or senescence), and IL-4 (promoting B cell activation and antibody production). With disease progression, cytotoxic and Th1 dominant inflammatory infiltrate shifts towards an increase in Th17 positive cells. Cytotoxic T cells induce apoptosis or senescence through FasL-Fas interactions and the secretion of perforins and granzyme B; both cytotoxic T cells and Th1 cells produce IFNγ that promotes apoptosis or senescence; IL-17 secreting Th17 cells appear later and are positioned by CXCR3-CXCL10 and CCR6-CCL20 interactions. (D) Enzymes such as CYP7A1&2 convert cholesterol to bile acids (BA), which are then exported by bile salt exporter pumps. BA production may be reduced by FXR or FGF-19, through the ligation of FGFR4, PPARα or δ. In health, BA are chaperoned by phosphatidylcholine and exported by MDR3. (E) In PBC, impaired activity of the apical AE2 and bicarbonate secretion lead to unchaperoned BA directly interfering with the BEC membrane. BEC are then vulnerable to the pro-senescent and pro-apoptotic effects of BA; unchaperoned BA further inhibit the activity of AE. This further weakens the bicarbonate umbrella, induces the expression of molecules that promote the immune response (CD40, HLA-DR and CXCL10), and promotes apoptosis (via soluble adenylate cyclase). (F) Both senescent and apoptotic cells secrete mediators that activate hepatic stellate cells (although PPARγ and PPARδ ligation may reduce this activation), perpetuate inflammation, and promote fibrosis and further biliary stasis. Hepatic sinusoidal endothelial cells, pro-inflammatory macrophages and other cell types also contribute to fibrogenesis. BEC death releases further PDC-E2. AE, anion exchanger; AMA, antimitochondrial antibodies; BA, bile acids; BEC, biliary epithelial cell BSEP, bile salt exporter pump; CCL, CC chemokine ligand; CD, cluster of differentiation; CXCL, chemokine (C-X-C motif) ligand; CYP7A1&2, cholesterol 7-alpha-hydroxylases A1 & A2; ET1, endothelin1; Fas/FasL, CD95/CD95 ligand; FGF19, fibroblast growth factor 19; FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; HLA-DR, human leukocyte antigen – antigen D related MHC II subclass; IFNγ, interferon-gamma; IL, interleukin; JAK, Janus kinase; MDR3, multidrug resistance protein 3; MHCII, major histocompatibility complex class II; MMP, matrix metalloproteinase; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PC, phosphatidylcholines; PDC-E2, pyruvate dehydrogenase complex E2 subunit; PDGF, platelet derived growth factor; PPARα/γ/δ, peroxisome proliferator-activated receptors alpha/gamma/delta; ROS, reactive oxygen species; sAC, soluble adenylate cyclase; TCR, T cell receptor; TGFβ, transforming growth factor beta; Th1/Th17, T helper type 1 and type 17 cells; TNFα, tumour necrosis factor-alpha; VEGF, vascular endothelial growth factor.

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[25–27]. Cholestasis in PBC is associated with pro-inflammatory (a) reductions in AE2, SLC9A3 (Na/H^+ exchanger), and inositol 1, 4, 5- triphosphate receptors; (b) reduced biliary bicarbonate content; and (c) reduced biliary alkaline phosphatase (ALP) activity [28]. Additional advances in understanding the aetiology of liver injury in PBC have arisen through increased knowledge of the gut-liver axis, including the farnesoid X receptor (FXR)/fibroblast growth factor (FGF)-19 signalling pathway. FXR is a central transcriptional sensor of bile acid metabolism, and one of its key target genes in the gut is *FGF-19*, which encodes an enterokine released into portal blood, following bile acid binding to FXR.

PBC impacts patients both through progression to end-stage liver disease (*i.e.* cirrhosis and the need for liver transplantation), and symptomatically. The symptoms associated with PBC impact on QoL, and include: cholestatic pruritus, sicca complex, abdominal discomfort and fatigue [29,30]. Patient surveys have also reported restless legs, sleeplessness, depression and cognitive dysfunction. Increased understanding of PBC has led to the distinction of high- and low-risk disease, recognised after evaluation of response to the first-line agent, ursodeoxycholic acid (UDCA). Age at onset, sex (male), stage at presentation, and selected biochemical/serologic indices pre- and post-therapy with UDCA, are used to identify those at greatest risk of disease complications [20]. Although current international registry studies report a 10-year survival approaching 80% for UDCA-treated patients, it is important to recognise the risks of untreated PBC. Historic population-based cohorts in the UK showed that patients with untreated PBC had an average survival of ~9–10 years from presentation, with ~25% developing liver failure during this time [31]. A Yale study showed a better median survival of up to 16 years in 'asymptomatic' patients [32], demonstrating the heterogeneity in findings of disease risk. In the absence of effective therapy, the median time to develop extensive liver fibrosis is ~2 years, with approximately one-third of patients remaining in early-stage disease over 4 years follow-up [33–35]. Conversely, some early-stage studies indicated that the rates of progression to cirrhosis after a follow-up period of 6 years, reached ~1 in 2 for those receiving penicillamine or placebo (as compared to 1 in 10 in patients receiving UDCA).

In summary, the importance of a structured, life-long and individualised approach to the care of patients with PBC is clear. The aim of this clinical practice guideline (CPG) is to provide a framework to help clinicians to diagnose and effectively manage patients with PBC.

Guideline development process

A panel of clinicians with an interest in liver disease and PBC, approved by the EASL Governing Board, wrote and discussed this CPG between November 2016 and March 2017. The guidelines were independently peer reviewed, and all contributors to the CPG disclosed their conflicts of interest by means of a disclosure form provided by the EASL Office prior to work commencing. The EASL Ethics Committee reviewed the composition of the panel to eliminate the potential for real or perceived bias. The CPG panel conflict of interests are declared in this submission. The RARE-LIVER European Reference Network (ERN) was represented on the CPG panel, and patient representatives were invited to feedback to the RARE-LIVER ERN co-ordinator.

Grading

These guidelines have been produced using evidence from PubMed and Cochrane database searches before 1 March, 2017. Where possible, the level of evidence and recommendation are cited (Table 1). The evidence and recommendations in these guidelines have been graded according to the grading of recommendations assessment development and evaluation (GRADE system). The strength of recommendations thus reflects the quality of underlying evidence. The GRADE system offers two grades of recommendation: strong or weak (Table 1) [36]. The CPG thus consider the quality of evidence: the higher, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted. Where no clear evidence exists, guidance is based on the consensus of expert opinion in the literature and the writing committee. Recommendations must also be interpreted in a context specific manner.

The diagnostic approach to cholestasis

Effective biliary secretion is essential for adequate hepatic detoxification and an intestinal digestive function. Cholestasis is the impairment of bile formation and/or bile flow which can be asymptomatic, or manifest with fatigue, pruritus, right upper quadrant abdominal discomfort and jaundice [37]. Early biochemical markers include increased serum ALP and gamma-glutamyltranspeptidase (GGT), followed by conjugated hyperbilirubinemia at more advanced stages. Cholestasis is considered chronic if it lasts >6 months [37], is classified as intrahepatic or extrahepatic, and includes hepatocellular and cholangiocellular forms of impaired bile formation. Jaundice (icterus) is the yellow discoloration of skin, sclera and mucous membranes due to hyperbilirubinemia, which can be a sign of severe cholestasis, but also has a broader diagnosis including pre-, intra- and post-hepatic causes (see Tables 2 and 3).

Chronic cholestatic liver diseases often have an asymptomatic course over months or years, and can be identified by elevated serum ALP [37]. Serum ALP can have different sources (*e.g.* liver, intestine, bone, placenta). Therefore, its elevation can be caused not only by cholestatic liver disease, but also rapid bone growth in children, extrahepatic diseases (*e.g.* bone diseases such as Paget's disease), vitamin D deficiency or pregnancy. In clinical practice, the hepatic origin of elevated serum ALP is usually supported by simultaneous elevation of serum GGT (or 5′ nucleotidase) and/or conjugated bilirubin. Differentiation of ALP isoforms from different organs is possible, but not commonly used. For the above reasons, in paediatric practice, serum GGT is a better marker of cholestasis than ALP. A structured algorithm of clinical, biochemical and technical diagnostic measures in chronic cholestasis is provided in Fig. 2, which may lead to a diagnosis in most patients with cholestatic liver disease. The approach to patients should be systematic:

History, physical examination, abdominal ultrasound

Careful personal, social, travel and family history taking may provide critical clues for the diagnosis of a cholestatic liver disease of unknown origin [37]. Diseases associated with PBC include:

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Table 1. Grading evidence and recommendations (adapted from GRADE system) [36].

Grade of evidence	
I	Randomised controlled trials
II-1	Controlled trials without randomisation
II-2	Cohort or case-control analytic 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. Recommendation is made with less certainty, higher cost or resource consumption

autoimmune Hashimoto's thyroiditis, Sjögren disease/sicca complex ('dry eye, dry mouth'), celiac disease, or systemic sclerosis. Inflammatory bowel disease frequently accompanies primary sclerosing cholangitis (PSC). A history of intensive care therapy and/or severe polytrauma is linked with secondary sclerosing cholangitis; and long-term exposure to paints, diesel and other oil products or industrial gases has been observed in immunoglobulin (Ig)G4 associated cholangitis. Drug history should not only include current and former prescribed medications, but also herbal preparations, other paramedical compounds, and any kind of drug abuse (*e.g.* anabolic steroids, laxatives) as well as alcohol and smoking. About 30% of patients with drug-induced liver injury (DILI) show a cholestatic serum enzyme pattern [37]. Antibiotics such as amoxicillin/clavulanic acid and trimethoprim/sulfamethoxazole, anabolic steroids or azathioprine can be relevant potential injurious agents [38]. When administered between 5 and 90 days prior to development of cholestasis, these medications should be stopped (if they have not been stopped already), and intensity of cholestasis should be followed. The Roussel Uclaf causality assessment method score as well as the National Institutes of Health website (https://livertox.nih.gov) can be helpful for assessing a patient's risk profile for DILI. Previous surgery and blood transfusions should be listed.

Physical examination should include screening for hepato- and splenomegaly as well as extrahepatic signs of advanced liver disease, such as icterus of sclera, skin and mucous membranes, xanthelasma, palmar and plantar erythema, nail abnormalities, or scratch lesions particularly on the arms and legs.

Abdominal ultrasound is the first recommended imaging technique for all patients to exclude mechanical bile duct obstruction, mass lesions (in and outside the liver) and abnormalities of the gallbladder. It is sensitive, non-invasive, portable and relatively inexpensive. Its findings, however, are operator-dependent and abnormalities of bile ducts may be missed. In the context of a normal abdominal ultrasound, a diagnosis of intrahepatic cholestasis is most likely.

Serological tests

In patients with chronic intrahepatic cholestasis, determination of serum AMA and PBC-specific antinuclear antibodies ANA (immunofluorescence and/or specific anti-sp100/anti-gp210 testing by Western blotting or enzyme-linked immunosorbent assay [ELISA]) is recommended as the next diagnostic step [39,40]. AMA may be of limited specificity in acute hepatic injury [41], but is highly sensitive and specific for PBC in the context of otherwise unexplained chronic cholestasis (for details, see 'Initial diagnosis of PBC'). AMA testing is not specific for PBC, and should always be targeted: the population frequency of AMA positivity is high (up to 1/1000) whereas PBC prevalence is lower (up to 0.4/1000) [42,43]. In some populations (*e.g.* people of native Cheyenne origin in Colorado) the prevalence of AMA or ANA specific for PBC is 15%, however, no clinical evidence for PBC is shown [44].

Extended imaging

Magnetic resonance cholangiopancreatography (MRCP) in cholestatic patients is a safe and accurate imaging method for the intra- and extrahepatic biliary tree, when performed by experienced practitioners [37]. Detection of intra- and/or extrahepatic bile duct stenoses and dilatation is essential for the diagnosis of primary or secondary sclerosing cholangitis (Table 2). Endoscopic ultrasound (EUS) is clinically equivalent to MRCP in the detection of bile duct stones and lesions causing extrahepatic obstruction, particularly of the distal bile duct.

Liver biopsy

A liver biopsy should be performed when the diagnostic steps summarised above have not revealed a cause of chronic intrahepatic cholestasis. A biopsy of adequate quality should contain at least 11 portal fields. Biopsy findings can be classified under:

(i) Disorders involving the bile ducts such as chronic non-suppurative cholangitis or fibrosing obliterative cholangitis, as well as less frequent cholangiopathies (Table 3).
(ii) Disorders not involving bile ducts, such as a variety of storage, infiltrative or inflammatory liver diseases, granulomatous diseases, nodular regenerative hyperplasia, peliosis, sinusoidal dilatation and cirrhosis of different cause.
(iii) Hepatocellular cholestasis with minimal or no histologic abnormalities, as observed in benign recurrent intrahepatic cholestasis (BRIC), oestrogen or anabolic steroid therapy, sepsis, total parenteral nutrition or as a paraneoplastic phenomenon.

