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Authors:
Albert Parés, Albert Parés on behalf of Leading PBC Group*

* Leading PBC Group: Albert Parés

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Practical management of primary biliary cholangitis

Albert Parés[1] on behalf of Leading PBC Group*

[1]Hospital Clínic de Barcelona, CIBERehd, IDIBAPS, University of Barcelona

Corresponding author:

Albert Parés

Liver Unit, Hospital Clínic de Barcelona, CIBERehd, IDIBAPS, University of Barcelona.

Carrer de Villarroel, 170 - 08036 Barcelona (Spain)

e-mail: pares@ub.edu

ABSTRACT

Primary biliary cholangitis (PBC) is a chronic and cholestatic liver disease of autoimmune pathogenesis that mainly affects middle-aged women. Patients show elevated alkaline phosphatase and bilirubin levels as the disease progresses. The main symptoms of the disease are pruritus and fatigue, which interfere with the quality of life of patients. Progressive damage leading to end stage liver disease could require liver transplantation. Despite the efficacy of ursodeoxycholic acid (UDCA), the current standard of care for PBC, up to 40% of patients have an inadequate response to the treatment, requiring a second-line therapy. Obeticholic acid is the only second-line treatment approved for PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in patients intolerant to UDCA. Although different clinical guidelines for the diagnosis and management of PBC have been published, PBC is still challenging for many physicians. In this article we briefly review the main characteristics of the disease and include a practical user-friendly algorithm for the diagnosis and management of PBC developed by Spanish PBC experts and based on the European Association for the Study of the Liver recommendations.

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Keywords: Primary biliar cholangitis. Autoimmune disease. Patient management. ursodeoxycholic acid. Obeticholic acid.

Abbreviations:

AIH autoimmune hepatitis
ALP alkaline phosphatase
ALT alanine aminotransferase
AMA anti-mitochondrial antibodies
ANA anti-nuclear antibodies
APRI AST/platelet ratio index
AST aspartate aminotransferase
EASL European Association for the Study of the Liver
ELF enhanced liver fibrosis
GGT gamma-glutamyl transpeptidase
HLA human leukocyte antigen
HVPG hepatic venous pressure gradient
LLN lower limit of normal
LSM liver stiffness measurement
OCA obeticholic acid
PBC primary biliary cholangitis
QoL quality of life
UDCA ursodeoxycholic acid
ULN upper limit of normal
VCTE vibration-controlled transient elastography

1. Introduction

Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, is a non-suppurative, granulomatous, lymphocytic cholangitis, mainly affecting women (ratio women:men of 10:1), that leads to cholestasis, ductopenia, and progressive fibrosis (1). Since it is a rare disease, very few epidemiological studies have been published. The estimated annual incidence rate in Spain ranges between 0.51-3.86 cases per 100,000 inhabitants (2). The incidence of PBC may have changed during the last years due to an increase in the number of early diagnoses, diagnose of overlap syndromes,

and the development of more sensitive diagnostic tests (2).

This article describes a practical easy-to-use algorithm for the diagnosis and management of PBC. This algorithm was developed by PBC experts based on the European Association for the Study of the Liver (EASL) recommendations.

2. Characteristics of the disease

PBC is an autoimmune disease in which the immune system targets the cholangiocytes leading to the destruction of intrahepatic bile ducts. However, it is suggested that other genetic and environmental factors could participate (3,4). Several studies have evaluated which genetic and environmental factors are related to PBC, but the only ones that have been shown to significantly increase the risk of PBC are a family history of PBC, psoriasis, recurrent urinary infections, and history of smoking (5,6). Although the main factor that suggest a genetic component is family history of PBC, human leukocyte antigen (HLA) has been confirmed to be associated with PBC (1,7).

2.1. Natural history

PBC develops in four phases (1). The first one is a pre-clinical phase with a median duration of >10 years, in which only auto-antibodies generated by the immune system are detected, specifically anti-mitochondrial antibodies (AMA). However, it is known that approximately 20% of the patients with elevated levels of AMAs will eventually develop PBC (8). Other auto-antibodies specific to this disease are the anti-nuclear antibodies (ANA), anti-gp210 and anti-sp100 (1).

In the second and third phase (asymptomatic and symptomatic), with a median duration of >5 and <10 years respectively, there are high levels of the enzymes of cholestasis such as alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT). As the disease progresses, the increase in inflammation and necrosis in hepatocytes and cholangiocytes lead the fibrosis evolution. In fact, fibrosis has been considered a histological factor though to predict long-term outcome in PBC (9).

