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Position Paper

Position paper of the Italian Association for the Study of the Liver (AISF): Management and treatment of primary biliary cholangitis

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1. Introduction

Primary biliary cholangitis (PBC) is an autoimmune chronic cholestatic liver disease characterized by immune-mediated inflammation and destruction of the intrahepatic, small bile ducts. In PBC patients untreated or under-treated a progressive cholestasis leads to biliary fibrosis and ultimately liver cirrhosis. Disease presentation may differ within a wide spectrum, particularly based on the stage of the disease at onset; from asymptomatic, in most

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cases, or symptomatic, typically with pruritus and/or fatigue; jaundice may be present at presentation due to late diagnosis at cirrhotic stage or due to a premature severe ductopenia.

Historical cohorts [1] and more recent large-scale studies [2–5] from secondary and tertiary centers confirmed a ratio of 9 females to 1 male; female predominance is likely driven by genetic and epigenetic factors [6–8]. The disease occur more frequently in first-degree relatives [9]. Recent reports from administrative databases challenged this ratio highlighting more male patients affected with a ratio of 4–6:1 [10]. However, administrative registry studies suffer from several bias since they are mainly designed for administrative purposes (e.g. medical claims for reimbursement, records of health services, medical procedures, prescriptions) rather than research purposes and might have a less stringent case ascertainment.

The pooled worldwide incidence and prevalence rates of PBC are roughly estimated at 1.76 and 14.6 per 100,000 individuals, respectively [11]. However, these figures display significant variation in the literature based on factors such as the search methodology employed, the size of the study population, and the thoroughness of case identification. However, there may be pure differences in epidemiology estimates secondary to genetic susceptibility and environmental factors. Interestingly, the incidence and prevalence of PBC experienced a consistent increase globally until the year 2000 [11].

While this shift likely arises from multiple factors, early detection of the disease and the effectiveness of ursodeoxycholic acid (UDCA) in preventing health complications and fatalities are believed to be major contributing factors [2]. These disparities can be partially explained by genetic susceptibility and environmental factors, with PBC being more prevalent in industrialized or polluted areas and among individuals who smoke tobacco and use nail polish and hair dye products [9,12,13].

Epidemiologic figures in Italy come from electronic medical records from 900 general practitioners [14] (part of the QuintilesIMS™ Longitudinal Patient Databases) where the disease was captured using the International Classification of Diseases, Ninth Revision, of biliary cirrhosis code 571.6. Point prevalence of PBC was calculated as 27.90 per 100,000 and incidence as 5.31 per 100,000 inhabitants/year. A National PBC Registry in Italy is expanding to enroll all healthcare liver services across the country and will provide more accurate figures [15].

Over the past two decades, substantial advancements have occurred in enhancing our comprehension of PBC, from a deeper understanding of the disease's phenotypes and the mechanisms driving it, to the factors influencing patient risk and the variability of risk among individuals, as well as the characterization and consequences of symptoms. This increased knowledge has been harnessed for the development of effective medications able of potentially decelerating disease advancement.

2. Development process of statements

2.1. Position paper development process

This position paper has been developed as a consensus document by the AISF to assist clinicians in diagnosing and managing PBC patients (Fig. 1). The writing committee comprised gastroenterologists, hepatologists, transplant physicians, and methodologists. For each clinical question the medical literature on Medline, Embase and Cochrane Library databases were systematically searched using both free terms and Thesaurus MESH indexed terms. In addition, a further hand-search was performed on the bibliography of articles and previously developed guidelines.

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system has been fundamental in fram-

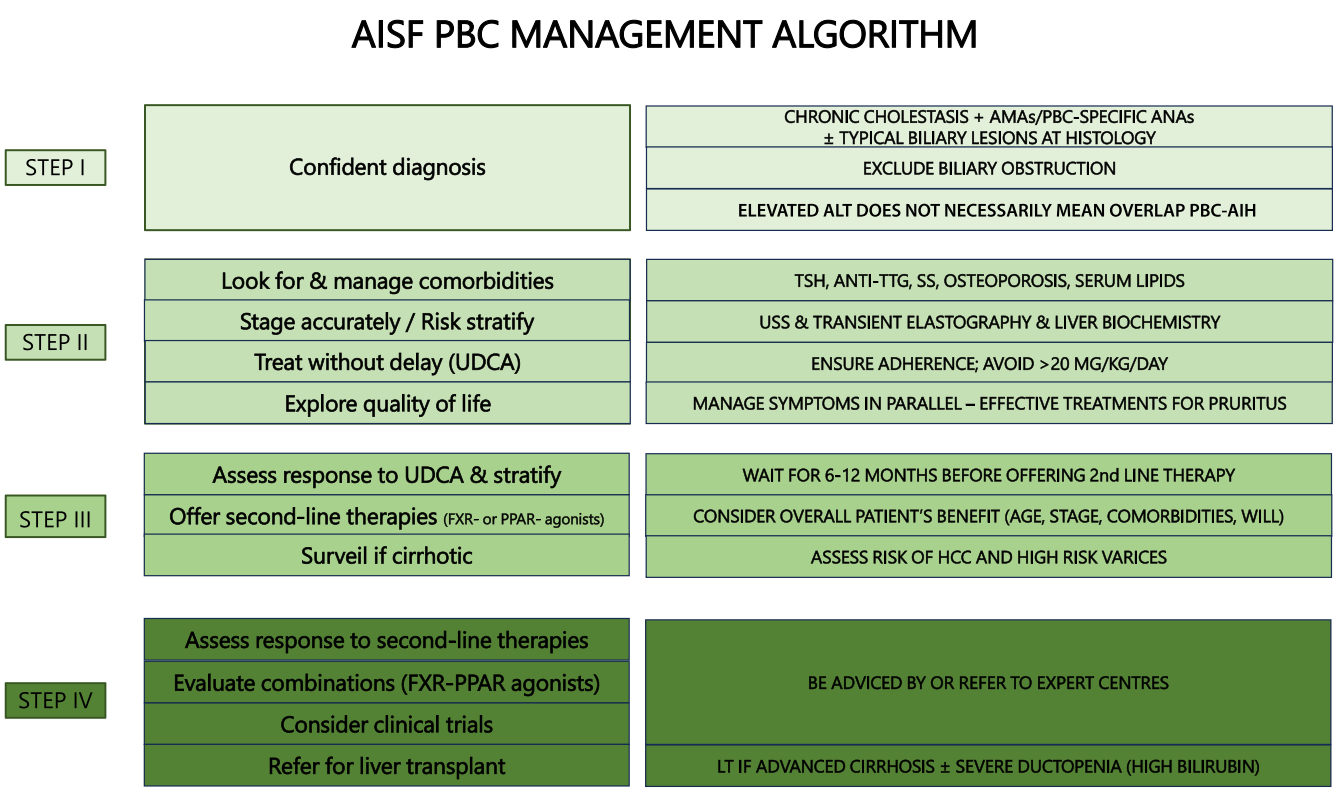

Fig. 1. This figure presents a summary of the guidelines for the management of Primary Biliary Cholangitis (PBC). The figure covers various aspects of PBC management, including diagnosis, treatment options, monitoring, and follow-up recommendations.
ABBREVIATIONS: AIH, autoimmune hepatitis; FXR, farnesoid X receptor; HCC, hepatocellulare carcinoma; Kg, kilogram; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; SS, sistemic sclerosis; TSH, thyroid-stimulating hormone; TTG, tissue transglutaminase; UDCA, ursodeoxycholic acid; USS, ultrasound scan.