Genetic testing

Numerous genetic syndromes associated with cholestasis have been described (https://www.ncbi.nlm.nih.gov/omim/?term=cholestasis). Among the most studied monogenetic cholestatic syndromes are mutations in the transporter genes *ATP8B1*, *ABCB11* and *ABCB4*. These can clinically present in early childhood, adolescence or adulthood as progressive familial intrahepatic cholestasis type 1–3 (PFIC1-3), BRIC, persistent hepatocellular secretory failure (PHSF), intrahepatic cholestasis

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Table 2. Differential diagnosis of intra- and extrahepatic cholestasis in adults.

Hepatocellular cholestasis
Alcoholic and non-alcoholic steatohepatitis
Benign Infiltrative diseases (amyloidosis, sarcoidosis)
Drug-induced cholestasis (DILI, cholestatic form)
(Mono-)Genetic diseases (*e.g.*, benign recurrent intrahepatic cholestasis type 1–3, progressive familial intrahepatic cholestasis type 1–3, intrahepatic cholestasis of pregnancy, persistent hepatocellular secretory failure, erythropoietic protoporphyria)
Infiltration by malignant diseases
Nodular regenerative hyperplasia
Paraneoplastic (Hodgkin's disease, renal cell carcinoma)
Sepsis
Total parenteral nutrition
Vascular diseases (*e.g.* Budd-Chiari syndrome, sinusoidal obstruction syndrome, congestive hepatopathy)
Viral hepatitis, cholestatic form
Cholangiocellular/biliary cholestasis
Primary biliary cholangitis
Primary sclerosing cholangitis
IgG4-associated cholangitis
Secondary sclerosing cholangitis, *e.g.* due to cholangiolithiasis, ischemia (Shock, polytrauma, intensive care therapy), telangiectasia, vasculitis, infectious diseases (AIDS or other immunodeficiency)
Cystic fibrosis
Drug-induced cholangiopathy ("drug-induced liver injury")
'Ductal plate malformations': von Meyenburg complexes (biliary hamartomas), Caroli syndrome, congenital liver fibrosis
Graft-*vs.*-Host disease
Idiopathic ductopenia
Langerhans cell histiocytosis

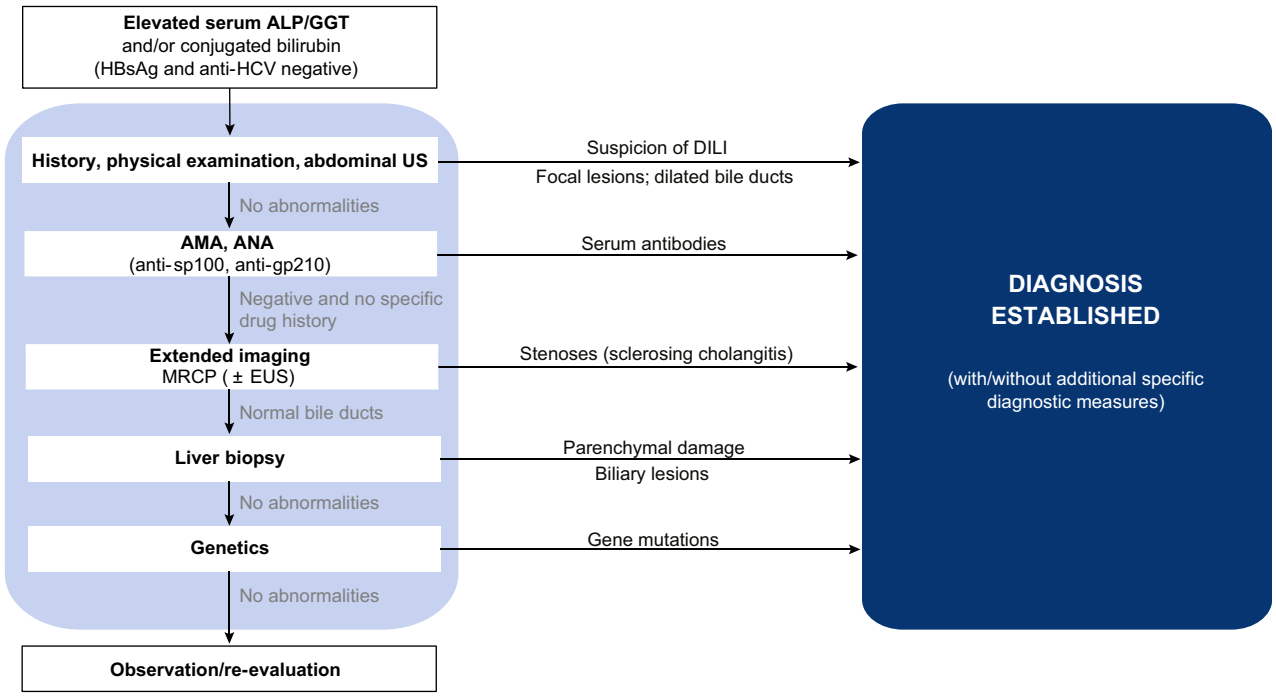


Fig. 2. Algorithm of clinical, biochemical and technical diagnostic measures in chronic cholestasis. In patients with cholestasis a structured approach is recommended to reach a safe and secure diagnosis, facilitating prompt interventions as appropriate.

of pregnancy (ICP) or low phospholipid associated cholelithiasis syndrome.

Genetic testing for these mutations is carried out in specialist laboratories and should be used when all other diagnoses have been ruled out, and family history, clinical symptoms, biochemical and imaging findings suggest an underlying (mono-) genetic cholestatic disorder. Additional genetic analysis of extremely rare cholestatic syndromes such as Alagille syndrome (*Jagged*, *Notch2*),

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PFIC4 (*TJP2*), or those associated with mutations in *MYO5B* (Villin) or *FXR* should be restricted to highly specialized centres and when clinical suspicion is substantial.

Recommendations

1. EASL recommends taking a detailed history and physical examination when evaluating patients with biochemical tests that suggest cholestatic liver disease (**III**, **1**).
2. EASL recommends ultrasound as the first-line non-invasive imaging procedure, in order to differentiate intra- from extrahepatic cholestasis (**III**, **1**).
3. EASL recommends performing serologic screening for AMA and PBC-specific-ANA by immunofluorescence in all patients with unexplained cholestasis (**III**, **1**).
4. EASL recommends imaging by MRCP in patients with unexplained cholestasis. EUS can be an alternative to MRCP for evaluation of distal biliary disease (**III**, **1**).
5. EASL recommends considering liver biopsy after serologic screening and extended imaging, in patients with ongoing unexplained intrahepatic cholestasis (**III**, **1**).
6. EASL recommends considering genetic tests for inherited cholestatic syndromes in patients where clinically appropriate (**III**, **1**).

Initial diagnosis of PBC

Clinical and biochemical abnormalities

PBC should be suspected in patients with persistent cholestatic abnormalities in serum liver tests or symptoms including pruritus or fatigue (Table 4). An abnormal serum level of ALP is typical in patients with PBC, and is associated with ductopenia and disease progression; other factors can modulate ALP values independently of cholestasis, such as: blood group, ABH secretor phenotype (secretion of ABO blood group antigens) and high IgG values in autoimmune hepatitis (AIH)-PBC 'overlap' syndromes [28]. Another biochemical feature of PBC is increased immunoglobulin concentrations, particularly IgM, which may be driven by epigenetic changes [45]. Patients with PBC may also have elevated serum transaminase (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) activity, which reflects the degree of liver parenchyma inflammation and necrosis, especially when associated with increased IgG [46–48]. An AST/ALT ratio greater than 1 may be a marker of ongoing liver fibrosis and elevated GGT can be identified prior to rises in ALP. Hyperbilirubinemia occurs as PBC progresses, and significant elevations are typical of advanced disease. When occurring alongside a falling platelet count, reduced albumin concentration, and elevated international normalised ratio (INR), it signifies the development of clinically significant cirrhosis. Cholestasis effects lipids, and patients with PBC can have raised cholesterol as well as development of xanthoma and xanthelasma. However, patients with PBC have not been robustly reported to have an associated increased cardiac risk [49,50]. Individual risk factors for PBC identified through epidemiologic studies include mucosal infections (especially recurrent urinary infections) and cigarette smoking.

Immunological markers

The hallmark for diagnosis of PBC is serological positivity for AMA, which target the E2-subunit of the pyruvate dehydrogenase complex (PDC-E2). AMA positivity is observed in more than 90% of patients with PBC [51]; immunofluorescence >1/40, or immunoenzymatic reactivity observed during cholestatic serum liver testing, is highly specific to the disease [52]. Although AMA positivity is a strong indicator of PBC in patients with otherwise unexplained abnormal liver biochemistry, AMA reactivity is only sufficient to diagnose PBC when combined with abnormal serum liver tests. Only one patient out of six with AMA positivity and normal ALP develops PBC within 5 years [17].

ANA are present in approximately 30% of patients with PBC. Some of these are specific for PBC (>95%), although have a low sensitivity. Immunofluorescent staining of nuclear dots (suggesting anti-sp100 reactivity) and perinuclear rims (suggesting anti-gp210 reactivity) are useful in the diagnosis of PBC in the 5–10% (depending on the assay) of patients with PBC who are AMA negative [37,51–54].

Immune markers should always be interpreted alongside clinical findings by an experienced practitioner to avoid misdiagnosis. For example, some systemic diseases (particularly haematological disorders, and granulomatous hepatitis) have low incidental AMA reactivity.

Imaging

PBC does not cause any abnormality to liver morphology that may be detected by imaging. However, patients with suspected PBC should have an abdominal ultrasound to rule out extrahepatic causes of cholestasis or liver neoplasms. Liver imaging is also useful to identify signs of advanced PBC, which are similar to other chronic liver diseases, and include: focal liver lesions, portal hypertension, splenomegaly or ascites. The presence of hilar lymphadenopathy is frequent in patients with PBC.

Histology

PBC is characterised by chronic, non-suppurative inflammation, which surrounds and destroys interlobular and septal bile ducts,

Table 3. Differential diagnosis of biliary lesions at histological analysis after liver biopsy.

Non-suppurative cholangitis
Primary biliary cholangitis
Primary sclerosing cholangitis
Autoimmune hepatitis
Drug-induced liver injury
Sarcoidosis
ABCB4 deficiency
Fibrosing obliterative cholangitis
Primary sclerosing cholangitis
Secondary sclerosing cholangitis
IgG4-associated cholangitis
Sarcoidosis
ABCB4 deficiency
Other cholangiopathies
Malignant cholangiopathy
Lymphoma
Systemic mastocytosis
Neutrophilic cholangitis
Eosinophilic cholangitis
Langerhans cell histiocytosis

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Table 4. Overview of utility of investigations in PBC.

Test	Finding	Suspicion	Diagnosis	Prognosis	Notes
ALP	↑	✓	✓	✓	Values associated with disease progression
AST/ALT	↑	✓		✓	Prominent elevation may be suggestive of PBC with features of AIH
GGT	↑	✓			Reflects cholestatic liver injury
IgM	↑	✓			Elevated values associated with disease
AMA (>1/40)	+		✓		Diagnostic hallmark in over the 90% of patients in correct clinical context
Specific ANA	+		✓		Specific immunofluorescence patterns: Perinuclear rims, nuclear dot, centromere; 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 except in patients with ductopenic non-cirrhotic variant
Platelets	↓			✓	Indicative of cirrhosis
INR	↑			✓	Indicative of cirrhosis
Albumin	↓			✓	Indicative of cirrhosis

ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltranspeptidase; IgM, immunoglobulin M; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; INR, international normalised ratio.