In the pre-terminal phase (<3 years), the most advanced phase of PBC, fibrosis progresses to cirrhosis and critical complications emerge because of portal hypertension, including ascites, variceal bleeding or jaundice. Moreover, as end-stage

of PBC, cirrhotic patients could develop a hepatocellular carcinoma. Once liver damage reaches a critical threshold, liver function is so impaired that the only options are liver transplantation or death (1).

In addition to the typical form above described, there are two other forms of PBC namely PBC with features of autoimmune hepatitis (AIH) and the ductopenic form, which affect 10-20% and 5-10% of patients, respectively. Both forms show a more severe course, even with a quick progression towards cirrhosis in less than 5 years (10).

2.2. Symptoms and clinical presentation

Common symptoms of PBC are fatigue and pruritus (1). Although not all patients develop these symptoms, many PBC patients present them. Regardless the fact that the disease arises primarily in middle-aged women, osteopenia (33%) and osteoporosis (11%) are observed, mainly as a result of decreased bone formation (11). In addition, hypercholesterolemia is also common in PBC patients, though it is not correlated with an increased risk of cardiovascular events (12).

Fatigue can be present in up to 85% of PBC patients and is often associated with depression (1,13). Severe fatigue can disturb patient's quality of life (QoL) and may be associated with overall decrease of survival, although its severity is poorly correlated with the clinical stage of the disease (14). A substantial proportion of PBC patients have severe fatigue even after liver transplantation (1,13). There are no specific interventions to reverse fatigue in PBC, although supportive care will improve patients' capacity to cope (15). Only modafinil has been reported to provide significant benefit for PBC patients with fatigue and prominent daytime somnolence (Table 1) (16).

Pruritus affects 20-70% of patients with PBC, having a negative impact on QoL (1,13). Although pruritus underlying physio-pathological mechanism is still unknown, it is thought that lysophosphatidic acid may play a critical role in cholestatic pruritus (17). Moreover, uncontrolled and refractory pruritus is an indication for liver transplantation among PBC patients (15). For the management of this symptom, EASL guidelines recommend bile sequestrants as first-line treatment, such as cholestyramine and colesevelam; rifampicin as second-line agent; naltrexone as third-line; and selective serotonin reuptake inhibitors and anti-histamines as alternatives

(Table 1). Other therapeutic strategy proposed to treat pruritus are fibrates such as bezafibrate. These drugs have shown to improve liver biochemistries in patients with PBC, but also to improve moderate to severe pruritus in these patients, achieving a complete or partial itching relief (18,19).

Patients with PBC, particularly women, have a higher incidence of comorbidities associated to autoimmune diseases. These disorders might impair QoL but do not decrease survival rates in PBC. The most frequent concomitant autoimmune diseases reported in women with PBC are Sjögren's syndrome (7-34%), Raynaud's syndrome (9-13%), Hashimoto's thyroiditis (11-13%), rheumatoid arthritis (3-8%), psoriasis (6%), CREST syndrome (1-2%) and inflammatory bowel disease (1%) (4).

3. Reaching a secure diagnosis of PBC

The main diagnostic recommendations for PBC include assessing clinical and biochemical abnormalities, detecting immunological markers, and imaging procedures (15,20). Patients presenting symptoms such as fatigue or pruritus or persistent cholestatic abnormalities in liver biochemistries should be suspected for PBC. Aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio >1 may be a marker of ongoing liver fibrosis. In addition, GGT can be identified prior to rises in ALP. Hyperbilirubinemia is observed as PBC progresses and in patients with the ductopenic presentation (15,20).

The main laboratory markers include a combination of abnormal high levels of ALP (PBC subrogate gold-standard marker) and the presence of AMAs in serum (titer >1/40). However, ANA immunofluorescence or ELISA tests (detecting anti-gp210 and anti-sp100) should be assessed among patients with suspected PBC but without elevated AMA levels (15,20). AMAs are very sensitive and specific for PBC. These auto-antibodies are detected in nearly 95% of patients with this disease (1). However, some patients have elevated AMA levels in the absence of elevated ALP (8). In these cases, a close follow-up is recommended to detect any potential elevation episode of ALP levels. Since between 50-70% of PBC patients showed elevated levels of ANAs, the detection of specific anti-gp210 or anti-sp100 ANAs should be considered for the diagnose in those patients with normal levels of both AMAs and ALP (21,22). Despite

the utility of these markers, up to 31% of patients initially diagnosed with PBC are lost during the follow-up, so the current prevalence of PBC may be underestimated (23).