Table 1
Graduation of certainty of evidence.

Certainty of evidence	Significance	Consequence
High	High degree of confidence in the results	It is very likely that the true treatment effect is similar to the estimated one
Moderate	Fair degree of confidence in the results	The true treatment effect is likely to be similar to the estimated one but there is the possibility that the effect is different
Low	Results not very credible	Confidence in the estimate of the effect is limited: the true effect could be substantially different from the estimated one
Very Low	Data examined totally unreliable	Confidence in the estimate of the effect is very limited: it is likely that the true effect is substantially different from the estimated one

ing our recommendations, serving as the backbone for classifying evidence levels [16] (Table 1).

Recommendations, based on the GRADE system, are categorized as either strong or weak and hinge on various crucial factors such as the quality of evidence, a balance of benefits against harms, variability in patient values and preferences, and resource implications. A recommendation is likely to be stronger when there is a pronounced difference between the desirable and undesirable consequences of an intervention, robust quality of evidence, and consistency in values and preferences. Conversely, a recommendation tends to be weaker when there is a closer margin between the benefits and risks, significant variation or uncertainty in values and preferences, or if the intervention is resource-intensive. Strong recommendations signify that the majority of well-informed patients would opt for the recommended approach, allowing clinicians to guide patient interactions accordingly. Conditional recommendations, however, imply a divergence in patient choices based on individual values and preferences, necessitating clinicians to tailor patient care in alignment with these individual considerations.

Recommendations were formulated applying the GRADE Approach [16]. All the aspects concerning questions, assessment of evidence and conclusions were discussed among panel members and voted. Before voting panel members declared their potential conflict of interest (COI) relevant to clinical questions

The panel members provided justifications for the final recommendation (strong for, conditional for, conditional against and strong against) including relevant consideration on the possible implementation, monitoring and assessment indicators and priorities for future research.

In addition, for each clinical question each panelist scored the both the quality of evidence and the strength of recommendations; consensus among panelists was always $>80\%$.

3. Statements

3.1. Diagnosis

3.1.1. How do we interpret isolated AMA positivity in clinical practice?

Recommendation 1: The presence of isolated AMA positivity with normal serum liver tests is not sufficient to make the diagnosis of primary biliary cholangitis. However, in consideration of the potential for disease progression, these patients should be monitored on an annual basis with liver biochemistry to detect early signs of abnormal liver tests.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

All patients with suspected PBC should undergo to an abdominal ultrasound at presentation to rule out biliary obstruction. The presence of antimitochondrial antibodies (AMA) at a title $>$ 1:40 or highly specific PBC-specific ANAs (nuclear dots, perinuclear rims on immunofluorescence, sp100, gp210 by ELISA) [17] in the context of chronic cholestasis (i.e. abnormal ALP and GGT), without alternative explanation, is sufficient to diagnose PBC.

Clinical Presentation: PBC is often asymptomatic or presents with non-specific symptoms such as pruritus, fatigue, and sicca syndrome. While women over 40 years old are considered to be at higher risk for PBC, it can affect individuals of any age and gender, except for children. Heightened awareness of the disease and widespread blood testing for screening purposes within the general population have contributed to changes in the clinical presentation of PBC in recent years, with younger patients with early stage of disease being the most common clinical presentation.

Laboratory Investigations: PBC should be suspected in the setting of chronic cholestasis after ruling out other causes of liver disease and biliary obstruction. Key laboratory parameters include serum alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), transaminases, and bilirubin levels. In PBC, ALP is typically elevated, and numerous studies have shown it to be a reliable surrogate of prognosis [5,18]. GGT, although less specific, is often elevated in PBC, even preceding ALP elevations, and is correlated with prognosis [19]. Additionally, subjects with PBC may often exhibit elevated serum transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)), reflecting the extent of liver parenchymal inflammation and necrosis, but this should not be considered indicative of an autoimmune Hepatitis (AIH) variant syndrome *per se*. Elevated IgM levels are commonly observed in PBC and can offer supportive evidence for the diagnosis.

Hyperbilirubinemia occurs as PBC progresses. Similar to other causes of liver disease, a decline in platelet count, decreased albumin concentration, and an elevated international normalized ratio (INR), indicates the development of advanced liver disease and/or portal hypertension.

The hallmark for diagnosis in PBC is the presence of antimitochondrial antibodies (AMAs), that specifically target the E2-subunit of the pyruvate dehydrogenase complex (PDC-E2). AMA positivity in patients with chronic cholestasis has a specificity for PBC $>95\%$. Therefore, testing for AMAs is recommended as an initial screening test for PBC in individuals with chronic cholestasis. A titre of above 1 in 40 for any autoantibody linked to PBC is conventionally regarded as being positive. AMAs can be detected using either indirect immunofluorescence (IIF, with titers above 1:40) or enzyme-linked immunosorbent assays (ELISAs). The choice between these approaches (IIF vs ELISA) depends on local experience and availability, as both methods are accepted for AMA testing and there is no clear evidence of superiority. For routine cases, with clear-cut high-titre reactivity in the primary assay used, there is usually no additional value from a confirmatory second assay. Lastly, there is no recommendation for repeat AMA measurement after diagnosis, as there is no evidence suggesting that AMA titers holds prognostic significance.

Low titre AMA positivity in the context of normal LFTs, i.e. isolated AMA reactivity, is seen in $\sim$0.5% of the population [20]. It is unknown whether this reflects a false positivity or rather a pro-

dRomel phase of the disease. This scenario is not sufficient to diagnose PBC, yet these subjects should undergo annual monitoring, as they may develop PBC over time [21,21]. Further, transitory AMA positivity can be observed in case of acute liver injury [22].