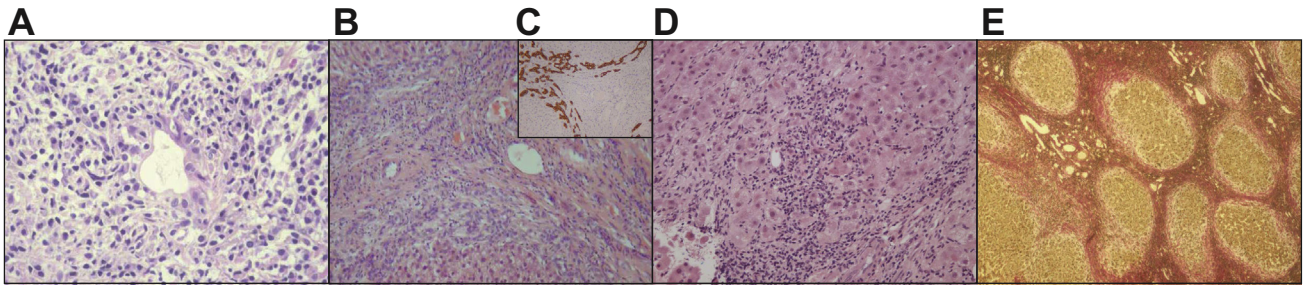


Fig. 3. Histopathologic features of PBC. Histologically the term "grading" is used to describe features of ongoing/active liver injury (*e.g.* inflammation), which may lead to the development of chronic (irreversible) liver damage, but may be treatable. In contrast, "staging" refers to features of progressive liver injury, that can lead to end-stage liver disease, and which reverse less readily. The manifestation of PBC is best captured as a non-suppurative, granulomatous, lymphocytic cholangitis that leads to cholestasis, ductopenia, and progressive fibrosis. Histological features relevant to staging chronic biliary diseases include fibrosis, bile duct loss and copper associated protein deposits. Panels A-E illustrate relevant disease features in PBC including: (A) Lymphocytic cholangitis: Florid duct lesion showing a dense periductal inflammatory infiltrate associated with disruption of bile duct epithelium (H&E); (B and C) Bile duct loss and ductular reaction: an expanded portal tract contains arterial branches without accompanying bile ducts. There is a marginal ductular reaction associated with loose fibrosis (biliary interface activity; H&E). Immunostaining for keratin 7 confirms the absence of any properly formed bile ducts and highlights the presence of prominent marginal ductular reaction (immunoperoxidase); (D) Interface hepatitis: 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. (H&E); (E) Cirrhosis: there is 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). The two staging systems, which have been most widely used in assessing disease severity in PBC are those described by Scheuer in 1967 [56] and Ludwig in 1978 [55]. Both systems recognise four stages, which are subdivided on the basis of various combinations of portal/periportal inflammation, ductular reaction & fibrosis (stage 4 = cirrhosis). A more recent staging system for PBC proposed by Nakanuma in 2010 incorporates three features thought to be important in disease progression – fibrosis, bile duct loss and orcein-positive granules [58].

and termed 'florid duct lesions' (Fig. 3). These are often identifiable at early stages. The inflammatory infiltrate consists mostly of T lymphocytes associated with few B lymphocytes, macrophages and eosinophils; epithelioid granulomas can also be observed. A progressive increase in bile duct damage leads to ductopenia, inflammation and collagen deposition, and can be used to stratify four (1–4) 'stages' of PBC (when classified as per Ludwig and Scheuer). Stage 4 indicates the presence of cirrhosis [55–57]. A new staging system for PBC was recently proposed, based on the assessment of chronic cholangitis and hepatitis activity [58–60]. This approach identifies four different stages by attributing a score of 0–3 to three histologic components: fibrosis, bile duct loss and deposition of orcein-positive granules. A total score of 0 identifies stage 1 (no or minimal progression), 1–3 identifies stage 2 (mild progression), 4–6 identifies stage 3 (moderate progression), and 7–9 identifies stage 4 (advanced progression). When compared to established staging methods, the new system more accurately predicted patient outcome at 10 years, particularly the development of cirrhosis and its complications [60].

Given the high specificity of serological markers, liver biopsy is not necessary for the diagnosis of PBC; however, it is still essential when PBC-specific antibodies are absent, or when co-existent AIH or non-alcoholic steatohepatitis (NASH) is suspected. Liver biopsy may also be appropriate in the presence of other co-morbidities (systemic/extrahepatic).

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Recommendations

7. EASL recommends that in adult patients with cholestasis and no likelihood of systemic disease, a diagnosis of PBC can be made based on elevated ALP and the presence of AMA at a titre >1:40 (**III**, **1**).
8. EASL recommends that 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**).
9. EASL recommends against liver biopsy for the diagnosis of PBC, unless PBC-specific antibodies are absent, co-existent AIH or NASH is suspected, or other (usually systemic) co-morbidities are present (**III**, **1**).
10. AMA reactivity alone is not sufficient to diagnose PBC. EASL recommends following-up patients with normal serum liver tests who are AMA positive with annual biochemical reassessment for the presence of liver disease (**III**, **1**).

Stratification of risk in PBC

Even when patients are receiving UDCA treatment, PBC can remain a progressive disease, with a risk of liver-related complications and death [61–63]. Thus, all patients should be evaluated for their risk of developing end-stage complications and, consequently, their potential need for additional treatments (Fig. 4). The markers of risk stratification in PBC can be split into dynamic and static parameters according to whether response to treatment is considered specifically or not. Static markers can be used at presentation or at any time during treatment. They may consist of demographics, symptoms, standard biochemistries, serological profiles, serum markers of fibrosis, liver stiffness measurement (LSM), histological features, and direct measurement of portal pressure.

Demographics

Age and sex have been shown to influence both response to treatment and long-term outcome of patients with PBC. Patients who present at a younger age (<45 years) are often symptomatic and less likely to respond well to standard treatment with UDCA [6]. This may translate into a higher standardised mortality ratio within this age category, particularly for liver-related deaths, whilst elderly patients are more likely to die from non-liver-related causes [64]. Male sex is associated with later diagnosis, more advanced disease at presentation, poorer biochemical response to UDCA therapy, and higher risk of developing hepatocellular carcinoma (HCC) [6,8,65]. Whether sex can be used as an independent prognostic factor to determine PBC outcome, however, remains to be shown [65,18].

Symptoms

Fatigue or pruritus affects over 50% of patients with PBC [31] and the symptom burden for patients is important and broad in nature as discussed in "Management of symptoms and extrahepatic-hepatic manifestations"; it is however, complex in association with disease severity markers. Advanced disease is more likely to be associated with symptoms.

Symptom presence itself, may predict a poorer response to UDCA and prognosis [66,67]. A premature ductopenic variant of PBC has been described, in which severe pruritus is associated with progressive icteric cholestasis, and is not responsive to UDCA. Histology reveals bile duct loss without significant fibrosis or cirrhosis, and these patients usually progress to needing transplantation [68].

Inconsistent data in the literature, regarding the prognostic impact of symptoms [31,70] may reflect various issues, including: non-discrimination between pruritus and fatigue, non-standardisation of quantification methods, lack of consideration of symptom development, surveillance and confounding biases, and intrinsic variability, as well as poor specificity of such subjective features [70,71]. Fatigue severity in patients with PBC does not necessarily relate to the severity of underlying liver disease in an individual; a reported prognostic value may be linked to an increased risk of non-liver-related deaths [69].

Standard serum liver tests

Serum bilirubin has been recognised since the 1970s as a major predictor of poor outcome in PBC [72,7]. Baseline bilirubin and albumin values, considered together, are able to discriminate UDCA-treated patients efficiently into low (both normal bilirubin and albumin), medium (abnormal bilirubin or albumin), and high (both abnormal bilirubin and albumin) risk groups [61]. The Mayo risk score and the model for end-stage liver disease (MELD) are also effective in defining risk groups under UDCA treatment [73,74]. However, since bilirubin and albumin values are altered at a very late phase of PBC, they are not realistic markers for the risk stratification of early-stage populations. In those patients, the assessment of the biochemical response to UDCA therapy is indicated.

Serological profiles

PBC-specific ANA (antibodies against gp210 and sp100 antigens) are more frequently observed in patients with severe PBC and their presence may also be predictive of an unfavourable course, irrespective of serum bilirubin [75–77,63,78]. Anti-centromere antibodies have also been reported to have potential prognostic impact (portal hypertensive phenotype) [79,80,78]. However, longitudinal studies are still limited, and whether autoantibody patterns may be used in clinical practice as reliable markers of prognosis remains to be validated.

Serum markers of fibrosis

Some serum markers of fibrosis enable clinicians to separate patients with PBC into different risk groups. Hyaluronic acid was the first marker to show significant association with clinical outcomes [81,82]. The enhanced liver fibrosis (ELF) score, which is computed from the simultaneous measurements of serum concentrations of hyaluronic acid, procollagen III peptide and tissue inhibitor of metalloproteinase 1, have shown similar predictive capacity [74]. More recently, the aspartate aminotransferase-to-platelet ratio index (APRI) has been validated from different

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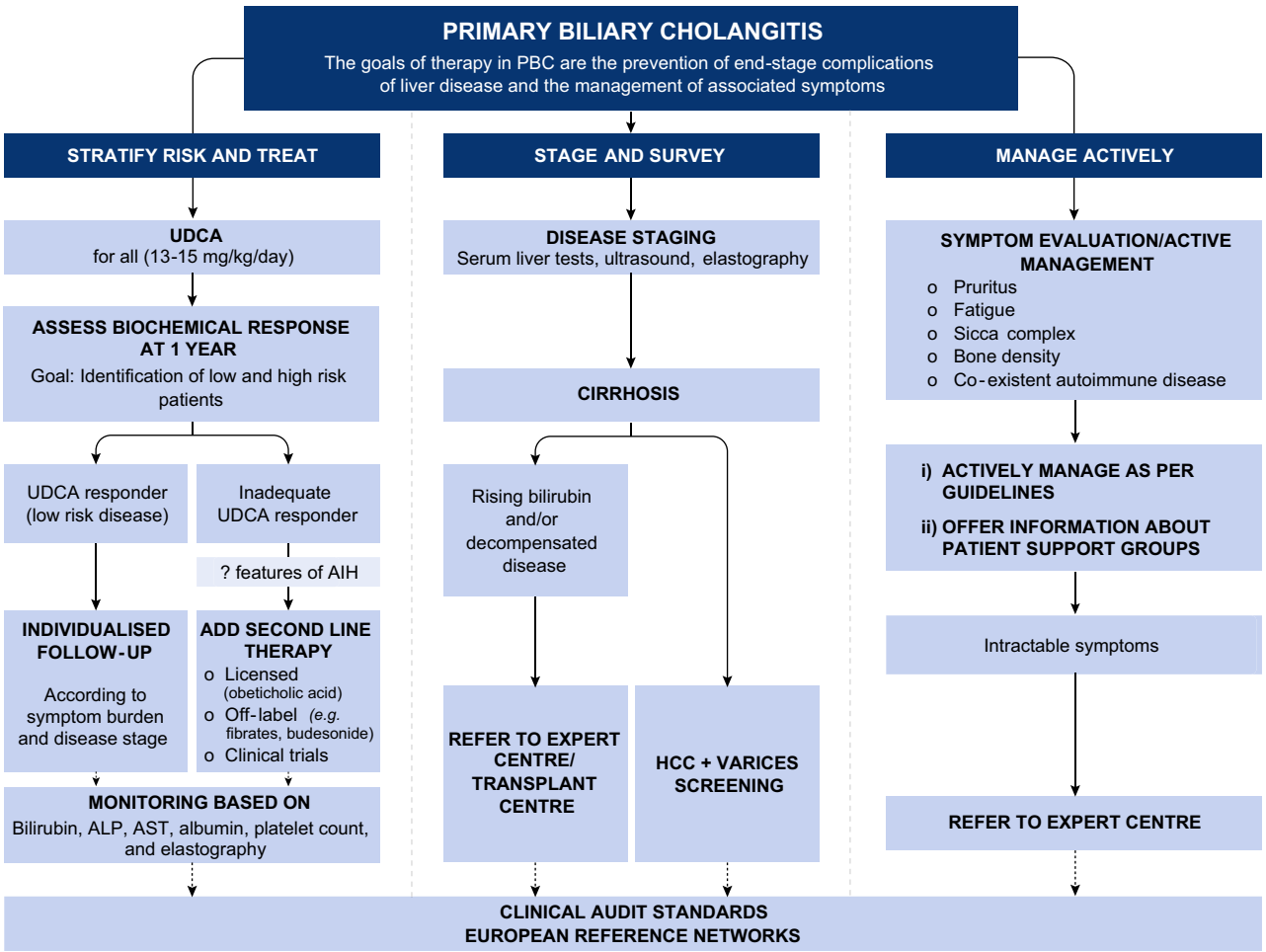


Fig. 4. EASL Clinical practice guideline in PBC management flow chart. In patients with PBC, a structured approach to their life-long care is important and recommended. Care should focus around three 'pillars' of practice, a) stratification of risk and treatment; b) staging and surveying disease; and c) active patient management. Whilst care always needs to be tailored to the individual patient and the health care environment, these three guiding themes are central to effective patient management.

cohorts as a predictor of adverse events, independently and additively of UDCA-response [83]. Serum levels of wisteria floribunda agglutinin-positive mac-2 binding protein (WFA^+-M2BP) and cytokeratin 18 have also shown prognostic ability in PBC, but validation is required [84,85].