Regarding imaging procedures, an abdominal ultrasound should be done in patients with suspected PBC to discard extrahepatic causes of cholestasis or liver neoplasms. Imaging of the liver can also identify features of advanced disease, which are similar to other chronic liver diseases (15).

Since serological markers provide a high specificity, liver biopsy is not necessary for PBC diagnosis, though it may be still essential when PBC-specific antibodies are absent and high levels of ALP are detected, or when there is clinical suspicion of overlap of PBC with other diseases, such as AIH or non-alcoholic steatohepatitis (15). In early stages, PBC is characterized by non-suppurative inflammation (mostly of T lymphocytes associated with few B lymphocytes, macrophages and eosinophils), which surrounds and destroys interlobular and septal bile ducts. Classically, four stages of PBC can be identified according to the histological classification of Ludwig and Scheuer in the biopsy sample. This classification is based on the progressive increase in bile duct damage that leads to ductopenia, inflammation and collagen deposition (15,24-26). However, a new staging system for PBC has been proposed (Nakanuma scoring system) that considers the necroinflammatory activity and histological heterogeneity (27). This Nakanuma's histological staging system considers three histological features reflecting the progression of PBC: fibrosis, bile duct loss and the deposition of copper-binding proteins (27).

4. Prognostic markers for disease risk stratification

All patients should be evaluated for the risk of developing end-stage complications and the need for additional treatments. Markers for risk stratification in PBC may consist of demographic data, symptoms, serum liver tests, serological profiles, serum markers of fibrosis, liver stiffness measurement, histological features, and direct measurement of portal pressure (15,28-32).

Age is one of the risk factors that significantly determines a poorer prognosis (30). Younger patients (<45 years) often are symptomatic and less likely to have good response to standard treatment with ursodeoxycholic acid (UDCA). On other hand,

mortality rates in older patients with asymptomatic PBC are similar to general population (29). Additionally, PBC male patients have a worse prognosis probably because of a delayed diagnosis, more advanced disease at presentation, lesser biochemical response to UDCA, and higher risk of developing hepatocellular carcinoma (28).

The impact of the disease symptoms on the survival of PBC patients is still unknown. While some studies report that asymptomatic patients at diagnosis show no significant survival differences compared to matched healthy controls (33), other studies suggest that the presence of symptoms at diagnosis decreases survival or increases mortality rates (33-35). Nevertheless, it has been reported that the presence of fatigue and pruritus at the time of diagnosis is associated to more aggressive variants of PBC (36).

PBC-specific ANAs are more frequently observed in patients with severe PBC, since the presence of these ANAs have been reported to be associated to higher rates of portal hypertensive phenotype (37). Moreover, serum bilirubin is a major predictor of poor outcome in PBC. Indeed, both abnormal bilirubin and albumin values are able to categorize UDCA-treated patients in high-risk (38). An elevated International Normalized Ratio (INR) and a lower platelet count are also markers of poor prognosis (15,39).

Fibrosis allows clinician to assess patient risk accordingly. Enhanced Liver Fibrosis (ELF) and AST/platelet ratio index (APRI) scores have been validated as predictors of worse prognosis (39,40). Liver stiffness measurement (LSM) is shown to be one of the best surrogate markers for the detection of cirrhosis or severe fibrosis in PBC patients and it is assessed by noninvasive vibration-controlled transient elastography (VCTE) (31). A baseline LSM >9.6 kPa and an increase of 2.1 kPa/year are associated with 5.1- and 8.4-times increased risk of adverse outcome, respectively (31). The newest EASL Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis recommends that in patients with PBC, LSM by transient elastography is the best surrogate marker for ruling in severe fibrosis/compensated advanced chronic liver disease and should be used for this purpose using a cut-off of 10 kPa (15).

Advanced histological features are associated with poor prognosis. Although liver biopsy is not mandatory for diagnostic purposes, it may be useful to characterize and

quantify histological features that underlie the treatment resistance (i.e., patients who have an inadequate response to UDCA). A new histological and grading system has been shown to reflect liver dysfunction before UDCA treatment and to correlate with the future development of cirrhosis-related conditions (41). Finally, direct measurement of hepatic venous pressure gradient (HVPG) in PBC has been shown to correlate with the probability of death or liver transplant (32).