Specific anti-nuclear antibodies (ANAs), i.e. anti-sp100 and anti-gp210, are present in approximately 30% of patients with PBC [23]. IIF staining, revealing nuclear dots and/or perinuclear rims, is highly specific for PBC and can aid in the diagnosis, albeit with low sensitivity. Specific immunoassays can be employed to test for ANA reactivities. It is worth noting that anti-gp210 reactivity has been linked to disease severity.

Imaging: PBC does not cause any disease-specific abnormalities in liver morphology that can be detected through imaging. Abdominal ultrasonography is recommended at diagnosis to rule out biliary duct obstruction. The presence of hilar (benign) lymphadenopathy is frequent in patients with PBC Moreover, in patients with cirrhosis, abdominal ultrasound can detect signs of portal hypertension, such as a dilated portal vein, splenomegaly or ascites, and it is mandatory for HCC surveillance. Large bile ducts at magnetic resonance cholangiopancreatography (MRCP) are typically normal in patients with PBC.

3.1.2. What is the role of liver biopsy in PBC at diagnosis?
Recommendation 2: Liver biopsy is not generally required in the diagnosis of PBC in AMA positive patients or for monitoring disease progression as it does not add to the diagnostic accuracy.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 3: In the setting of chronic cholestasis with the absence of diagnostic autoantibodies and normal MRCP, liver biopsy is required to explore the diagnosis (and confirm PBC).

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 4: Liver biopsy should be considered if there is a clinical suspicion of co-existing diseases, such as autoimmune hepatitis, steatotic liver disease, or liver localization of systemic disease, or to confirm a ductopenic variant, either at diagnosis or during follow-up.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

PBC is characterized histologically by chronic, non-suppurative peri/portal inflammation that leads to the destruction of interlobular bile ducts. Florid duct lesions show intense inflammatory changes and necrosis surrounding the bile ducts. The inflammatory infiltrate localizes in close proximity to the basal membrane of necrotic cholangiocytes and consists of plasma cells, macrophages, and polymorphonuclear cells, particularly eosinophils. Portal epithelioid granulomas may also be present in some cases. Ductopenia, defined as the presence of fewer than 50% of portal tracts containing bile ducts, can be observed. Liver biopsy can assist in assessing the stage of disease and the degree of fibrosis, providing valuable prognostic and treatment-related information [24].

Liver biopsy for diagnostic purposes in cases with clear cut cholestatic liver tests and autoantibody reactivity is not recommended as it does not add to the diagnostic accuracy [25]. In addition, the tissue damage can have a patchy distribution in PBC, with potential for sampling error. For these reasons, it has progressively become obsolete in PBC, for both diagnostic and staging purposes.

However, liver biopsy remains essential in case of clinical suspicion where PBC-specific antibodies are negative or when coexisting conditions such as AIH or metabolic dysfunction-associated steatohepatitis (MASH) are suspected (see previous problem response clarifying this already).

Specifically, liver biopsy is strongly recommended when there are features of autoimmune hepatitis such as: AST/ALT > five times the upper limit of normal (ULN), IgG > twice the ULN, or with positivity to autoantibodies (ANA (excluding gp210 and sp100), SMA, LKM-1, LC-1, SLA/LP). Interface hepatitis may often be found in PBC, but it is typically mild or, more rarely, moderate [24]. The presence of severe interface hepatitis in the right clinical context is a hallmark of AIH. The differential diagnosis between PBC-AIH variant syndrome and difficult-to-treat PBC (partial/null response to UDCA) is complex and referral to tertiary care centers is advisable.

The concomitant presence of features of metabolic dysfunction-associated steatotic liver disease (MASLD) and PBC will be progressively seen more in the future, due to the growing incidence of diabetes and obesity worldwide. Laboratory tests are nor sensitive nor specific enough to achieve non-invasive discrimination between the two entities. Raised GGT and ALT are often part of the spectrum of abnormal liver tests in MASLD. More recent data show that raised ALP can also be found in patients with pure MASLD without PBC or other cholestatic conditions [26]. On the contrary, histological patterns are specific, considering that PBC mostly involves the portal tracts, while MASLD more commonly affects the lobule.

Additionally, liver biopsy may also be appropriate in the presence of systemic co-morbidities (such as liver involvement in sarcoidosis) or when a ductopenic variant is suspected (i.e.in patients with elevated direct bilirubin, normal biliary tree at imaging and no clinical sign of cirrhosis) [27].

Sarcoidosis with liver involvement is usually associated with biochemical cholestasis [28]. Both diseases can be associated with hepatic granulomas; sarcoid granulomas are small, well delineated and discrete and can be found in either portal tracts and/or lobules, whereas granulomas in PBC are confined to the portal tracts, or in zone 1 of the lobule. Giant cells with multiple nuclei can be present, and caseation is absent. In male patients of black ethnicity sarcoidosis might cause an overt cholestatic syndrome with pruritus, weight loss, and jaundice; these cases typically show marked portal tract damage with widespread bile duct loss.

The premature ductopenic variant is a clinico-pathological entity rarely described and mainly affecting women with PBC characterized by marked jaundice associated with divergent histological findings: less than 10% of interlobular bile ducts without significant fibrosis [27]. From a clinical point of view these cases are characterized by progressive cholestasis, severe pruritus and weight loss, and are generally treatment-refractory. Biopsy is performed in this context for differential diagnosis and staging. Other ductopenic conditions should be considered in autoantibody-negative cases, including drug-induced vanishing bile duct syndrome and genetic cholestasis.

Recent studies highlight the importance of an additional parameter in liver histology such as the ductular reaction. This is a known mechanism of tissue repair associated with the establishment of junctions with bile canaliculi, which seeks to compensate for the damage in the bile flow, and with fibrogenetic cell activation. Ductular reaction in the index biopsy correlates with a severe clinical phenotype, the lack of response to first-line therapy with ursodeoxycholic acid and the individuals' estimated survival, independently from other histological parameters, particularly disease stage. Of note, no peripheral markers are associated with ductular reaction, which can therefore only be picked up with liver sampling. The quantification of ductular reaction on liver biopsy might represent a relevant tissue biomarker for staging and prognostic purposes [29–32].

3.2. Comorbidities

3.2.1. In patients with PBC what other conditions (autoimmune and not) do we need to look for?

Recommendation *5:* All patients with PBC should have a risk assessment and management for osteoporosis. Serum levels of vitamin D, calcium, phosphorus, and PTH should be evaluated at diagnosis and annually. DEXA should be performed at diagnosis and every 1–4 years based on osteoporotic fracture risk and the degree of cholestasis. Oral bisphosphonates should be avoided in patients with esophageal varices because of the potential to precipitate a variceal hemorrhage.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 6: Symptoms of Sjögren's syndrome (SS), specifically sicca syndrome, should be sought in all PBC patients since their management can be an important part of controlling the overall symptom burden in PBC.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation *7:* All PBC patients should be screened for thyroid diseases with TSH testing at diagnosis and then annually or in presence of symptoms suggesting thyroid dysregulation.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation *8:* All PBC patients should be screened for celiac disease by serological testing at diagnosis.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation *9:* When signs of systemic sclerosis (SSc) are present, anti-centromere antibodies (ACA) should be sought. Management of patients with PBC and SSc should be performed in conjunction with the rheumatologist.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation *10*: Patients with concomitant features of metabolic syndrome should be offered lipid-lowering therapy based on their cardiovascular risk assessment. There are no PBC-specific contraindications to the use of statins; caution should be used in patients with Child-Pugh score B-C, and when statins and fibrates are concomitantly prescribed.