Liver stiffness measurement

LSM, assessed by vibration-controlled transient elastography (VCTE), has been shown as one of the best surrogate markers for the detection of cirrhosis or severe fibrosis (*i.e.* bridging fibrosis) in patients with PBC [86–88]. Furthermore, values of LSM >9.6 kPa are associated with a 5-fold increased risk of liver decompensation, liver transplantation or death [86]. In addition, worsening LSM showed a higher performance than LSM itself in predicting patients' outcomes, suggesting that LSM may be used as a surrogate marker of PBC progression [86]. This study showed that patients with cirrhosis treated with UDCA had a significant progression of LSM during follow-up. Based on these results, the European Association for the Study of the Liver – Asociacion Latinoamericana para el Estudio del Higado (EASL-ALEH) CPG recommend the use of VCTE to monitor PBC progression, even though more data is needed to define the optimal prognostic thresholds and time-frame between repeated examinations [89]. Very recent data show that inadequate biochemical response to UDCA is more likely to be associated with worsening of LSM, and that the use of VCTE may improve the ability of the new prognostic scores to predict patients' outcomes [90,91]. One large collaborative study showed LSM and IQR/median as the two independent criteria of VCTE reliability [92] and EASL-ALEH CPG guidelines provide current recommendations on performing VCTE [89].

Histological features

Advanced histological stages are consistently associated with a poor prognosis in PBC [93,94,47,63,95]. As the use of liver biopsy for diagnostic purposes is no longer recommended, and VCTE can now be used as a convenient option for detecting cirrhosis or severe fibrosis, the histological examination of the liver may appear of limited relevance to assess PBC prognosis. However, liver biopsy may be useful in patients who have an inadequate

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response to UDCA in characterising and quantifying the histological lesions that underlie the resistance to treatment [96,91]. The degree of lymphocytic interface hepatitis has been identified as an independent predictive factor of cirrhosis development or major events [97,63,95]. The presence of ductopenia predicts histological stage progression, along with biochemical response to UDCA [98]. Furthermore, classical histological staging improved the power of the biochemical response to UDCA to predict long-term outcomes [95]. Finally, a new histological staging and grading system has been shown to reflect liver dysfunction before UDCA treatment and to correlate well with the future development of cirrhosis-related conditions [58,60]. Liver biopsy may therefore add to risk stratification in PBC. Considering the benefit/risk ratio of this invasive procedure, its use may be advocated in patients with poor biochemical response to UDCA.

Direct measurement of portal pressure

The direct measurement of the hepatic venous pressure gradient (HVPG) in PBC has been shown to correlate with the probability of death or liver transplant [99]. Furthermore, reduction in the HVPG after 2 years of UDCA therapy may identify a subgroup of patients with good outcomes [99]. However, the emergence of non-invasive methods (*e.g.* elastography) for assessing portal hypertension indirectly, now avoids the use of such an invasive procedure in routine practice.

Defining inadequate response to treatment

Treatment failure must be defined on validated surrogate endpoints to account for the slow progression of disease, *i.e.* endpoints that have significant reproducible prognostic performance in different cohorts of patients [100]. Although promising, change in LSM remains insufficiently validated to be used as a surrogate marker for disease progression [89]. In contrast, standard serum liver tests under treatment have been extensively validated over the last decade as a simple and robust prognostic tool. The biochemical response to UDCA can be either assessed using qualitative definitions based on discrete binary variables or quantitative scoring systems computed from continuous parameters (Table 5).

Qualitative binary definitions

Several definitions of the biochemical response to UDCA have been proposed [101,62,63,102,103,98,104]. All except the Toronto criteria were established retrospectively from small-to-medium-sized single-centre longitudinal cohorts. The Toronto criteria were defined to predict histological stage progression. Of the other definitions, most were designed to enable practitioners to predict hard clinical outcomes, *i.e.* death or liver transplantation. Whilst most of them have been validated at 12 months from UDCA initiation, recent reports suggest that evaluation at 6 months may have equivalent predictive performance [105]. Inadequate biochemical response to UDCA is observed in 25% to 50% of the patients in most cohorts, depending on which definitions were used [102,105]. The international consensus is that the two most important parameters in evaluating response to UDCA are ALP and total bilirubin [7]. This may explain the improved reported performance of the Paris-I criteria in discriminating low- and high-risk patients in numerous large independent cohorts [102,6,83,8,106]. Furthermore, a combination of the Paris-I criteria with APRI applied after 1-year of UDCA, improved risk stratification [83]. Of note, although all thresholds of ALP are predictive of outcomes, their accuracy for use in identifying high-risk patients was not found to differ significantly between 1.5x upper limit of normal (ULN), 1.67× ULN, and 3.0× ULN [7]. Since disease stage is known to affect biochemical response to UDCA [63,102], stage-specific thresholds may be important. Therefore, the Paris-II criteria have been designed specifically to better fit early-stage patients, who represent more than two-thirds of patients in recent cohorts [104].

Continuous scoring systems

Prognostic tools based on dichotomous criteria are simple and easy-to-use in clinical practice, but may lead to both the loss of predictive information and relatively high disagreement rates when separating patients among low- and high-risk groups [106]. Furthermore, most of them do not take into account other prognostic variables, such as markers of disease stage. Consequently, efforts from the Global PBC Study Group (http://www.globalpbc.com/globe) and the UK-PBC consortium (www.uk-pbc.com) have led to the development of new

Table 5. Assessing response to UDCA therapy in PBC.

Qualitative binary definitions	**Time (months)**	**Treatment failure**
Rochester [101]	6	ALP ⩾2× ULN or Mayo score ⩾4.5
Barcelona [62]	12	Decrease in ALP ⩽40% and ALP ⩾1× ULN
Paris-I [63]	12	ALP ⩾3× ULN or AST⩾ 2× ULN or bilirubin >1 mg/dl
Rotterdam [102]	12	Bilirubin ⩾1× ULN and/or albumin <1× ULN
Toronto [98]	24	ALP >1.67× ULN
Paris-II [104]	12	ALP ⩾1.5× ULN or AST ⩾1.5× ULN or bilirubin >1 mg/dl
Ehime [103]	6	Decrease in GGT ⩽70% and GGT ⩾1× ULN
Continuous scoring systems	**Time (months)**	**Scoring parameters**
UK-PBC [107]	12	Bilirubin, ALP and AST (or ALT) at 12 mo. Albumin and platelet count at baseline
GLOBE [106]	12	Bilirubin, ALP, albumin, and platelet count at 12 mo. Age at baseline

ALP, alkaline phosphatase; ULN, upper limit of normal; AST, aspartate aminotransferase; GGT, gamma-glutamyltranspeptidase.

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continuous scoring systems incorporating both measures of treatment response and parameters of disease severity [106,107]. Thus, both the GLOBE score and the UK-PBC score have shown better performance for the prediction of death or liver transplantation than the Paris-I criteria, which have the best performance among binary models. The two continuous models have shown comparable risk quantification [108]. Compared to the Paris-I criteria, the GLOBE score improves the global classification of patients into low- and high-risk groups by nearly 10% [106]. According to the GLOBE score, approximately 40% of patients under UDCA are expected to have shorter transplant-free survival times than matched healthy individuals [106]. No such data are currently available for the UK-PBC score. The performance of the two new prognostic models at shorter times of evaluation, as well as from non-occidental populations has not yet been validated. Whether LSM may provide added predictive value to these models also remains to be determined [91].

Prognostic tools for PBC in practice: Guidance

The prognostic tools discussed may have several important applications in clinical practice. First and most important, is the selection of patients for second-line therapies, either in routine care or in therapeutic research. Second is the stratification of risks for clinical trials in order to account for the prognostic disparity between patients at inclusion. Table 6 summarises and grades the prognostic tools of PBC according to different levels (high, moderate, indeterminate) of applicability and validity.

The biochemical response to UDCA measured after 12 months of treatment are the most validated and easily applicable means to select patients in needs for second-line therapies. A 12-month period is conventionally used, but evaluation at 6 months may be equally discriminatory. The chosen tool should include ALP and bilirubin measurements, because they are the two strongest variables used to predict PBC prognosis. The Paris-I/II criteria are recognised as simple, easy-to-use and robust selection tools with only a modest loss of accuracy when compared with the continuous risk scores. In therapeutic research, both qualitative and quantitative approaches can be rationally applied.

Baseline disease stage, can be defined as early or advanced disease according to:

(i) Histology (when a biopsy is available) – absent or mild fibrosis *vs.* bridging fibrosis or cirrhosis.
(ii) Elastography (LSM $\leqslant$9.6 kPa *vs.* >9.6 kPa).
(iii) Serum levels of bilirubin and albumin – both parameters normal *vs.* at least one parameter abnormal.

These are simple and potent discriminant tools for the stratification of risk in clinical trials. VCTE has proven to be powerful and reliable for detecting advanced stages of PBC, and is now available in numerous countries and expert centres. Thus, it should now be considered the method of choice for stratifying patients at trial inclusion. Furthermore, VCTE can be used to monitor PBC progression, as worsening LSM predicts patients' outcomes.

Recommendations

11. EASL recommends that therapy in PBC should aim to prevent end-stage complications of liver disease and manage associated symptoms. (**III**, **1**).
12. EASL recommends evaluating all patients for their risk of developing progressive PBC (**III**, **1**).
13. EASL recommends recognition that patients at greatest risk of complications from PBC are those with inadequate biochemical response to therapy, and cirrhosis (**II-2**, **1**).
14. EASL recommends actively recognising 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**).
15. EASL recommends evaluating all patients for their 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**).
16. EASL recommends that elevated serum bilirubin and ALP can be used as surrogate markers of outcome for patients with PBC, and routine biochemistry and haematology indices should underpin the clinical approaches to stratify individual risk of disease progression (**II-2**, **1**).
17. EASL recommends recognising that the transplant-free survival for early-stage patients with ALP <1.5× ULN and a normal bilirubin after one year of therapy with UDCA, is not significantly different to a control healthy population (**II-2**, **1**).
18. EASL recommends using elastography and risk scores (such as the GLOBE and UK-PBC score) for patients with PBC, to help better define the individual risk of development of complications of advanced liver disease in the future (**III**, **1**).

Treatment: Therapies to slow disease progression

Treatment of PBC has been dominated by bile acid based approaches to therapy [109]. Several other agents have been studied, including immunosuppressants, but reproducible and/or consistent evidence of benefit is lacking. Failed alternate therapies will not be summarised here, but prior reviews and guidelines describe outcomes [2,110].

PBC progresses slowly and therefore, individual trials lack the power to address end-points such as death or liver transplantation. Many studies have attempted to demonstrate clinical efficacy for UDCA (most notably), and most have shown beneficial effects on accepted surrogate biochemical parameters. Differences in trial inclusion criteria, and some without reference to individual disease risk and stage, may have led to the heterogeneous reports about treatment efficacy: low-risk patients may remain low-risk regardless of intervention and high-risk

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individuals may have an impaired response to intervention. Recognising this, as well as the impact of slow disease progression on treatment response is essential for understanding the PBC trial data available: the impact of an intervention is not a uniform function of drug mechanism, and must account for a patient's disease severity risk and liver disease stage.

Licensed indications

Ursodeoxycholic acid

The efficacy of oral UDCA has been widely studied [111]. Its use is already recommended for all patients with PBC by the American Association for the Study of Liver Diseases (AASLD) and EASL, as well as in this new guideline [35,112–121].

UDCA accounts for about 1–3% of bile acids and with pharmacotherapy becomes the predominant bile acid; the degree of bile enrichment is correlated with improvement in serum liver tests [4,122–124]. UDCA is a post-transcriptional secretagogue in hepatocytes and cholangiocytes and stimulates the transfer of transport proteins and channels into their target membranes via potent post-transcriptional signalling. This mechanism and the subsequent secretion of HCO_3^-, bile acids, bilirubin and numerous other cholephils is impaired under cholestatic conditions [4]. UDCA also exerts cytoprotective (*e.g.* anti-apoptotic) effects in hepatocytes and cholangiocytes [4]. Data suggest that the optimum dose is 13–15 mg/kg per day, which can be given as a single oral daily dose or divided doses if tolerability is an issue; anecdotally some patients tolerate liquid preparations better. In PBC, a dose of 13–15 mg/kg/day has been reported to be superior to 5–7 mg/kg/day or 23–25 mg/kg/day. When evaluating UDCA trial data, treatment dose used should be noted – some early studies applied lower dosages than those now considered optimal.

UDCA is very safe, with minimal side effects when administered to patients at its recommended dose (weight gain of ~3 kg in the first 12 months, hair thinning, and, rarely, diarrhoea and flatulence are reported). There are no data to suggest that UDCA is teratogenic. Evidence-based advice over use in pregnancy and breast feeding is lacking, but it is considered safe to use before and during the first trimester and beyond, as well during breast feeding; it has a good safety profile for use in ICP [125,126].