5. Treatment

The main treatment recommendations of the EASL guidelines include oral UDCA as the first-line therapy for all patients with PBC. Obeticholic acid (OCA) is recommended as the second-line therapy in combination with UDCA for patients with an inadequate response to UDCA, or as monotherapy in those intolerants to UDCA (Table 1). These guidelines also propose off-label treatments for PBC, such as budesonide or fibric acid derivatives, but EASL does not offer any recommendations about them since the results of their studies were not published at the time the guideline was written (15).

5.1. Ursodeoxycholic acid

Current standard of care for PBC is UDCA (15). UDCA is a bile acid that is present in human bile and has been used for more than 25 years in the treatment of cholestatic liver diseases. This drug is administered at a dose of 13-15 mg/kg/day and has four mechanisms of action: 1) diluting the bile acid pool; 2) increasing bile acid secretion; 3) cytoprotective effects; and 4) immune response effects. In patients with an adequate biochemical response, UDCA improves liver biochemistries, delays histological progression and increases liver transplant-free survival and overall survival (42). This treatment should be given as soon as possible because patients who receive treatment in advanced stages of the disease have lower survival (42). It has been shown that significant duct loss at baseline predicted both failure to UDCA treatment and histological progression. In addition to cirrhosis, elevated GGT and ALP at diagnosis has been recently identified as associated risk factors for incomplete response to UDCA (43). Up to 83.3% of patients with an inadequate response to UDCA have histological progression, as compared with 20.5% of responders, according to a 10-year

histological progression of disease study (9).

In recent years, different response criteria to UDCA in PBC have been validated, but the percentage of non-responders is different among them (9,44-48). Using Barcelona criteria, biochemical response to UDCA after 1 year is associated with similar survival to matched control population. On the other hand, survival of patients without biochemical response was lower compared to control population though higher than that predicted by the Mayo model (patients without any treatment) (44).

Most response criteria evaluate both ALP and bilirubin levels, as they are surrogate markers of the disease. EASL guidelines state that survival rates of early-stage PBC patients with ALP <1.5 x upper limit of normal (ULN) and normal bilirubin after one year of therapy with UDCA, are not significantly different from healthy population. In contrast, patients with ALP >1.5 x ULN and abnormally high bilirubin levels have a compromised survival compared to the control population (15).

5.2. Obeticholic acid

OCA is a farnesoid X receptor agonist recommended for PBC in combination with UDCA in patients with an inadequate response to UDCA, or as monotherapy in patients intolerant to UDCA, at a starting dose of 5 mg once daily, and a maximum dose of 10 mg once daily in patients who are non-cirrhotic or with Child-Pug A cirrhosis (49). This indication was approved under accelerated approval based on the results of the POISE trial, a phase III double-blind study that assessed the 12-month efficacy and safety of OCA in combination with UDCA in patients with PBC who had an inadequate response to UDCA (93%) and as monotherapy in patients who experienced unacceptable side effects to UDCA (7%). These patients showed a persistent serum ALP >1.67 xULN and/or elevated total bilirubin <2 xULN. Patients were randomized to receive 10 mg of OCA, 5 mg with adjustment to 10 mg of OCA if applicable (5-10 mg group) or placebo (50).

Patients in the 5-10 mg group and those in the 10 mg group showed a greater decrease in ALP levels than those treated with placebo (−113 and −130 U/L, respectively, *vs.* −14 U/L; p<0.001 for both comparisons), and a significant reduction in total bilirubin (−0.02 and −0.05 mg/dl, respectively, *vs*. 0.12 mg/dl; p<0.001 for both comparisons).

However, an improvement in survival or disease-related symptoms has not yet been stablished. The most common adverse event associated with OCA treatment was pruritus (56% in the 5-10 mg group and 68% in the 10 mg group *vs.* 38% in the placebo group) (50).