Quality of Evidence: Low
Strength of Recommendation: Strong for

Osteoporosis is frequent in PBC and is considered linked to reduced absorption of fat-soluble vitamins secondary to cholestasis. PBC is also commonly associated with other autoimmune conditions reflecting shared immunogenetic susceptibility, such as Sjögren's syndrome, most frequently secondary sicca complex, thyroid disease, celiac disease, and systemic sclerosis. The presence of associated anemia with an immune/autoimmune etiology (including pernicious anemia and autoimmune haemolytic anemia) should also be considered in patients with prominent fatigue.

3.2.2. Osteoporosis

Osteoporosis is a common complication in cholestatic liver disease, including PBC. The prevalence of osteoporosis in PBC ranges from 30% to 40% [33–37], with the highest rates in individuals with cirrhosis [38]. Therefore, it is important to assess the risk of osteoporosis in all PBC patients. Additional risk factors for low bone density, such as alcohol and tobacco abuse, and prolonged steroid treatment, should also be evaluated and addressed if present. At the time of diagnosis, serum levels of vitamin D, calcium, phosphorus, and parathyroid hormone (PTH) should be checked, and these levels should be monitored annually. Bone mineral density (BMD) evaluation using dual-energy X-ray absorptiometry (DEXA) should be performed at the time of PBC diagnosis and then reassessed every 1–4 years, depending on the individual's osteoporosis risk. Fracture risk is significantly higher in PBC [39], even with a T-score below 1.5 [40].

Currently, there is insufficient data to recommend or refuse the use of vitamin D and calcium supplements in PBC patients for the prevention of osteoporosis. Several studies have demonstrated that third-generation bisphosphonates are effective in increasing BMD in patients with PBC [41,42] and, therefore, they should be used when indicated. Oral bisphosphonates may cause oesophageal ulceration and so should be avoided in patients with oesophageal varices because of the potential to precipitate a variceal hemorrhage.

There is no robust evidence to recommend other osteoporosis therapies in PBC patients. A single center-study from Japan on 10 patients with PBC followed up to 3 years suggests that denosumab is safe and effective [43].

3.2.3. Sjögren's syndrome

Sjogren's syndrome (SS) is a chronic autoimmune disorder characterized primarily by dryness of the eyes and mouth [44]. The coexistence of SS in PBC patients ranges from 3.5% to 73% [45–47]. Of note, sicca syndrome, i.e. dry eyes and dry mouth, may be present in PBC also without the full clinical picture of SS.

Clinicians should specifically enquiry about symptoms of sicca syndrome. Serological markers, i.e. antinuclear antibodies (ANA), and anti-Ro/SSA, can aid in the diagnosis. Treatment strategies primarily focus on the use of artificial tears, saliva substitutes, and topical lubricants [44].

3.2.4. Thyroid diseases

Thyroid diseases, particularly Hashimoto thyroiditis, and less frequently Graves' disease, are more common in PBC compared to healthy controls, with prevalence ranging from 10% to 20% [47–49]. Therefore, it is recommended the annual check of thyroid stimulant hormone (TSH), or earlier if symptoms such as fatigue or sleep disorders are present.

Celiac disease is the most common gastrointestinal disease associated with PBC, with a prevalence of up to 10% [47,50]. Serological screening for celiac disease is recommended in all PBC patients at baseline. However, in PBC patients, IgG and IgA tissue transglutaminase antibodies have been shown a high rate of false positives [51], based on the type of substrate used in the assay.

3.2.5. Systemic sclerosis

Although systemic sclerosis (SSc) and PBC predominantly affect different organ systems, studies have revealed the coexistence of both conditions in a subset of patients. The exact prevalence of SSc among PBC patients remains uncertain, with estimates ranging from 1% to 17% [47,52,53].

Clinical manifestations that may suggest the presence of overlap between PBC and SSc include Raynaud's phenomenon, skin thickening, puffy fingers, telangiectasia, positive anti-centromere antibodies (ACA), capillary abnormalities observed through nailfold videocapillaroscopy, and pulmonary hypertension [53].

The identification and recognition of PBC/SSc overlap are crucial for initiating early treatment to address the distinct manifestations of each disease. A multidisciplinary approach involving

rheumatologists is essential. Screening PBC patients for ACA is not mandatory; it should only be considered when SSc-related signs and symptoms are present.

3.2.6. Hyperlipidemia

Hypercholesterolemia, a major modifiable risk factor for cardiovascular disease, is frequent in patients with PBC due to increased hepatic synthesis of cholesterol, which stems from impaired intestinal absorption caused by cholestasis, and reduced biliary lipid secretion. However, evidence has been mixed on whether PBC patients do have higher cardiovascular risk [54,55].

Some authors have suggested that the increase levels of high-density lipoprotein and the finding of the unusual lipoprotein X represent a countereffect of the body to inactive excess bile acids, likely functioning as a compensatory mechanism [56].

In the early stages of PBC, patients tend to exhibit elevated levels of serum total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol [54]. As PBC progresses, LDL cholesterol may further increase, while HDL may decrease due to reduced hepatic synthesis [56].

Individuals with concomitant features of metabolic syndrome should be offered lipid-lowering therapy based on their cardiovascular risk assessment; in patients with PBC with no additional cardiovascular risk factors, individual risk/benefit discussion on lipid-lowering treatment should be considered [56]. Hepatologists should regularly evaluate lifestyle habits, including diet and physical activity, in PBC patients and promote a healthy lifestyle to minimize the risk of developing metabolic syndrome and associated steatotic liver disease. Statins are safe and effective at lowering LDL cholesterol in PBC patients, but they should be used with caution in decompensated cirrhosis [56] and when statins and fibrates are concomitantly prescribed. No studies are available in terms of safety and efficacy for proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors in PBC.

3.3. Staging, risk stratifying & monitoring

3.3.1. How do we stage liver disease at diagnosis?

Recommendation 11: Liver stiffness by VCTE can be used for assessing the disease stage.