Three large double-blind randomised trials used the same dose of UDCA (13–15 mg/kg per day), and thus the results have been analysed according to an intention-to-treat principle [116]. In two of these, a composite 'treatment failure' measure was used; in the third, the percentage change in total serum bilirubin over 2 years was used as the primary outcome measure. Few adverse effects of UDCA were reported and the withdrawal rate was less than 20% in all three studies. In two of the three trials, a crossover design was adopted, with some patients initially randomised to a placebo before switching to open-label UDCA after the first 24 months. However, the results were analysed according to intention-to-treat, so the patients who were initially randomised to receive placebo and subsequently switched to receive UDCA, remained in the placebo group for the purposes of analysis. This combined analysis of the three trials (548 patients) showed a one-third reduction in the risk of death or transplant for patients with moderate to severe PBC. Subgroup analysis did not show any benefit in patients who had a total serum bilirubin of less than 68 μmol/l and/or stage I/II liver histology at baseline. An important observation was that the patients crossed over to UDCA, continued to have a poorer clinical course. A further trial (151 patients) employed a lower dose (10–12 mg/kg bodyweight daily) and a different preparation of UDCA. After 2 years of treatment no difference in survival was seen (eight deaths in patients randomised to UDCA and 12 in those randomised to placebo). Prolonged follow-up also showed no survival benefit.

In a French study [35] there was a fivefold lower annual progression rate from early-stage liver disease to extensive fibrosis/-cirrhosis in patients taking UDCA (7% *vs.* 34% under placebo, $p < 0.002$) (8), with a 4-year probability of remaining in early-stage disease of 76% (*vs.* 29% in the placebo-treated arm). The protective effect of UDCA on the development of oesophageal varices has also been addressed prospectively, and in a study of 180 patients with PBC, the 4-year probability was significantly lower in treated *vs.* untreated patients (16% *vs.* 58%; $p < 0.001$) (10). The strongest non-trial evidence of therapeutic efficacy is provided by an individual patient meta-analysis, conducted by the Global PBC Study Group [7] (n = 4,845), which revealed a significantly improved liver transplant-free survival in treated *vs.* untreated individuals across several time-points (at 5 years, 10 years and 15 years: 90%, 78%, and 66% *vs.* 79%, 59%, and 32% for UDCA-treated and non-treated group, respectively; $p < 0.001$ for all comparisons).

Of the 16 randomised clinical trials evaluating UDCA against placebo, nearly half had a high-risk of bias [127]. In all the studies, the administration of UDCA was associated with an improvement of serum liver tests. An updated Cochrane meta-analysis showed that overt ascites and jaundice are less frequent in patients randomised to UDCA, but there was no difference in the number of patients with bleeding varices or hepatic encephalopathy [121]. These data suggest that prolonged treatment with UDCA, started at early stages of disease, is likely required to exert the maximal positive effect. This meta-analysis was confined to trials using an appropriate dose of UDCA (>10 mg per kilogram of body weight per day) with sufficient follow-up (at least 2 years) and included 1,038 patients (522 who received UDCA and 516 who received placebo) [120]. Treatment with UDCA resulted in significantly improved serum liver tests. Histological evidence of disease progression was similar for the two treatment groups, but patients without evidence of fibrosis (stages I and II) who were treated with UDCA had slower disease progression than patients in the placebo group. A total of 160 patients who were treated with UDCA and 186 control patients died or underwent liver transplantation. The difference between the groups approached marginal significance in a fixed-effect model (odds ratio, 0.76; 95% confidence interval [CI], 0.57 to 1.00; $p = 0.05$) but not in a random-effects model (odds ratio, 0.77; 95% CI, 0.50 to 1.21; $p = 0.30$).

Recommendation

19. EASL recommends oral UDCA at 13–15 mg/kg/day as the first-line pharmacotherapy for all patients with PBC. UDCA is usually continued for life (**I**, **1**).

Obeticholic acid

FXR is a nuclear 'ligand-activated' receptor abundantly expressed in tissues involved in the enterohepatic circulation of bile acids [4,128,21,129]. Unlike UDCA, which functions at a

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post-translational level, FXR signalling directly regulates genes involved in bile acid synthesis, secretion, transport, absorption and detoxification; additionally, FXR signalling impacts on inflammation, metabolic regulation and liver fibrosis. Obeticholic acid (OCA) is a semi-synthetic hydrophobic bile acid analogue that is highly selective for FXR. It has an exponential activation potency relative to its endogenous counterpart, chenodeoxycholic acid. OCA also induces expression of gut derived hormones, particularly FGF-19.

The first randomised, double-blind controlled trial of OCA in PBC evaluated the therapeutic efficacy of three doses (10, 25, and 50 mg/day) as an add-on therapy to UDCA in a multicentre study restricted to patients with persistent elevations in serum ALP (>1.5× ULN) [130]. In this study, the primary endpoint was a significant reduction in serum ALP from baseline, and was met across all three doses of OCA *vs.* placebo. Moreover, 87%, 69% and 7% of all OCA-treated patients who completed therapy achieved a decline in serum ALP of at least 10%, 20% or complete normalisation (*vs.* 14%, 8% and 0% with placebo) (3). Data from the PBC OCA International Study of Efficacy phase III clinical trial (POISE) have been published [131]. The POISE study specifically recruited patients with PBC and a persistent elevation in serum ALP (prior biochemical non-response according to modified Toronto criterion; ALP >1.67× ULN and/or elevated total bilirubin <2× ULN). The primary endpoint during the 12-month double-blind period was attainment of both an ALP value <1.67× ULN (with a ⩾15% reduction from baseline) and a normal serum bilirubin level. In an intention-to-treat analysis, biochemical response was met in 10% of the placebo group relative to 47% and 46% in the 10 mg and 5–10 mg dose-titrated OCA groups, respectively (p <0.0001 for both). Moreover, the mean decrease in serum ALP from baseline was 39% and 33% in the 10 mg and titrated OCA groups, respectively, *vs.* 5% for patients in receipt of placebo (p <0.0001 for both). Both OCA groups met predefined secondary end-points including reduction in serum AST and total serum bilirubin (both p <0.001 *vs.* placebo).

Double-blind controlled data of OCA in PBC remain limited to follow-up periods of 12 months, with open-label extension data beyond this time-point. Longer-term efficacy of OCA and generalizability to the patient population needs confirmation in prospective follow-up studies. Survival benefit has yet to be demonstrated, and a long-term randomised trial is currently ongoing for that purpose. There are no data available regarding therapeutic efficacy, stratified according to the magnitude of serum ALP elevations at the point of trial inclusion. Assessment of further surrogates for clinical outcome (including AST/platelet ratio or LSM derived via transient elastography) would be of additional benefit.

Treatment with OCA is associated with a dose dependent exacerbation in pruritus, leading to treatment discontinuation in 4–10% of patients [130,131]. These observations emphasise the importance of dose titration as well as the timely provision of therapy for symptom control. Rifampicin may be preferred, given potential interactions with bile acid sequestrants, leading to faecal OCA loss. OCA-treated patients may also exhibit (reversible) alterations in serum lipid levels; specifically, a decrease in high density lipoprotein (HDL) coupled with an increase in total and low density lipoprotein (LDL) cholesterol [130,131]. It is not yet known whether these consequences impact long-term cardiovascular risk. To date there is limited cost-effectiveness analysis.

Recommendation

20. In a phase III study, evidence of biochemical efficacy of oral OCA has been demonstrated in patients with ALP >1.67× ULN and/or bilirubin elevated <2× ULN. Oral OCA has been 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. EASL suggests considering its use in such patients (initial dose 5 mg; dose titration to 10 mg according to tolerability at six months) (**I**, **2**).

Unlicensed indications

Budesonide

Budesonide is a synthetic corticosteroid with high first-pass metabolism within the liver, resulting in minimal systemic side effects when compared to prednisolone [132]. Nevertheless, the pharmacokinetics of budesonide become augmented as liver disease progresses, and can result in deleterious outcomes in patients with cirrhosis and portal hypertension [132]. In patients with PBC exhibiting 'florid' interface hepatitis on biopsy, there are anecdotal data demonstrating the efficacy of budesonide in improving liver histology and biochemistry when used in combination with UDCA. The premise behind therapy is in part a reflection of the association between serum transaminases and interface hepatitis, and their association with disease progression in PBC. However, elevated transaminases in PBC may also be a feature of hepatocyte injury from the effects of cholestasis, as opposed to representing parenchymal inflammation: bile acids induce inflammatory mediator expression and secretion at non-toxic, non-detergent concentrations, whilst at high concentrations induce apoptosis (or even necrosis at very high concentrations). In this regard, immunosuppression may not be beneficial; it is notable, however, that budesonide and UDCA *in vitro* are synergistic in increasing AE2 expression, a process that may be biliary protective [133].

A 1999 randomised placebo-controlled trial (n = 39) was the first to study budesonide (9 mg/day) as add-on therapy to UDCA in patients with early-stage PBC [134]. Over the 2-year study period, patients receiving combination therapy exhibited a significant reduction in serum ALP as well as improvement in liver histology according to the Ludwig classification system. Moreover, in a subsequent 3-year randomised, non-blinded study performed in non-cirrhotic PBC patients (n = 77), budesonide 6 mg/day + UDCA (n = 46) was associated with a 25% regression in liver fibrosis [135]. However, despite encouraging results, there was a high rate of fibrosis progression (an increase of 70%) in patients receiving UDCA monotherapy. A US based open-label study [136] of 22 biochemical non-responders (ALP persistently >2× ULN) reported only a very minimal additional benefit of budesonide to UDCA, with a significant increase in the Mayo PBC score prognostic index, and significant deterioration in bone mineral density. True comparison is challenging, however, because this cohort may have had patients at later stages of disease. Several reports have undertaken network meta-analysis [137,138] or retrospective analysis to see if corticosteroids are efficacious and positively impact patients with PBC treated with both UDCA and corticosteroids. A phase III

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Table 6. 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 using either qualitative or quantitative tools • Baseline (early *vs.* advanced) 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

ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; LSM, liver stiffness measurement; APRI, aspartate aminotransferase/platelet ratio index; ELF, enhanced liver fibrosis; PBC, primary biliary cholangitis; ANA, antinuclear antibodies.

double-blind randomised placebo-controlled trial evaluating UDCA + budesonide *vs.* UDCA + placebo is awaiting final evaluation (Eudra CT number 2007-004040-70).

Fibric acid derivatives

Fibrates exert potent anti-cholestatic effects through the variable activation of peroxisome proliferator-activated receptors (PPAR), in addition to downregulation of several pathways leading to bile acid synthesis [139]. Whilst there is long-standing interest regarding these agents in cholestatic liver disease [138,140,141], in some jurisdictions, drug labelling has documented contraindication to their use in PBC because of concerns over reported hepatotoxicity. Fibrates at high dose inhibit some CYP enzymes, particularly CYP2C9. Interestingly, CYP2C9 controls the pharmacokinetics of nonsteroidal anti-inflammatory drugs (NSAID), and special care should be taken to ensure that NSAIDs are not prescribed in association with high doses of fibrates. At therapeutic doses, fibric acid derivatives increase serum ALT and AST levels, which may relate to known transcriptional effects on liver transaminase synthesis. In cases of creatinine elevation, hyperproduction from muscle may be occurring, and concern over nephrotoxicity requires ongoing investigation and caution. Other adverse effects are recognised: 5–10% of patients experience musculoskeletal pain (mostly with bezafibrate treatment).

Early studies have evaluated the use of bezafibrate (400 mg per day) as an adjunctive therapy to UDCA, in which normalisation of serum ALP was reported in ~45% of patients who did not respond to UDCA *vs.* ~18% taking placebo [142]. More recently, a non-blinded prospective randomised-controlled study (n = 27; 100–120 months of treatment) reported that patients' serum ALP levels were significantly lower following combination therapy (UDCA + bezafibrate), and were associated with a trend towards improved overall survival (log-rank $p = 0.057$) [143]. Data from an open-label study (n = 28) also showed a significant improvement in itch severity in patients treated with bezafibrate, wherein all 12 patients who reported itch prior to starting treatment achieved complete or partial symptom resolution [144]. Moreover, 20 and 24 patients who did not respond to UDCA attained a serum ALP reduction >40% within 6 and 12 months, respectively, with combination bezafibrate therapy.

Pilot studies using fenofibrate + UDCA combination therapy have resulted in improvements to serum ALP [145,146]; according to one meta-analysis, a pooled complete biochemical response rate was achieved in 69% of patients [147]. A retrospective uncontrolled study [148] described improvements in short-term, liver decompensation-free and transplant-free survival using combination UDCA + fenofibrate therapy across a cohort of 120 prior UDCA non-responders, independently of liver biochemical changes ($p < 0.001$). However, concern remains about the nature of patient ascertainment, and the deterioration of some patients with rising bilirubin values.

The use of fibrates in PBC improves surrogate markers of long-term prognosis, however, the evidence supporting their use remains limited to small groups of patients with limited follow-up. Additionally, many studies have employed undefined biochemical end-points to measure treatment success, with only a few adopting standardised biochemical response criteria. The effects on fibrosis progression are also unclear, as some investigators report improvement through histological assessment, whereas others report a deterioration [149,150]. Moreover, the biochemical improvements associated with fibric acid derivatives have not been shown to alter sufficiently the long-term probability of liver-related death or the need for transplantation when stratified according to the UK-PBC risk score [151], and may be counterbalanced by possible negative impact on renal function [143]. As such, meta-analysis of existing bezafibrate randomised clinical trials show no significant improvement in patient survival compared to UDCA monotherapy [152], although liver transplantation and liver-related death were not presented as clinical end-points. Results from a phase III clinical trial of bezafibrate in PBC are not yet published (NCT01654731).