The 3-year interim analyses from the 5-year open-label extension of the POISE trial have been published (51,52). The results showed that long-term treatment with OCA was associated with durable improvements in markers of cholestasis, liver enzymes, markers of inflammation and improvement or no progression in fibrosis stage and collagen morphometry. ALP and bilirubin concentrations were significantly reduced compared with baseline at month 12 (mean change −105.2 U/L for ALP [p<0.0001] and −0.9 µmol/L for bilirubin [p=0.0042]) and month 48 (mean change −95.6 U/L for ALP [p<0.0001] and mean change −0.8 µmol/L for bilirubin [p=0.016]). Fibrosis stage (Nakanuma Fibrosis Score) improved in 12% of patients and remained stable in 59%, and collagen area ratio, collagen fiber density, and collagen reticulation index as assessed by SHG/2PE microscopy were reduced significantly (52). In addition, the tolerability and safety profile were similar to that observed previously, with pruritus and fatigue being the most common adverse events (51).

New data on the real-world subset of patients has been recently published, showing similar results to those found on the POISE trial (53-55). Benefits in ALP, AST, ALT, and total bilirubin were found both in patients reaching or not the POISE and Paris-II criteria after 12 months of therapy with OCA, suggesting that we should consider that some patients are slow responders, instead of non-responders. In addition, a significant improvement of continuous prognostic risk score GLOBE-PBC score at 1 year of follow up was shown (53).

5.3. Liver transplantation

Although the prevalence of PBC is increasing, liver transplant indication for this disease has declined over the past decades, from 20% in 1986 to 4% in 2015 (56). According to EASL clinical practice guidelines, the indication of liver transplantation in PBC should be given when patients have complications of cirrhosis such as ascites, variceal bleeding, and/or hepatic encephalopathy. Moreover, patients with PBC could be transplanted

due to persistent high bilirubin (5-6 mg/dl) and uncontrolled and intolerable pruritus refractory to all medical therapies (15).

The outcome of liver transplant is usually favorable, with 5-year patient survival rates of 80-85%, though the rate of recurrent PBC is 20% (15). However, older age, dialysis or ventilator use, and lower albumin were associated with high post-liver transplantation mortality (57). In any case, there is a risk of recurrence of PBC after transplantation. Recurrence rate is 22% after 5 years and 36% after 10 years. Younger age at the time of diagnosis with PBC or at liver transplantation, tacrolimus use, and biochemical markers of cholestasis after liver transplantation are associated with PBC recurrence (58). Thus, strategies are needed to prevent PBC recurrence or reduce its negative impact in the graft and patient survival. Preventive UDCA after liver transplantation for PBC is associated with a reduced risk of disease recurrence (59).

6. Consensus care pathway for the diagnosis and management of PBC

The EASL, the American Association for the Study of Liver Diseases (AASLD), and the British Society of Gastroenterology have published clinical practice guidelines for the management of PBC, though PBC management is still challenging for physicians (15,60,61). Recently, a group of PBC experts from Europe and Canada developed an international consensus for the diagnosis and management of PBC to uniform pan-healthcare professionals practice based on the EASL guidelines (62). They discussed the information needs, clinical assessments, and criteria to include and agreed that the Clinical Care Pathway should give practical advice on PBC diagnosis confirmation, performing baseline clinical and risk assessment, initiating first-line treatment, performing on-treatment risk stratification at 6 to 12 months based on response to first-line treatment and identifying patients who require second-line treatment and/or further assessment. As a result of this consensus, a diagram was outlined (Figure 1) (62).

The diagram starts with reaching a secure diagnosis of PBC. Firstly, it proposes to identify patients with suspected PBC diagnosis that show persistent cholestatic abnormalities in serum biochemistries (elevated ALP/GGT/AST/ALT and/or conjugated bilirubin) and symptoms such as pruritus, sicca, arthralgia or fatigue. Then, the

algorithm proposes an initial assessment of the patient, including a complete clinical history, serum biochemistry (ALP) and serology (AMA and/or PBC-specific ANA) to establish a reliable diagnosis of the disease (elevated ALP, AMA-positive >1/40, or anti-gp210/anti-sp100-positive) (62).

Once the diagnosis is established, the algorithm recommends starting treatment with UDCA at a dose of 13-15 mg/kg/day and, at the same time, perform a baseline clinical assessment to determine the risk of disease progression, including age, gender, history of complications, symptoms, blood tests, liver ultrasound and liver stiffness measurement. Using these baseline assessments, the disease should be staged and the risk profile is determined according to the levels of ALP, bilirubin, albumin, state of fibrosis or cirrhosis and pruritus (62).