Quality of Evidence: Moderate
Strength of Recommendation: conditional for

Recommendation 12: If a liver biopsy is performed, the Nakanuma staging system should be preferred to the Ludwig and Scheuer's staging systems.

Quality of Evidence: Low
Strength of Recommendation: Conditional for

Fibrosis assessment at diagnosis in PBC has been usually neglected and not integrated into a paradigm of management such as the biochemical response. Large cohort studies from the GLOBAL PBC and the UK-PBC study groups reported that histological fibrosis grants prognostic value beyond biochemical response at 1 year [57,58]; this highlighted the need to incorporate liver fibrosis stage, or its surrogate markers such as liver stiffness measurement (LSM) assessed by vibration-controlled transient elastography (VCTE), into paradigms of risk stratification of PBC at diagnosis. A multicenter study of treatment-naïve PBC patients described, and externally validated, two cutoffs of LSM ($\leq$6.5 and $>$11.0 kPa) that could discriminate, at diagnosis, the absence or presence, respectively, of advanced fibrosis in PBC patients [59]. For patients with LSM between these two cutoffs, this is not reliable, and a repeat assessment or liver biopsy should be considered to improve the staging accuracy. In this study, BMI and liver biochemistry did not affect LSMs. Whereas the Baveno guidelines support the threshold of 10 kPa as reference for compensated advanced chronic liver disease, despite not being PBC-specific [60].

In individuals with PBC undergoing diagnostic liver biopsy the histology provides important prognostic information [57,58]. Four stages (1–4) are recognized based on the extent of ductopenia, inflammation, and collagen deposition, as classified by Ludwig and Scheuer. Stage 4 in both scoring systems indicates the presence of cirrhosis. In alternative, the staging system of Nakanuma assigns a score of 0–3 to three histologic components: fibrosis, bile duct loss, and deposition of orcein-positive granules. Considering its inclusion of features of cholate-stasis, this may reduce inaccuracy from sampling. The Nakanuma correlates well with clinical and laboratory features and is more useful than previously described staging systems in predicting adverse outcomes in patients with PBC [24,61,62].

3.3.2. How do we perform risk stratification and monitoring?

Recommendation 13: Risk assessment in PBC should include the evaluation of disease activity (i.e. liver biochemistry) at baseline and during treatment, disease stage at imaging (liver ultrasound and vibration-controlled transient elastography), patient demographics and comorbidities.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 14: LSM by VCTE should be used as a biomarker to assess disease progression.

Quality of Evidence: High
Strength of Recommendation: Strong for

Recommendation 15: Patients are defined at low risk of medium-long term events if non-cirrhotic, and UDCA-responsive. Whereas patients at high-risk are those with signs of advanced disease and/or abnormal ALP and/or GGT and/or transaminases after 6–12 months of therapy with UDCA.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 16: Patients at high risk of clinical events in the short term are those with advanced liver disease (overt cirrhosis, elevated bilirubin, low albumin level, a/or platelet count $<150\times10^3/\mu$l); clinicians should have a low threshold for recognizing and referring these patients for further expert assessment, e.g. liver transplant center.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 17: The early identification (i.e. at diagnosis) of individuals at high risk of failure to first-line therapy with UDCA (with the UDCA-response score) can be used for patients counselling. Early therapeutic escalation (e.g. combination therapy at diagnosis) should be performed only within clinical trials.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 18: All individuals with PBC should undergo regular serum liver tests control (every 6–12 months) and liver stiffness measurement (every 12–24 months), based on the disease activity and disease stage.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Risk stratification at baseline and on treatment should consider the patient history including age, sex, history of complications of cirrhosis, symptoms of pruritus, fatigue, and sicca complex, as well as bone density measurement. An assessment of coexistent autoimmune disease, cardiovascular risk and metabolic syndrome is also recommended.

Early age at diagnosis (e.g. <45 years) is a recognized risk factors for inadequate response to UDCA therapy, sometimes with more aggressive hepatitic component, and therefore disease progression.

Male patients have been described as having more advanced disease at presentation.

LSM has been recently validated in a large, retrospective, international cohort study as a robust predictor of PBC outcome. Its predictive value was stable in time and improved the prognostic ability of biochemical response criteria, fibrosis scores, and prognostic scores [3]. 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. The thresholds of 8 kPa and 15 kPa optimally discriminated patients into low, medium, and high-risk groups.

The severity of symptoms does not necessarily correlate with the disease stage in PBC. However, severe pruritus can indicate an aggressive ductopenic variant of PBC, which is associated with a poorer prognosis.

The changes in liver biochemistry on treatment, with a conventional 6–12-month's period for the assessment, are used to define the biochemical response to UDCA and this has been declared as the cornerstone of risk stratification in PBC. Indeed, an insufficient response to UDCA is related with an increased risk of disease progression and should be considered for second-line therapy after assessing the benefit to the patient on a case-by-case basis.

ALP and bilirubin are the strongest individual parameters. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are often elevated, indicating an accompanying parenchymal inflammation [30,18], but they only occasionally should raise the suspicion of an overlap with AIH (that requires histological confirmation). Gamma-glutamyl transferase (GGT) levels at 12 months after UDCA initiation (<3.2 vs. ≥3.2) have also proven useful in identifying patients in need of additional management [19].

ALP thresholds in defining inadequate response to UDCA are currently potentially ambiguous and not consistent. Recent evidence shows that the lower the ALP, the better and we should aim to achieve a complete normalization of ALP, wherever possible and if cost-effective.

While the response to UDCA has traditionally been assessed at 12 months [18,63], emerging evidence suggests that response can be reliably predicted at an earlier time point, such as 6 months [64], or even at baseline [30]. These approaches, if validated, might allow clinicians an early escalation therapy with the potential to prevent fibrosis progression.

Risk assessment should be performed as an ongoing process through the patients' journey, and should be based on biochemistry, and any evidence (direct or indirect) of fibrosis or signs of decompensation.

3.4. Surveillance

3.4.1. How do we perform surveillance for portal hypertensive complications?

Recommendation 19: All PBC patients with LSM<20 kPa and platelet count >150,000/mm^3 can safely avoid screening endoscopy for gastro-esophageal varices**,** according to Baveno recommendations (until PBC-specific evidence are available)

Quality of Evidence: Low
Strength of Recommendation: Strong for

Recommendation 20. All PBC patients with LSM≥20 kPa and/or platelet count ≤150,000/mm^3, and not already on treatment with non-selective beta-blockers (NSBBs), should be managed according to Baveno recommendations (until PBC-specific evidence are available).

Quality of Evidence: Low
Strength of Recommendation: Conditional for

Recommendation 21. PBC patients with small and medium-large varices should be managed according to Baveno recommendations, both in terms of treatment and surveillance over time (until PBC-specific evidence are available).