Recommendation

21. Data from phase III randomised trials for budesonide (in non-cirrhotic patients), and bezafibrate, both in combination with UDCA, are not yet published; EASL suggests currently a recommendation for therapy cannot be made (**II-2**, **2**).

Special settings: Pregnancy

Most patients are diagnosed at an age when pregnancy is not a relevant consideration, however, an important minority of patients with PBC are women of reproductive age. In this younger age range of patients with PBC, pregnancy may either be a reason

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for diagnosis (failure of resolution of obstetric cholestasis) or may be complicated by worsening pruritus. Significant medical risks are infrequent but can be relevant if patients have cirrhosis and portal hypertension; in this setting, management is no different to any other patient with an aetiology of cirrhosis (*e.g.* gastroscopy if there is concern over portal hypertension; exclusion of splenic artery aneurysm by ultrasound).

PBC-specific experience in pregnancy is limited to case-series but expert clinical opinion is that UDCA is safe during conception, pregnancy and post-partum [153]. Additionally, cholestyramine and rifampicin (third trimester onwards) are considered safe in pregnancy, although the data are limited [125,154]. In rare cases, the itch during pregnancy becomes unbearable and plasmapheresis may help [155]. In those with notable cholestasis, fat-soluble vitamin deficiency should be avoided. Post-partum cholestatic flares have been described, and clinical follow-up in the post-partum period is important.

Pre-pregnancy counselling should be pragmatic and individualised. Some reports have described added cholestasis in late pregnancy and post-partum, which may be deleterious particularly to those with an already intense ductopenic PBC variant. Similarly, patients with portal hypertension have the greatest risks associated with pregnancy, and should be appropriately counselled. Variceal bleeding can occur in patients with cirrhosis of any aetiology as a consequence of pregnancy-related increase in portal pressure. Such patients should undergo elective endoscopy for the evaluation of varices in the second trimester and be managed appropriately.

Recommendations

22. EASL recommends expert consultation for all pregnant patients to guide therapy, noting that pregnancy is typically well tolerated in non-cirrhotic patients with PBC. EASL recommends the continued use of UDCA in pregnancy, even though supporting data are limited. Pruritus management is important and may require specialist advice, noting that rifampicin has been used by experts during the third trimester (**III**, **1**).
23. Pregnancy in patients with cirrhosis carries a higher risk of maternal and foetal complications. EASL recommends offering patients pre-conception counselling and relevant specialist monitoring (**III**, **1**).

PBC with features of autoimmune hepatitis

PBC is characterised by varying degrees of hepatic inflammation. Classical PBC presents with only minimal lobular and interface hepatitis activity, however, around 8–10% of patients demonstrate features characteristic of AIH [156]. These patients are referred to as having 'AIH-PBC overlap syndrome', 'hepatitic form of PBC', or 'PBC with secondary AIH'. The pathogenesis of these variants is poorly understood [156–158]. Many regard PBC with features of AIH as the one end of the spectrum of hepatitis activity in PBC, however, others regard this syndrome as a separate disease. Here, the focus is on the pathways of diagnosis, which aim to identify patients who may benefit from combined treatment with immunosuppressants and UDCA.

Definition and diagnosis

Typical features of PBC and AIH usually present in patients simultaneously [156,158], but separate manifestations in patients with a prior diagnosis of PBC or AIH may occur even years after the primary diagnosis [159–161]. In patients with PBC that does not sufficiently respond to treatment with UDCA treatment after 6–12 months, features of additional AIH should always be investigated.

Patients presenting with features of PBC and AIH simultaneously
The Paris criteria are most commonly used to define the presence of PBC with features of AIH [162], and have been endorsed by EASL [37]. According to these criteria, a diagnosis can be made in a patient with PBC with at least two of the following:

(i) ALP >2× ULN or GGT >5× ULN.
(ii) AMA >1:40.
(iii) Florid bile duct lesion on histology.

And two of the following three features:

(i) ALT >5× ULN.
(ii) IgG serum levels >2× ULN or smooth muscle autoantibody positive.
(iii) Moderate or severe interface hepatitis on histology.

Liver biopsy is however considered mandatory in clinical practice [37].

It must be kept in mind that the Paris criteria differ from the respective single disease definitions of PBC or AIH [37,163]. The criteria have been shown to identify patients who have received corticosteroid treatment for the inflammatory component of their disease with a high specificity, albeit moderate sensitivity. The criteria are in line with the treatment indications for AIH defined in the current AASLD practice guidelines [164]. Most experts would agree that patients fulfilling the Paris criteria, especially regarding histological interface activity, should be considered for treatment with additional immunosuppression. However, it is unclear whether these cut-offs identify all patients with PBC who would potentially benefit from immunosuppression. This is important because the recent EASL Guidelines on AIH recommends treatment for patients with AIH at lower cut-offs for transaminase or IgG levels and a modified histological activity index as low as 4 (or more) out of 18 points [163].

Both the revised AIH score [165], and the more recently simplified AIH score [166] have been used to identify patients with PBC treated with corticosteroids retrospectively. These scores were not developed to diagnose cholestatic variants of AIH or to diagnose AIH in patients with PBC and therefore should not be used in clinical practice.

Autoantibodies against soluble liver antigen (SLA)/liver pancreas (LP) and double stranded DNA have been associated with presence of AIH in patients with PBC [167–169]. Therefore, testing these autoantibodies should be considered in the workup of PBC patients with suspected AIH.

Patients with known diagnosis of PBC who develop features of AIH
PBC patients under UDCA treatment may develop increasing hepatitis activity even years after the initial PBC diagnosis was made

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[161,160]. A liver biopsy should be obtained in these patients to determine the degree of interface hepatitis.

Patients with known diagnosis of AIH who develop features of PBC
Patients with diagnosed AIH and persistent elevation of cholestatic liver enzymes should be evaluated for the presence of PBC. PBC should also be included in the differential diagnosis of patients with AIH who develop elevated cholestatic liver enzymes over time along with typical symptoms for PBC (pruritus, sicca syndrome). AMA may be present in patients with acute hepatitis, with titres usually decreasing over time; this should be recognised when diagnosing PBC in a patient with pre-existing AIH, as well as that acute AIH may be associated with considerable bile duct damage [170]. Persistent presence of AMA in patients with AIH may not manifest as bile duct damage on histology or a clinical course different from AIH without AMA [171,172,158].

Treatment and prognosis

Patients with features of PBC and AIH presenting simultaneously or with PBC first
The prognosis of patients with PBC and features of AIH is worse than for PBC alone and patients tend to present with more advanced fibrosis [160,173,174]. As discussed, interface hepatitis has been reported as one of the histological predictors of PBC progression. However, larger long-term studies on the prognosis of patients treated with UDCA and corticosteroids or combined immunosuppression are lacking. Controlled clinical trials have not been – and probably will not be – performed in these patients. The PBC component should be treated with UDCA at a standard dose. The available data suggest that patients who fulfil the Paris criteria for the diagnosis of AIH either at presentation or during the course of their PBC may benefit from additional immunosuppression in the short- and medium-term [160,162,175,176]. Severe interface hepatitis, as the most reliable marker of hepatitis activity, mandates immunosuppression [175], and by extrapolating evidence from old controlled trials of AIH, patients with aminotransferase levels above 5× ULN and gamma-globulins >2× ULN have a poor prognosis if left untreated [163]. In patients with moderate interface hepatitis, immunosuppression should be considered. It remains unclear whether patients with a lower degree of interface hepatitis could benefit from immunosuppressive treatment, as was recently recommended for patients with AIH only [163].

Most patients have been treated with corticosteroids (mainly prednisolone/prednisone) and have shown overall response rates similar to patients with AIH [162,169,177–179]. When compared to patients with AIH, combined treatment with corticosteroids and azathioprine may result in less cumulative steroid-induced side effects. This combined treatment regime has been used in patients with PBC and features of AIH with high response rates [160,161,175,180]. It has been suggested that these patients respond to less intense immunosuppressive treatment and have higher rates of successful withdrawal of immunosuppression than patients with AIH only [175,176]. It is very important to be aware of corticosteroid side effects, particularly in patients with an underlying cholestatic liver disease. Withdrawal of immunosuppression should be considered in patients in remission, to avoid unnecessary treatment-related side effects. The time interval should be assessed based on the individual.

Patients with AIH who develop features of PBC
It is unclear whether patients with AIH who develop serological or histological features of PBC, benefit from additional therapy with UDCA. Given the low rate of adverse effects and the potential long-term benefit, it may be pragmatic to add UDCA to the treatment regime, especially in younger patients who may experience ductopenia and biliary cirrhosis during their lifetime.

Areas of uncertainty

Currently, there are several areas of uncertainty regarding patients with features of PBC and AIH:

(i) What are the cut-offs for IgG/gamma-globulins and transaminase levels used in clinical practice to indicate requirements for liver biopsy and subsequent immunosuppression in patients with PBC?
(ii) What is the grade of hepatitis activity (or level of surrogate parameters thereof) defining patients who will benefit from immunosuppression?
(iii) Is there a scoring system that allows identification of patients with PBC and AIH in clinical practice and studies?
(iv) What degree of histological bile duct damage defines PBC in patients with additional diagnosis of AIH and do these patients require treatment with UDCA in addition to immunosuppression?

Recommendations

24. Patients with PBC may present with additional features of AIH in around 10% of cases, most often simultaneously, but sometimes sequentially even years after diagnosis of PBC. EASL recommend that a 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**).
25. Patients with PBC and typical features of AIH may benefit from immunosuppressive treatment in addition to UDCA. EASL suggests immunosuppressive treatment in patients with severe interface hepatitis, and consideration in patients with moderate interface hepatitis. EASL suggests counselling for patients to inform them of the side effect profile of immunosuppressive treatments (**III**, **2**).

Management of symptoms and extrahepatic-hepatic manifestations

The symptoms associated with PBC have a significant impact on QoL for patients [29], and can be broad. Beyond the classical symptoms (pruritus, sicca complex and fatigue), patient-reported concerns may include bone pain, joint pain, abdominal pain, and restless legs. Currently, there is significant variation in patient management between centres and individual clinicians [6]. These guidelines will help standardise the approach to symptom management.

Screening for the presence of symptoms by asking patients about them specifically, followed by formal quantification of

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their impact on the patient, is essential for understanding the full impact of disease on the individual. Screening approaches can include Likert (a psychometric scale, commonly involved in research, that employs questionnaires) or visual analogue scales (well established for itch), and the use of more complex patient-derived measures, such as the multi-domain PBC-40 QoL measure [181,182]). Therapies for symptoms should be continuously evaluated rather than on an *ad hoc* basis, and it is important to re-evaluate symptoms and response to therapy. There is also a risk of symptoms recurring after therapy cessation, and most patients require long-term treatment. Patient support organisations (see "Patient support") are important sources of help for patients developing self-management approaches to their symptoms. The symptoms of PBC typically do not correlate with disease severity and do not improve with approved first-line (UDCA) and second-line (OCA) therapy.

Recommendation

26. EASL recommends the evaluation of all patients for the presence of symptoms, particularly pruritus, sicca complex and fatigue. Whilst end-stage liver disease is associated with progressive symptom burden, severity of symptoms does not necessarily correlate with stage of disease in PBC (**III**, **1**).

Pruritus

Pruritus is one of the characteristic cholestatic symptoms in PBC and results in impaired health-related quality of life (HRQoL) [183]. Many patients, however, will not experience it and its absence should not be considered when diagnosing the disease. Pruritus can occur at any stage of the disease process, and it has been reported to improve as liver disease worsens [184]. Patients with the ductopenic variant of PBC have particular problems with itch [68]. Follow-up of patients, and evaluation of change in pruritus and potential side effects, is appropriate when changes are made in anti-pruritic therapy. A structured approach to the management of pruritus has been shown to be effective. There is no evidence to suggest that UDCA has any effect on pruritus [6,127], whilst OCA at higher doses can exacerbate it.

Bile duct obstruction must be excluded as the cause of pruritus, given the increased risk of gallstone disease and related complications in PBC [185], although in practice this distinction is rarely problematic. Practical advice must also be given to patients and should encompass aspects of care including:

(i) Use of emollients and oat meal extract to improve dry and inflamed skin.
(ii) Use of cold water for baths or showers to provide some symptom relief of pruritus triggered or exacerbated by heat/warmth (at night).
(iii) Psychologic intervention for addictive scratching/scratch dependence.
(iv) Searching for added allergens, especially in patients with associated hypereosinophilia or IgE-mediated allergy.