The algorithm recommends a regular follow-up and asses the response to UDCA treatment within 6-12 months by measuring ALP, bilirubin, AST, ALT, GGT, albumin and platelets and evaluating features of fibrosis/cirrhosis. Based on this response to treatment, risk of progression is assessed. Patients with low risk of progression (adequate response to UDCA: ALP <1.5 x ULN, normal bilirubin, early fibrosis) remain receiving UDCA and response must be assessed every 12 months. Those with intermediate-to-high risk (intolerance to UDCA or inadequate response to UDCA: ALP >1.5 x ULN, high bilirubin, low albumin, advanced fibrosis/cirrhosis and/or severe pruritus) are considered for further assessment and referred to be evaluated for a second-line therapy (62).

OCA is the only licensed second-line therapy. However, the algorithm also indicates that alternative off-label therapies (i.e., fibrates, budesonide) could be considered, especially in patients developing pruritus. Prior to OCA therapy, several assessments must be done: a) Review first-line therapy, re-assessing the quality of the response to UDCA; b) Assess pruritus, determining severity and impact on patient's QoL; and, c) Assess hepatic status, including events of complications of cirrhosis, signs of decompensated cirrhosis, and blood tests.

If the patient is non-cirrhotic (Child-Pugh A), dose of OCA must be selected according pruritus severity. In patients with no pruritus or mild pruritus, OCA should be prescribed at a dose of 5 mg once daily. If there is a history of moderate or severe

pruritus, OCA should be administered at a dose of 5 mg three times weekly. Once pruritus is under control, OCA at a 5 mg dose should be administered once daily for the following 6 months and then reassessed. If the patient has not achieved an adequate response, but tolerates therapy, the dose of OCA should be increased to 10 mg once daily (49).

In patients with decompensated cirrhosis (Child-Pugh B or C), transplantation must be considered. However, risk-benefit assessment of OCA treatment should be done on a case-by-case basis. If the risk-benefit balance is positive, OCA should be started at a dose of 5 mg once weekly, adjusting the dose according to pruritus severity. Once pruritus is under control, maintaining OCA on 5 mg once weekly revising therapy after 3 months should be the followed pattern. If the patient has not achieved an adequate response, but tolerates treatment, the dose of OCA should be increased to 5 mg twice weekly (at least 3 days away), with a further increase in dose to 10 mg twice weekly (at least 3 days away) based on response and tolerability. At 12 months, assessment of tolerability of OCA and biochemical response should be done with re-assessment of disease status (49).

7. Conclusions

PBC is a rare disease in which more studies are needed to expand its knowledge and improve treatment management. In order to increase the effectiveness of treatment, it is very important to diagnose and stratify the risk of the disease as early as possible, and this requires easy to use diagnostic algorithms. The development of diagnostic and therapeutic algorithms based on the experience of healthcare professionals caring PBC patients is a very valuable tool for clinical practice.

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*** Members of the Leading PBC Group:**

Name	Center
Antonio Olveira	Hospital Universitario La Paz
Conrado Fernández	Hospital Universitario Fundación Alcorcón
Esther Molina	Hospital Clínico Universitario de Santiago
Francisco Jorquera	Hospital Universitario de León
José Antonio Carrión	Consorci Mar Parc de Salut de Barcelona
Juan Arenas	Hospital Universitario Donostia
Juan Uriz	Complejo Hospitalario de Navarra
Lucía Bonet	Hospital Universitari Son Espases
Luisa García Buey	Hospital Universitario de La Princesa
Manuel Hernández Guerra	Hospital Universitario de Canarias
Marina Berenguer	Hospital Universitario y Politécnico La Fe
Marta Casado	Hospital Universitario Torrecárdenas
Miguel Ángel Simón	Hospital Clínico Universitario Lozano Blesa
Rosa Morillas	Hospital Universitario Germans Trias i Pujol

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Table 1. Effective drugs used for PBC and their symptoms

Drug	Dosage	Schedule
Treatments for PBC		
UDCA (42)	13-15 mg/kg/day	First-line
OCA (50)	5-10 mg/day	Second-line
Treatment of PBC related fatigue		
Modafinil (16)	100 mg/day	
Treatment of PBC related pruritus		
Cholestyramine (63)	3-9 g/day 2-4 h before any other medication	First-line
Sertraline (64)	25 mg/day up to 100 mg by 25 mg/4 weeks	First-line
Bezafibrate (19)	400 mg/day	First-line
Rifampicin (65)	300-600 mg/day or 10 mg/kg/day	Second-line
Naltrexone (66)	12.5 mg twice or thrice daily	Third-line