Quality of Evidence: Moderate
Strength of Recommendation: Conditional for

In PBC, the development of portal hypertension (pH) is associated with the risk of hepatic decompensation and worse outcomes [65,66]. Therefore, the identification of PBC patients with clinically significant portal hypertension (CSPH) is crucial in order to guide screening and surveillance strategies. pH can develop even in the early stages of PBC, either in association with or independently of nodular regenerative hyperplasia [66–68]. Notably, the hepatic venous pressure gradient (HVPG) may underestimate the actual portal pressure, in PBC due to the presence of a pre-sinusoidal component [60].

Several predictors of the presence of gastro-esophageal varices have been identified in PBC. These include a platelet count below 140,000/mm [65] and a Mayo risk score of 4.5 or higher [69]. Additionally, even in the early stages of disease a platelet count <200,000/mm [65], along with low albumin, high alkaline phosphatase and splenomegaly, have been associated with varices [69]. Liver stiffness measurement (LSM) at different cut-offs (ranging from 9.6 to 16.9 kPa) has been proposed to define advanced fibrosis in PBC [59,69–71]. The Baveno VII guidelines recently indicated a LS of 10 kPa or higher as suggestive of advanced chronic liver disease (ACLD), irrespective of the liver disease. Notably, differently from other ACLDs, a threshold to predict the presence of CSPH in PBC was not defined [71].

The Baveno VI Consensus Workshop suggested LSM below 20 kPa and a platelet count above 150.000/mm^3 as criteria to rule out the need for screening endoscopy [69], and this approach has been endorsed by the latest EASL PBC guidelines [72]. Although not specifically derived for PBC or other cholestatic diseases, these criteria were subsequently shown to result in a false negative rate of 0–5 % and could potentially reduce the number of unnecessary endoscopies by 40–76 % [73,74]. The LSM threshold for ruling out CSPH has been reduced to 15 kPa in the latest Baveno VII guidelines [71], which also recommend early treatment with nonselective beta-blockers (NSBB) for patients with CSPH, regardless of their variceal status. However, LSM by VCTE rules out and rules in effectively CSPH, better if combined with platelets, in patients with viral, alcoholic and non-obese NASH cACLD but there are no data on cholestatic liver disorders.

The management of gastro-esophageal varices, including therapeutic approaches and surveillance strategies, is not different in PBC than in other chronic liver diseases and should follow the recommendations by the Baveno guidelines and the latest EASL PBC guidelines [71,72,75].

3.4.2. Who and how do we surveil for HCC?

Recommendation 22: All PBC patients with confirmed or suspected cirrhosis should undergo ultrasound surveillance every 6 months.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Similar to other chronic liver diseases, individuals with PBC are at risk of developing hepatocellular carcinoma (HCC) [72,76]. The incidence of HCC in PBC patients is about 0.36 per 100 patient-years [72,76]. Notably, the prognosis of HCC in PBC appears to be worse compared to other liver diseases [77]. While HCC can arise in non-cirrhotic PBC patients [77,78], advanced liver fibrosis has been recognized as the main risk factor for the development of HCC [76–79]. Previous studies in PBC patients have shown that male sex [77–80], advanced age, and the presence of some coexisting factors such as viral hepatitis, diabetes, alcohol consumption and overweight, are associated with a greater risk of HCC [81–83]. There are conflicting results about the impact of biochemical response to treatment on the risk of HCC [77,79,84]. The current PBC guidelines recommend HCC surveillance in patients with suspected cirrhosis according to regional HCC screening strategies [72,85,86]. The American guidelines suggest extending surveillance to all male PBC patients [86]. The identification of additional risk factors may enable the customization of more specific surveillance strategies for PBC patients. Ultrasound examination is the standard screening test [87,88], although the use of alpha-fetoprotein as an additional tool for improving early-stage HCC detection remains controversial [87–89].

3.5. Treatment

3.5.1. Who do we select for second-line therapy?

Recommendation 23: Oral ursodeoxycholic acid at 13–15 mg/kg/day is recommended as the first-line therapy for all patients with PBC; if tolerated, it should be continued for life.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

A recent study by the Global PBC study group suggests that the therapeutic target for PBC should be achieving ALP levels within the normal range and/or bilirubin levels below 0.6 times the upper limit of normal [90]. Patients meeting these criteria have the lowest risk of liver transplantation or death. Similarly, the reduction of values of GGT below 3.2 times ULN are associated with improved long-term survival in patients with ALP $<$ 1.5 times the ULN [19].

Further, a model based on pretreatment variables that accurately predicts UDCA response has been derived and externally validated [30]. The association with histological features provides face validity, and this model offers an alternative approach to treatment stratification that can identify patients likely to fail UDCA treatment already at baseline.

Considering these pieces of evidence collectively, the identification of patients who require second-line therapy should: 1) consider the presence of significant fibrosis in addition to liver biochemistry; 2) be anticipated at 6 months in selected patients; and 3) aim to achieve ALP normalization, decrease GGT below 3.2 times ULN, and decrease bilirubin levels below 0.6 times ULN.

Finally, before initiating second-line therapy, PBC patients who have an inadequate response to UDCA should be evaluated for alternative etiologies, such as variant syndrome with AIH, as these cases may require immunosuppressive treatment [91].

Of note, treatment escalation should also consider patient's age, level of cholestasis, disease stage, her/his wish, and the potential impact on quality of life with a risk-benefit balance approach.

3.5.2. How do we treat PBC patients at diagnosis?

Recommendation 24: Patients with PBC who do not normalize ALP and/GGT and transaminases (inadequate biochemical response) after 12 months of UDCA therapy are candidate to second-line therapy.

Quality of Evidence: High
Strength of Recommendation: Strong for

Ursodeoxycholic acid (UDCA) is the 1st-line therapy recommended by the European and American guidelines for initial treatment of PBC patients [72,86]. UDCA exerts its mechanisms of action by reducing the secretion of hydrophobic bile acids and promoting bicarbonate production, which protects cholangiocytes and periportal hepatocytes from the harmful effects of endogenous bile acids. Additionally, UDCA demonstrates anti-inflammatory and immunomodulatory effects [92]. The recommended dose of UDCA is 13–15 mg/Kg per day, to be taken lifelong, and the drug is generally well tolerated and safe, including during pregnancy. Randomized controlled trials have confirmed the beneficial effects of UDCA on biochemical tests and liver histology [93]. A metanalysis of three clinical trials and multicenter cohorts conducted by the Global PBC Study and UK-PBC study groups further demonstrated the positive impact of UDCA on clinical outcomes in patients with advanced disease [94]. This benefit was observed even in patients with an incomplete response to UDCA or those receiving a lower dose ($<$13 mg/kg/day). However, the LT-free survival rate was lower in patients with UDCA $<$13 mg/kg/day compared to those receiving $\geq$ 13 mg/Kg/day. These studies support the clinical efficacy of UDCA in preventing LT or death and emphasize the importance of initiating prompt and lifelong UDCA treatment in all PBC patients.