Bile sequestrants are widely used as first-line therapy, despite a limited evidence base; tolerability is often an issue, with side effects including bloating and constipation [186]. Cholestyramine is a non-absorbable resin that may help relieve pruritus. Bile sequestrants must be given 2–4 h before or after other medications (including UDCA or OCA) as they interfere with intestinal absorption [187]. Patient education is important here (by clinicians and pharmacists) to avoid drug interactions. Colesevelam is a newer, often better tolerated, bile sequestrant, however, despite clinicians describing benefit and significant decreases in serum bile acid levels, a recent placebo-controlled trial failed to demonstrate effectiveness [188].

Rifampicin is a useful second-line agent, which probably acts through its function as a pregnane X receptor agonist [189]. Randomised, placebo-controlled trials have shown rifampicin to be effective in the management of cholestatic pruritus [190–193]. This effect has been confirmed in meta-analyses [194,195]. There are concerns over potential adverse effects with rifampicin (including hepatotoxicity and haemolysis) so patients commencing treatment require regular blood test monitoring [196]. Importantly, rifampicin also affects vitamin K metabolism and can lead to an increase in the INR, most notably in icteric patients [197].

Oral opiate antagonists (naltrexone and nalmefene) are used as third-line therapy as they can reduce the sensation of itching [194,198–200]. Naltrexone should be started at a low dose to avoid opiate withdrawal-like reactions in the first few days of treatment [201]. Long-term tolerability can be an issue, with many patients having ongoing opiate withdrawal-like reactions or reduced threshold to pain [202,203].

Selective serotonin reuptake inhibitors (SSRIs; *e.g.* sertraline) and gabapentin are used empirically in the management of cholestatic itch, typically in patients with pruritus unresponsive to other agents. SSRIs are presumed to act via altering the concentrations of neurotransmitters within the central nervous system. There are some reports of efficacy in the literature but only a single small placebo-controlled trial [204]. Side effects of SSRIs include dry mouth and patients should be warned about this. Gabapentin has been suggested as a potential treatment due to its proposed effect, increasing nociception threshold. However, a small trial failed to show benefit over placebo [205]. Further evaluation of gabapentin may be warranted, given the clinical experience. Anti-histamines sometimes have a non-specific anti-pruritic effect, which may be due to their sedative properties but are not recommended as specific therapy; they are, however, useful adjuncts for some.

Physical approaches, such as nasobiliary drainage [206,189,207,208], molecular absorbance recirculating system (MARS) [209] and ultraviolet (UV) light therapy [210] are all experimental, with case reports/series showing benefit but no formal trial evaluation [210,211]. UV light therapy is relatively easy to access in comparison to the other treatments. Nasobiliary drainage appears to provide transient relief from itching but requires repeated treatments, is technically complicated and difficult to tolerate; pancreatitis is recognised as a potentially significant complication. These techniques require further investigation. Their use should be restricted to specialist centres and as salvage therapy for patients with extreme pruritus unresponsive to medical therapy.

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Liver transplantation for cholestatic pruritus is highly effective in terms of rapid reduction in pruritus severity (frequently within the first 24 h of transplantation) [212]. Pruritus that is 'persistent and intractable' after therapeutic trials, is one of the variant syndromes, which is an indication for liver transplantation according to current guidelines.

Cholestatic pruritus is an area of active research, with several experimental agents and approaches under development. Trials of novel agents, including bile acid reuptake inhibitors and drugs targeting the autotaxin/lysophosphatidic acid pathway (recently implicated in cholestatic pruritus) are ongoing or in development [189,213]. New therapies are likely to emerge soon but need evaluation in a clinical setting [214].

Recommendations

27. EASL recommends treating pruritus using a step wise approach. Patients with severe pruritus may have an aggressively ductopenic variant of PBC, with a poor prognosis. EASL recommends the referral of these patients to an expert centre (**III**, **1**).
28. Given its favourable safety profile, EASL recommends cholestyramine as the first-line therapy for pruritus, despite its limitations. Attention should be paid to avoid interaction with other medications as a result of its anionic binding resin properties (**II-2**, **1**).
29. EASL recommends rifampicin as a second-line therapy for pruritus, usually at a dose of 150 mg–300 mg daily. EASL recommends monitoring serum liver tests after initial use (at 6 and 12 weeks following drug initiation) and following dose increase, because of potential hepatotoxicity The agent should be stopped if toxicity is observed (**II-2**, **1**).

Fatigue

Fatigue is frequently reported by patients (over 50%) and when severe (as it is in 20% of patients), it is a significant cause of QoL impairment [215–218,6,29]. There are peripheral and central components: central fatigue is frequently associated with cognitive impairment (poor memory and concentration), which can be mistaken for hepatic encephalopathy [219,220]. Fatigue is not related to severity of liver disease, with the exception of very end-stage patients where it is the norm [221], and it is not responsive to UDCA or OCA therapy [6,131]. The approach to fatigue and its management, therefore, needs to run in parallel with the management of the underlying disease process, as is the case for pruritus. Patients with post-transplant PBC typically experience ongoing fatigue, and thus, transplant for severe fatigue in the absence of other indications is not appropriate [221]. High quality clinical trials in this area are limited, and there is no licensed therapy. Fatigue in PBC, as in other chronic diseases, is inherently complex in nature and a structured approach is essential if improvement is to be seen [222]. A structured approach to management, quantifying fatigue and its impacts (through the use of tools such as the PBC-40 QoL measure), addressing contributing factors and helping patients to cope with its impact have been shown to be effective [222]. Emerging data show that social isolation can compound the QoL impairment seen with fatigue in PBC and this should be addressed with patients when developing coping strategies.

When addressing fatigue, it is important to identify other disease processes and therapies linked to PBC either directly or indirectly, which may be contributing. These include other autoimmune conditions such as hypothyroidism or autoimmune anaemias, and demography associated conditions or therapies, such as type II diabetes and anti-hypertensive therapy [223]. Pruritus at night, autonomic dysfunction, dehydration, restless legs, and concurrent medications (such as beta-blockers) can all be additive factors to fatigue burden. There is no evidence to suggest that exercise is harmful for patients with PBC fatigue. Indeed, there are pilot data to suggest that structured exercise may be beneficial when initiated at levels which can be tolerated by fatigued patients [224]. Modafenil has been used therapeutically, but any use should be limited to patients with formally diagnosed sleep disorders.

Recommendations

30. EASL recommends seeking and treating associated and alternate causes of fatigue, particularly anaemia, hypothyroidism and sleep disturbance (**III**, **1**).
31. EASL suggests advising patients with fatigue (which in some may be debilitating) on developing coping strategies, including the avoidance of social isolation, which can compound effects of fatigue (**III**, **2**).

Sicca complex

Sicca complex is common in PBC, and symptoms including dry eyes and/or dry mouth are frequently seen in patients [223,225]. Most patients have sicca symptoms rather than primary Sjögren's syndrome. Other symptoms may include dysphagia and vaginal dryness. Clinicians should specifically enquire about these symptoms. Artificial tears and saliva are often helpful. Pilocarpine or cevimeline (muscarinic receptor agonists) can be used if symptoms are refractory [226,227]. Patients with severe xerostomia should be given oral hygiene advice to prevent the development of dental caries. Clinicians should also be vigilant of the risk of oral candidiasis in patients with severe xerostomia. Vaginal moisturisers may be helpful but the use of oestrogen creams should be directed in primary care or by a gynaecologist (there are no concerns from a hepatology perspective). Specific guidelines for the management of sicca symptoms and Sjögren's syndrome should be consulted for further details [228]. Patients with refractory symptoms should be referred for specialist management, as evolving new therapies exist.

Recommendation

32. Sicca symptoms can be significant and reduce patient QoL; where appropriate EASL recommends considering patients for referral to expert clinicians (**III**, **1**).

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Miscellaneous

Up to one-quarter of patients with PBC have Raynaud's phenomenon which occurs due to spasmodic arterial contraction in the extremities (usually fingers and toes, but sometimes ears and nose) [223]. Patients should be asked specifically about the classical symptoms of their extremities turning white, then blue and finally red, often associated with pain/burning/tingling when the blood flow returns. Practical measures, such as wearing gloves, using hand warmers and avoiding cold environments, are often all that are needed for mild symptoms. For more marked symptoms, vasodilators such as calcium channel blockers, can be used [229]. Specialist rheumatological advice should be sought for severe symptoms and those at risk of digital ulceration. Approximately 8% of patients with PBC have limited scleroderma (CREST syndrome: calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia) [223]. These symptoms should be sought and if present, patients should be referred for rheumatology advice.

Recommendation

33. EASL recommends referring patients with symptoms resistant to medical therapy for specialist management, regardless of disease severity (**III**, **1**).

Management of complications of liver disease

Osteoporosis

Osteoporosis is a common complication in patients with PBC [230,231]. However, variations in studies (mainly in the case mix *e.g.* different age, disease severity and degree of cholestasis), mean that the degree of increased risk of osteoporosis in patients with PBC is unclear. Good nutrition is recommended to prevent and to treat osteoporosis, as well as the suppression of other risk factors (*e.g.* smoking cessation and weight bearing exercise). Supplements of calcium (if there is no history of renal stones) and vitamin D can be considered, with particular care in patients receiving resins, because their administration may reduce the intestinal absorption of vitamin D. Although calcium and vitamin D supplements are frequently provided, there are no data to support or to refute this treatment approach. In patients with normal nutritional status and lack of features of calcium malabsorption (such as acid-suppression or malabsorption) calcium supplementation is not recommended. Vitamin D levels can be monitored. There is no agreement concerning the appropriate time to start treatment, however, it seems reasonable to treat patients with a femur T-score lower than −1.5 [232]. Any intervention for osteoporosis must account for overall fracture risk, which can be calculated by the WHO FRAX score (http://www.shef.ac.uk/FRAX/) for example. Several trials have demonstrated that bisphosphonates, especially weekly alendronate and monthly ibandronate, are effective in increasing bone mass in patients with PBC [233]. The bone mass increase after treatment with alendronate in PBC is comparable to that described in patients with post-menopausal osteoporosis. Oral nitrogen-containing bisphosphonates may cause upper gastrointestinal gastritis or esophagitis [234], and therefore must be used with caution in patients with oesophageal varices; in such patients parenteral bisphosphonates (*e.g.* pamidronate, ibandronate or zoledronic acid) may be considered [235]. Hormone replacement therapy is effective in post-menopausal female patients [236]. Bone mineral density assessment (dual-energy X-ray absorptiometry [DEXA]) is a useful guide for treatment and should be undertaken at presentation, with follow-up assessment between 1 and 5 years later depending on outcome and general osteoporosis risk [237].

Recommendations

34. EASL recommends considering the risk for osteoporosis in all patients with PBC (**III**, **1**).
35. As part of evaluating the risk of osteoporosis, EASL recommends considering the use of DEXA to assess bone mineral density at presentation and at follow-up where indicated (**III**, **1**).
36. EASL suggests supplementing patients with PBC with calcium and vitamin D, according to local practice (**III**, **2**).
37. Bisphosphonates are safe and effective treatments for patients with PBC and significantly elevated fracture risk from osteoporosis but EASL recommends caution when using them in patients with varices. EASL recommends therapy initiation following specific osteoporosis guidelines (**II-2**, **1**).

Fat-soluble vitamin substitution

The cholestasis that affects patients with PBC and the subsequent reduced bile acid secretion, may result in increased risk of lipid malabsorption. However, deficiencies in the fat-soluble vitamins A, D, E, and K are uncommon in PBC [238–240]. In most patients with PBC, serum levels of 25-hydroxy vitamin D and 1–25 dihydroxy-vitamin D are normal, apart from in patients with prolonged jaundice, patients awaiting liver transplantation, and patients with osteomalacia. Children have higher degree of fat and fat-soluble vitamin malabsorption compared to adults with cholestasis. Measurement of serum vitamin D levels and other fat-soluble vitamins should be considered in patients with PBC; a lower threshold for supplementation should be applied, particularly if the patient is icteric. Vitamin K supplementation should be given prophylactically in severe cholestasis prior to any invasive procedure and in the context of bleeding episodes.

Recommendation

38. Fat-soluble vitamin malabsorption can occur in patients with PBC, particularly those with prolonged jaundice. EASL suggests that supplementation should be considered on an individual basis (**III**, **2**).

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Hyperlipidaemia

Serum lipids can be elevated in up to 80% of patients with PBC [49]; the underlying mechanism of hyperlipidaemia is different from that in other conditions. In early disease, elevated very low density lipoprotein (VLDL) and LDL concentrations are reported, as well as significantly elevated HDL values. As disease progresses, LDL may increase further, but HDL values fall (although they may still be elevated compared with controls). Triglyceride levels are usually normal or slightly elevated. Some of the excess LDL in PBC is composed of an abnormal lipoprotein particle (lipoprotein X), that is rich in free cholesterol and phospholipids, and is anti-atherogenic [241]. It is clinically significant that HDL cholesterol is elevated whilst LDL cholesterol is not, and patients with PBC are not at increased risk of death from atherosclerosis, which is the case for patients with increased serum lipid levels without PBC [49,50]. Patients are not treated routinely for PBC associated hyperlipidaemia, but in those with concomitant classical cardiovascular risk factors, treatment should be administered as per normal practice. Where clinical equipoise remains, review in a dedicated hyperlipidaemia clinic may be appropriate.