OCA; obeticholic acid; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid

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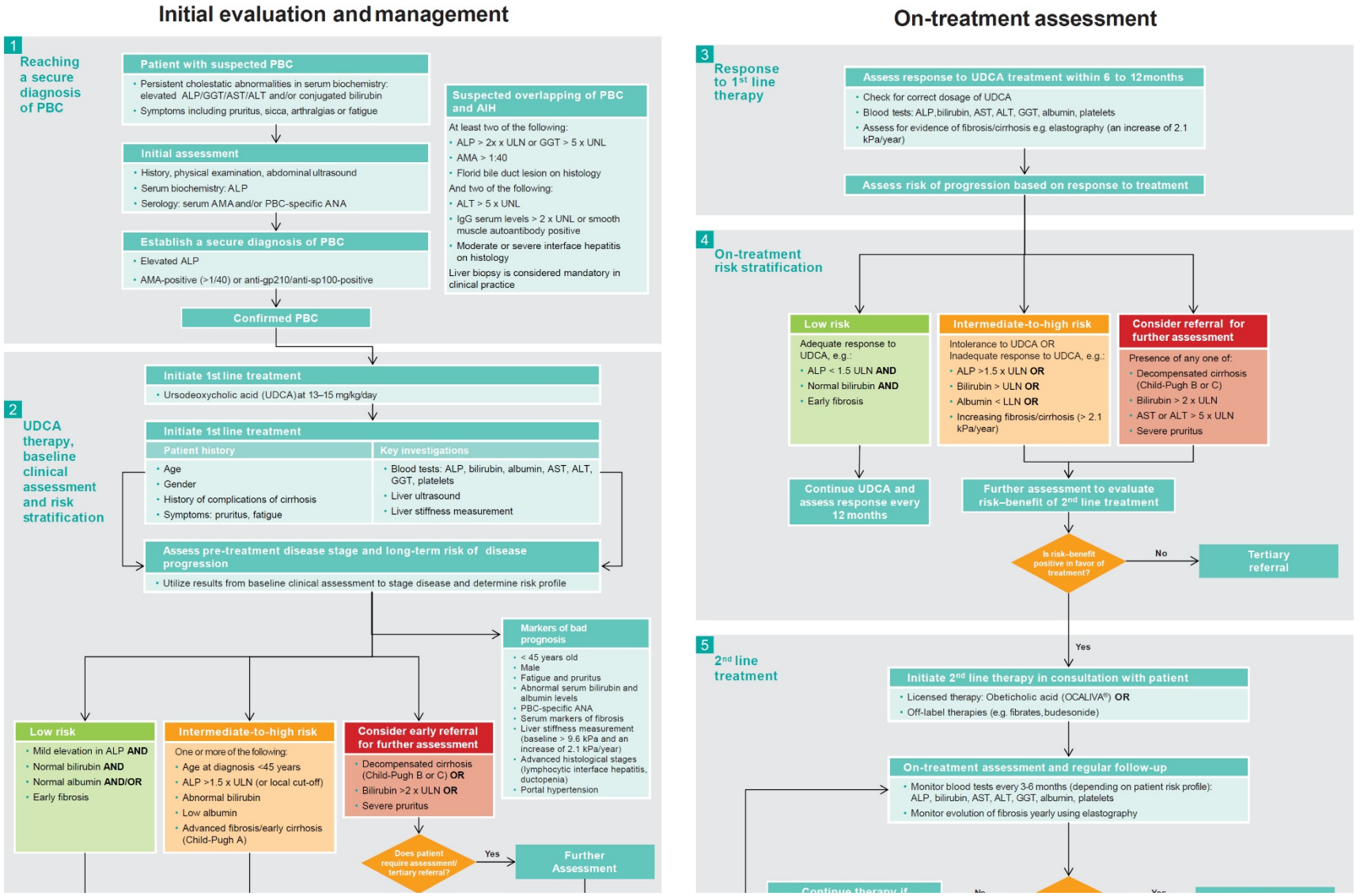
Initial evaluation and management
1
Reaching a secure diagnosis of PBC
Patient with suspected PBC
Persistent cholestatic abnormalities in serum biochemistry: elevated ALP/GGT/AST/ALT and/or conjugated bilirubin
Symptoms including pruritus, sicca, arthralgias or fatigue
Initial assessment
History, physical examination, abdominal ultrasound
Serum biochemistry: ALP
Serology: serum AMA and/or PBC-specific ANA
Establish a secure diagnosis of PBC
Elevated ALP
AMA-positive (>1/40) or anti-gp210/anti-sp100-positive
Confirmed PBC
Suspected overlapping of PBC and AIH
At least two of the following:
ALP > 2x x ULN or GGT > 5 x UNL
AMA > 1:40
Florid bile duct lesion on histology
And two of the following:
ALT > 5 x UNL
IgG serum levels > 2 x UNL or smooth muscle autoantibody positive
Moderate or severe interface hepatitis on histology
Liver biopsy is considered mandatory in clinical practice
2
UDCA therapy, baseline clinical assessment and risk stratification
Initiate 1st line treatment
Ursodeoxycholic acid (UDCA) at 13–15 mg/kg/day
Initiate 1st line treatment
Patient history
Age
Gender
History of complications of cirrhosis
Symptoms: pruritus, fatigue
Key investigations
Blood tests: ALP, bilirubin, albumin, AST, ALT, GGT, platelets
Liver ultrasound
Liver stiffness measurement
Assess pre-treatment disease stage and long-term risk of disease progression
Utilize results from baseline clinical assessment to stage disease and determine risk profile
Markers of bad prognosis
< 45 years old
Male
Fatigue and pruritus
Abnormal serum bilirubin and albumin levels
PBC-specific ANA
Serum markers of fibrosis
Liver stiffness measurement (baseline > 9.6 kPa and an increase of 2.1 kPa/year)
Advanced histological stages (lymphocytic interface hepatitis, ductopenia)
Portal hypertension
Low risk
Mild elevation in ALP AND
Normal bilirubin AND
Normal albumin AND/OR
Early fibrosis
Intermediate-to-high risk
One or more of the following:
Age at diagnosis <45 years