UDCA is generally well tolerated, with minimal side effects such as a minor weight gain in the first year, hair thinning, and rarely, diarrhea and flatulence. Moreover, UDCA is considered safe and can be continued during pregnancy and breast feeding.

3.5.3. How do we treat patients who fail to UDCA therapy?

Recommendation 25: Obeticholic acid (OCA) is conditionally approved as second – line treatment and can be used in combination with UDCA in patients with inadequate response to UDCA or in monotherapy in patients intolerant to UDCA. The initial dose is 5 mg daily with titration at 10 mg daily after 6 months, according to response and tolerability. OCA cannot be used in patients with current or previous decompensation.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 26: Bezafibrate can be used at the dose of 400 mg/day as off-label second– line therapy in combination with UDCA in patients with inadequate response to UDCA and with compensated liver disease.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 27: Budesonide at the initial dosage of 6–9 mg/day may be considered in selected, non-cirrhotic PBC patients with florid hepatic inflammation, with or without typical AIH features, but its long-term use is not recommended due to the increased risk of steroid-specific adverse events.

Quality of Evidence: Low
Strength of Recommendation: Conditional for

Recommendation 28: Immunosuppressive treatment in addition to UDCA is recommended only in patients with PBC and typical features of AIH.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Patients who have an inadequate response to UDCA should receive second-line therapy in combination with UDCA, as these patients have shown improved LT-free survival compared to untreated patients.

Obeticholic acid (OCA), a steroidal farnesoid X receptor agonist, received conditional approval from the FDA and EMA in 2016 as a second-line treatment in PBC in combination with UDCA for inadequate responders or as monotherapy for those intolerant to UDCA. This approval was based on the results of the 12-month, double-blind, placebo-controlled phase 3 POISE trial, which demonstrated the effectiveness of OCA in improving biochemical prognostic markers in 217 patients [95]. The primary endpoint, defined as a combination of ALP reduction and normal bilirubin levels, was more frequently achieved in the OCA groups (46%–47%) compared to the placebo group (10%). Pruritus was the most common adverse event, occurring in 56%–68% of patients treated with OCA versus 38% in the placebo group. Furthermore, the positive effect of the drug on biochemical markers was sustained for at least 3 years. Prospective studies are needed to demonstrate the impact of OCA on "hard" clinical endpoints. Notably, the COBALT study, which aimed to evaluate the effectiveness of OCA on long-term clinical outcomes, was recently halted for challenges in patient retention due to the availability of the drug on the market. An in-silico analysis (COPEC study) comparing transplant-free survival between 209 patients treated with OCA in the POISE trial and external controls inadequately responding to UDCA from the Globe and UK-PBC cohorts, showed superiority in patients treated with OCA, although this study was limited by a small number of events in the trial cohort [96]. Post-marketing studies conducted in Italy, Canada, and Spain on PBC patients with inadequate response to UDCA confirmed the efficacy and safety of OCA, consistent with the findings of the POISE trial [15,97,98]. Of note, the FDA updated the label of OCA in 2021 to restrict its use to patients without current cirrhotic decompensation, previous episodes of decompensation, and/or compensated cirrhosis with portal hypertension [99]. Similarly, the Italian Medicine Agency (AIFA) published an informative note in June 2022 recommending specific actions regarding the use of OCA in cirrhotic patients [99].

A study conducted in Italy, involving 100 PBC patients with cirrhosis treated with OCA, described that one-third of them experienced efficacy, while approximately 20% discontinued treatment due to pruritus or hepatic serious adverse events [100]. The occurrence of hepatic serious adverse events was associated with baseline biochemical parameters, such as elevated bilirubin (above 1.4 mg/dL).

Bezafibrate, the third drug proven effective in improving biochemical parameters in PBC after UDCA and OCA, belongs to the class of hypolipidemic agents called fibrates. Fibrates act as peroxisome proliferator-activated receptor (PPAR) agonists, which are transcription factors involved in fatty acid catabolism and inflammatory response. Additionally, fibrates have been shown to repress bile acid synthesis in the liver and increase phospholipid excretion into the bile for their anticholestatic effects [101]. Bezafibrate, a pan-PPAR agonist, and fenofibrate, a specific PPAR-alpha agonist, have shown beneficial effects in patients with PBC.

The BEZURSO trial, a 24-month-double blind, placebo-controlled, phase 3 trial using 400 mg daily of bezafibrate, included 100 PBC patients with inadequate response to UDCA according to the Paris-2 criteria. Bezafibrate treatment resulted in a complete biochemical response in 31% of patients, with a significant reduction of pruritus compared to placebo. Adverse event rates did not differ between groups, but the bezafibrate group experienced higher rates of myalgia and serum creatinine elevation. Long-term benefits of bezafibrate were observed in a retrospective cohort study of 3908 Japanese PBC patients, where the addition of bezafibrate to UDCA was associated with decreased mortality and need for LT. A systematic review on the safety of fibrates in cholestatic liver diseases confirmed their safety and tolerability in PBC patients. In light of this evidence, the recent AASLD practice guidance update suggested considering fibrates as off-label alternatives for PBC patients with inadequate response to UDCA, while cautioning against their use in patients with decompensated liver disease.

Fenofibrate has not been studied in a randomized controlled trial for PBC. However, data from small retrospective studies suggest its effectiveness in reducing or normalizing ALP and transaminase levels without increasing serum creatinine, and its potential to reduce bile acid toxicity. Additionally, a multicenter retrospective cohort study evaluating the combination of fibrates (bezafibrate or fenofibrate) with OCA and UDCA showed a significant fall in ALP levels compared to dual therapy alone.

Considering the convincing evidence regarding the efficacy and safety of fibrates in improving liver biochemistry and clinical outcomes in PBC, we consider bezafibrate as an effective and safe off-label alternative to OCA for patients who are unlikely to benefit from or are intolerant to, OCA.

Moreover, the combination of the two second-line therapies, OCA and bezafibrate, in addition to UDCA, can rescue an additional proportion of non-responders to UDCA plus a second-line drug. Safety data are limited and further studies are warranted [102].