Recommendation

39. Hyperlipidemia is a feature of cholestasis, for which there is no substantial evidence to support an elevated cardiovascular risk in patients with PBC. In the subgroup of patients with PBC and metabolic syndrome (with high cholesterol, low HDL cholesterol and high LDL cholesterol levels), EASL suggests considering a pharmacologic approach with cholesterol-lowering agents on a case-by-case basis; treatment is not contraindicated (**III**, **2**).

Varices

Patients with PBC may develop portal hypertension as a result of biliary cirrhosis [242,243], and this is associated with poor prognosis. In contrast to other liver diseases, portal hypertension in patients with PBC may develop in the early and pre-cirrhotic stage of the disease, in association with nodular regenerative hyperplasia, although this is rare [244]. In one study, however, [245] whilst 6% (8/127) of early-stage patients with PBC had varices, 95% of patients with varices, nevertheless had markers of high-risk disease: male sex, low albumin, elevated bilirubin, and/or elevated INR. This is consistent with prior studies showing that in patients with PBC, a platelet count of $<140 \times 10^9$ cells/L and/or a Mayo risk score of $\geqslant 4.5$ appears to identify those patients more likely to benefit from a screening endoscopy [246]. Another study [247] demonstrated that a platelet count of $<200 \times 10^9$ cells/L, serum albumin <4 g/dl and serum bilirubin >1.2 mg/dl were independent risk factors for the presence of esophageal varices (>90%). The management of gastroesophageal varices and variceal haemorrhage in patients with PBC can therefore be led by the Baveno-VI guidelines [248]. Screening, prophylaxis and treatment approaches should be applied in the same way as in other chronic liver disease settings [248]: LSM $\geqslant 20$ kPa or a platelet count $<150 \times 10^9$ cells/L. Non-selective beta-blockers are indicated in patients with large oesophageal varices, which is similar to liver cirrhosis due to other causes [248]; however, patients with fatigue may find added beta-blockade challenging symptomatically. Eradication of oesophageal varices by endoscopic variceal ligation is recommended to prevent an initial bleed in patients with varices at high-risk of bleeding. The Baveno-VI guideline [248] suggests that the availability of local resources and expertise should guide what intervention to use.

Recommendation

40. EASL suggests that the Baveno-VI guidelines for screening and management of varices apply equally to patients with PBC (**III**, **2**).

Hepatocellular carcinoma

As with almost any form of cirrhosis, patients with PBC may develop complications due to the chronicity of their disease. One of the most serious is the development of HCC. The incidence of HCC among patients with diagnosed PBC is estimated at 0.36 per 100 person years. Higher histological stage on liver biopsy denotes an increased risk for HCC in patients with PBC [249]. A recent multicentre study from North America and Europe, based on prolonged observation of 4,565 patients with PBC, showed an incidence rate of 3.4 HCC cases for every 1,000 patient-years [8]. This internationally representative cohort demonstrated that male sex was a confirmed risk factor for HCC development in PBC, as well as inadequate response to UDCA; indeed, men without advanced disease who are UDCA non-responders are at a higher risk of developing HCC than women with cirrhosis who respond to UDCA, highlighting the importance of risk stratification in the management of PBC [8]. Regular screening for HCC with cross-sectional imaging with or without alpha fetoprotein at 6-month intervals is currently recommended for patients with cirrhosis, according to EASL guidelines [250].

Recommendation

41. EASL suggests that in patients with suspected cirrhosis, HCC surveillance according to EASL guidelines is indicated (**III**, **2**).

Liver transplantation

Although its prevalence is increasing, PBC as an indication for liver transplantation has declined over the past decades [251–253]. Indications for liver transplantation in patients with PBC are similar to other aetiologies. Evaluation for liver transplantation, however, inevitably varies across centres and countries. It should be considered if complications of cirrhosis have occurred, based on disease severity scores (*e.g.* if the MELD score reaches 15 or more points), if bilirubin values are rising progressively above 50–85 μmol/L (3–5 mg/dl) [72] and in selected patients with intractable pruritus refractory to medical treatment [254,255] The outcome of liver transplantation usually is favourable, and

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with 5-year patient survival rates of 80–85%, better than for most other indications for liver transplantation [251–253]. Symptoms including fatigue frequently persist after transplantation [221,256] and fatigue is not an indication for transplantation. Post-transplant care should adhere to current guidelines and take into consideration the increased risk of osteoporosis and concomitant autoimmune diseases such as thyroid disease [255,257]. The use of tacrolimus has been associated with an increased rate of recurrent PBC. To date, however, there is insufficient data to recommend one immunosuppressive regime over another [255,253,257,258].

PBC recurrence has been reported in 20% of patients on average [253,258] but the rate of histological recurrence is likely higher [259]. AMA persists after liver transplantation. The diagnosis of recurrent PBC requires liver histology if sought because liver enzymes may be normal [258]. However, recurrent PBC infrequently leads to graft loss and current evidence does not suggest an impact on graft or patient survival after transplantation [253,257,258]. Therefore, to date, protocol biopsies cannot be recommended after transplantation for PBC for the early diagnosis of recurrent PBC. Treatment with UDCA lowers liver enzymes and may lower the incidence of recurrent PBC [259], but there is insufficient evidence to make an absolute recommendation for its use post-transplant. In practice, UDCA is considered in patients with suspected recurrent PBC, and frequently prescribed. Osteoporosis post-transplant should also be proactively managed.

Recommendations

42. EASL recommends considering patients for transplant assessment when they present 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. EASL recommends that listing for transplantation should follow local (usually national) guidelines (**II-2**, **1**).
43. EASL suggests that in patients with proven or likely recurrent PBC post liver transplant, the use of UDCA is safe and can improve liver biochemistry (**II-2**, **2**).

Organisation of clinical care delivery

The advent of stratified therapy in PBC (second-line therapies for patients under-responsive to UDCA and targeted therapies for symptoms) has increased both the complexity of management of PBC, and the challenge of effective and equitable delivery of optimal care in practice. Optimal care delivery models (in which the needs of high-risk patients or those with a high symptom burden are met, whilst avoiding the over-management of low-risk and asymptomatic patients) will need to be flexible to reflect different international health care delivery models. The delivery of care for patients with PBC in an equitable and effective manner in Europe will be aided by the development of the RARE-LIVER ERN (http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf_en), which will include in its remit, the implementation of these and other care guidelines in rare liver diseases into practice. The ERN will also be producing patient summaries of guidelines, with the goal that patients with PBC can be offered a lay version, available in their native language. The following aspects of care delivery should be considered:

Care pathways

Care pathways, which translate recommendations of clinical care delivery into practical clinical tools, facilitating structured clinical assessment and care delivery, represent an important opportunity. Pathways will play a key role in advising who should be responsible for the oversight of patients with PBC. Based on the nature and risk profile of their disease, this can potentially range from primary care physicians to tertiary/transplant-centre experts. It is recommended, however, that all patients with PBC undergo annual assessment of their disease in terms of treatment needs and symptom status, as a minimum. Pilot work in PBC has demonstrated an increased efficiency of care, and high patient satisfaction when local pathways are developed. A key task of the RARE-LIVER ERN network will be the development of a care pathway to accompany these guidelines, which will outline the key steps in management and facilitate their delivery in practice.

Recommendations

44. EASL recommends that all patients with PBC should have structured life-long follow-up, recognising that patients have different disease courses, and may require varied levels of attention (**III**, **1**).
45. EASL suggests the development of a Care Pathway for PBC based on these guidelines, following its approval (**III**, **2**).

Clinical care standards

Audit represents an essential tool for improvement of care delivery at the local level. To date there have been no recognised audit standards for treating patients with PBC, which can be used to develop local quality improvement programmes. The emergence of more complex management paradigms makes this increasingly important. Based on the guidance in this document, the following outline standards are proposed for phased implementation, according to local resources and practice.

(i) To exclude alternate aetiologies for cholestasis, all patients with suspected PBC should have an abdominal ultrasound as part of their baseline assessment **(standard 90%)**.
(ii) UDCA at 13–15 mg/kg/day is recommended for first-line use in all patients with PBC **(standard 90% of patients receiving therapy at adequate dose or documented to be intolerant)**.
(iii) To facilitate the identification of patients at risk of progressive disease, individualised risk stratification using biochemical response indices should be documented following one year of UDCA therapy **(standard 80% of patients receiving UDCA therapy to have their response status recorded in the notes and the criteria used recorded)**.

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(iv) To highlight the impact on QoL and to ensure appropriate investigation and treatment, all patients should be evaluated for the presence of symptoms, particularly pruritus, sicca complex and fatigue **(standard 90% of patients have the presence/absence of pruritus, sicca complex and fatigue recorded in the notes in the last year)**.

(v) To maximise the opportunity for all patients to be considered in a timely way for liver transplantation, all established patients with a bilirubin >50 μmol/l (3 mg/dl) or evidence of decompensated liver disease (variceal bleed, ascites, encephalopathy) should be discussed with a hepatologist linked to a transplant programme **(standard 90% documentation that discussion has taken place within 3 months of a relevant clinical event and the actions taken recorded)**.

(vi) To optimise prevention of osteoporotic bone fractures, all patients with PBC should have a risk assessment for osteoporosis. Treatment and follow-up should be according to national guidelines **(standard 80% assessment within the last 5 years)**.

(vii) To ensure timely but considered diagnosis and treatment, PBC with features of AIH should be recognised as rare, and when suspected, liver biopsy with expert clinicopathological assessment, is recommended to make the diagnosis **(standard 90% of patients in whom the diagnosis of PBC with features of AIH is made should have had liver biopsy confirmation and clinicopathologic discussion noted)**.

Recommendation

46. EASL suggests that clinicians caring for patients with PBC should use standardised clinical audit tools to document and improve the quality of care delivered to patients (**III**, **2**).

Patient support

Qualitative research has shown that factors such as knowledge, information, consistency, a positive approach, simplification and repetition, lead to a positive PBC diagnosis experience for patients [260]. Leaflets are available from a number of patient support groups and are written by clinicians with patient input. Several on-line resources are available for patients if they wish and relevant web-sites include:

- Austria: http://www.gesundeleber.at/
- Europe: http://www.elpa-info.org/
- France: http://www.albi-france.org
- Germany: http://www.leberhilfe.org/
- Italy: http://www.fondazionefegato.it/
- The Netherlands: http://www.leverpatientenvereniging.nl
- Norway: https://www.fal.link/
- Spain: http://www.albi-espana.org/
- United Kingdom: http://www.pbcfoundation.org.uk/

Fatigue is the symptom that has the biggest impact on patients. Fatigued patients perceive a poor QoL compared to controls, and their levels of social engagement are lower [29,30]. Very little is written in relation to social isolation and improving support mechanisms in PBC, but there are several telephone helplines and patient support groups that offer free qualified peer support to patients. It can be helpful for details of helplines to be suggested to patients who may be at risk of social isolation. There may be scope for psychological approaches, such as cognitive behavioural therapy, to be used to support patients with PBC. Such approaches have been found to be effective in other chronic conditions for managing distress resulting from debilitating symptoms. The psychological impact of fatigue in PBC was explored using semi-structured interviews and validated assessment tools for psychological symptoms. Patients with PBC who reported high levels of fatigue were found to be more vulnerable to emotional distress and were more likely to perceive that their QoL had been negatively affected [261]. It is recommended that a patient with profound psychological distress associated with fatigue should be referred to appropriate psychological services for assessment. It may also be relevant to provide additional family support.

Recommendation

47. EASL suggests that patients with PBC should be informed of the support available from patient support groups, including access to patient education material (**III**, **2**).

Conclusion

PBC is a common cause of chronic cholestasis, most notably in women over the age of 40. Disease progression results in end-stage liver disease, and many pre-treatment and on-treatment stratifiers of risk have been identified. Diagnosis can be made based on liver biochemical and serologic findings and UDCA treatment initiated in all, using a weight based approach to prescription. All patients need evaluation at diagnosis and on-treatment for their individual risk of disease progression based on biochemical, serologic and imaging markers that correlate with risk and stage of disease. For those with an inadequate biochemical response to UDCA, there is now a licensed second-line agent (OCA) as well as several new and repurposed drugs in late stage development and clinical trials. As a symptomatic disease, patients with PBC need attention in an ongoing manner, not only for the prevention of end-stage liver disease, but also for co-existent symptoms such as pruritus, sicca complex and fatigue. Treatment guidelines facilitate a holistic life-long approach to the management of patients with PBC, and care pathways should be developed locally to capture the needs of patients. These can be subject to independent quality evaluation.

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Conflict of interest

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