ALP >1.5 x ULN (or local cut-off)
Abnormal bilirubin
Low albumin
Advanced fibrosis/early cirrhosis (Child-Pugh A)
Consider early referral for further assessment
Decompensated cirrhosis (Child-Pugh B or C) OR
Bilirubin >2 x ULN OR
Severe pruritus
Does patient require assessment/ tertiary referral?
Yes
Further Assessment
On-treatment assessment
3
Response to 1st line therapy
Assess response to UDCA treatment within 6 to 12 months
Check for correct dosage of UDCA
Blood tests: ALP, bilirubin, AST, ALT, GGT, albumin, platelets
Assess for evidence of fibrosis/cirrhosis e.g. elastography (an increase of 2.1 kPa/year)
Assess risk of progression based on response to treatment
4
On-treatment risk stratification
Low risk
Adequate response to UDCA, e.g.:
ALP < 1.5 ULN AND
Normal bilirubin AND
Early fibrosis
Intermediate-to-high risk
Intolerance to UDCA OR Inadequate response to UDCA, e.g.:
ALP >1.5 x ULN OR
Bilirubin > ULN OR
Albumin < LLN OR
Increasing fibrosis/cirrhosis (> 2.1 kPa/year)
Consider referral for further assessment
Presence of any one of:
Decompensated cirrhosis (Child-Pugh B or C)
Bilirubin > 2 x ULN
AST or ALT > 5 x ULN
Severe pruritus
Continue UDCA and assess response every 12 months
Further assessment to evaluate risk–benefit of 2nd line treatment
Is risk–benefit positive in favor of treatment?
No
Tertiary referral
5
2nd line treatment
Yes
Initiate 2nd line therapy in consultation with patient
Licensed therapy: Obeticholic acid (OCALIVA®) OR
Off-label therapies (e.g. fibrates, budesonide)
On-treatment assessment and regular follow-up
Monitor blood tests every 3-6 months (depending on patient risk profile): ALP, bilirubin, AST, ALT, GGT, albumin, platelets
Monitor evolution of fibrosis yearly using elastography

Figure 1. Consensus Patient Care Pathway for the diagnosis and management of patients diagnosed with primary biliary cholangitis. Reproduced from Hirschfield GM, et al. (62)

AIH: autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondiral antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LLN, lower limit of normal; PBC, primary biliary cholangitis; UDCA, ursodeoxylcholic acid; ULN, upper limit of normal.