Budesonide, a potent synthetic corticosteroid with high first-pass metabolism in the liver, has been tested in a 3-year phase 3 trial in combination with UDCA for PBC patients with inadequate response to UDCA. Although the trial was underpowered and did not meet its primary histologic endpoint, a higher proportion of patients in the budesonide group achieved the biochemical endpoint compared to the placebo group at various timepoints. Notably, one-third of budesonide-treated patients achieved normalization of ALP levels. No significant differences in overall adverse events and serious adverse events were documented between the budesonide and placebo groups, although drug-specific adverse events were more frequent in the budesonide group and contributed to a higher frequency of premature medication discontinuation. Thus, budesonide should only be considered in non-cirrhotic PBC patients with florid hepatic inflammation, with or without typical AIH features. However, long-term use is not recommended due to the increased risk of steroid-specific adverse events.

While this position paper is written, evidence is becoming available on the efficacy of two novel selective peroxisome proliferator-activated receptor (PPAR) agonists, i.e. Elafibranor (alpha/delta - α,δ) [103] and Seladelpar (selective δ) [104]. Both molecules achieved the primary endpoint, i.e. the biochemical response (defined as an ALP level less than 1.67 times the upper limit of the normal range, with a decrease of 15% or more from baseline, and a normal total bilirubin level), significantly greater than with placebo. Specifically, in the Elafibranor trial the response was achieved in 51% of the patients who received the drug and in 4% who received placebo; whereas, in the Seladelpar trial, the response was achieved in 61.7% of the patients who received the drug and in 20% who received placebo. No concerning safety signals were reported associated with both drugs.

Additionally, preliminary results from a phase II RCT investigating Setanaxib, a NOX1/4 inhibitor, have shown that the primary endpoint, i.e. percentage change from baseline in GGT at Week 24, was not met. However, the secondary endpoints, i.e. change from baseline in ALP, liver stiffness, fatigue at Week 24, provided preliminary evidence for potential anti-cholestatic and anti-fibrotic effects in PBC [105].

Several new drugs may become available for treating pruritus in PBC, including ileal sodium-bile acid cotransporter (ASBT) or ileal bile acid transporter (IBAT) inhibitors, as well as other PPAR agonists.

Finally, immunosuppressive treatment in addition to UDCA is recommended in patients with PBC and typical features of AIH, particularly severe interface hepatitis, and may be considered in patients with moderate interface hepatitis according to current European guidelines.

3.5.4. How do we treat patients with chronic itch?

Recommendation 29: Bezafibrate 400 mg/day can be used as first-line treatment in patients with moderate to severe pruritus associated with PBC, due to its favourable effect on cholestasis, except in decompensated cirrhosis. Monitoring of serum liver tests Creatine phosphokinase and creatinine is recommended after their initial use.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 30: Rifampicin 150 mg to 300 mg twice daily can be used as an alternative to bezafibrate in patients with PBC and moderate to severe pruritus. Monitoring serum liver tests after initial use (at 6- and 12-weeks following drug initiation) and following dose increase because of potential hepatotoxicity is recommended.

Quality of Evidence: Moderate
Strength of Recommendation: Conditional for

Recommendation 31: Cholestyramine can be used as first-line therapy in patients with mild pruritus or in case bezafibrate or rifampicin are contraindicated or associated with adverse effects. Polypharmacy increases the risk of drug interaction; attention should be paid to avoiding interaction with other medications as a result of its anionic binding resin properties.

Quality of Evidence: Low
Strength of Recommendation: Conditional for

Recommendation 32: Naltrexone and sertraline can be considered in patients with pruritus if bezafibrate, rifampicin and cholestyramine are ineffective, contraindicated or associated with risk and/or adverse effects.

Quality of Evidence: Low
Strength of Recommendation: Conditional for

Recommendation 33: Patients with moderate to severe pruritus resistant or intolerant to commonly available antipruritic treatments should be referred to tertiary care centers where experimental therapies are available.

Quality of Evidence: Low
Strength of Recommendation: Conditional for

The 2017 EASL clinical practice guidelines recommended a stepwise approach to treating pruritus in PBC [72]. The initial treatment options include cholestyramine (1–4 times 4 g daily), rifampicin (150–300 mg daily), naltrexone (starting with 12.5 mg daily and increasing gradually up to 50 mg daily if well tolerated), and sertraline (50–100 mg daily), all of which have limited efficacy or tolerability.

Since then, the beneficial effect of bezafibrate on pruritus in PBC patients has been reported. This was observed in the retrospective PBC cohort from Barcelona [106], the BEZURSO trial [107], and the double-blind, randomized, placebo-controlled FITCH trial [108]. The FITCH trial aimed to evaluate the efficacy of bezafibrate (400 mg daily) compared to placebo for 21 days in treating moderate-to-severe pruritus in 74 individuals with PSC, PBC or secondary sclerosing cholangitis. Bezafibrate resulted in $a \geq 50\%$ reduction of severe or moderate pruritus in 55% of PBC patients (45% in the entire group) compared to 11% in the placebo group ($P = 0.003$). Secondary end points included reductions in morning and evening pruritus intensity, improvement in the 5D-Itch questionnaire, and a significant decrease in serum alkaline phosphatase levels (by 35%; $P = 0.03$ *vs.* placebo), correlating with improved pruritus. A mild increase in serum creatinine levels was observed (3% bezafibrate, 5% placebo; $P = 0.14$). In conclusion, bezafibrate is considered the first choice for treating patients with PBC with moderate-to-severe pruritus, except in cases of decompensated cirrhosis or other contraindications. Regular monitoring of serum creatinine, and liver function tests is recommended to promptly identify adverse effects and discontinue the drug.

Rifampicin, a PXR agonist, has been proven effective in treating PBC pruritus in four small randomized-controlled or crossover trials [109–112] and three meta-analysis [113–115]. While the drug is generally safe, 5% of patients develop rifampicin-induced hepatitis at a median of 70 (range 27–130) days after drug initiation [116]. Therefore, it is currently recommended to monitor liver function tests at 6 and 12 weeks after starting rifampicin, as well as with each dosage increase [72].

Due to its limited efficacy [114], poor tolerance [117] and the need to take cholestyramine at least 4 h apart from UDCA and other drugs [118], we consider the use of cholestyramine as first-line therapy only in patients with mild pruritus or those with contraindications to bezafibrate and rifampicin, which can comply with the dosing schedule.

In the near future, several new drugs may become available for treating pruritus in PBC, including ileal sodium-bile acid cotransporter (ASBT) or ileal bile acid transporter (IBAT) inhibitors, as well as other PPAR agonists.

Finally, we consider of utmost importance to refer patients with severe pruritus resistant or intolerant to common antipruritic agents to expert centers where experimental therapies are available [119]. Liver transplantation for severe pruritus should be considered as the primary indication in patients who continue to experience severe symptoms despite all therapeutic attempts [72].

3.5.5. How do we treat patients with chronic fatigue?

Recommendation 34: In PBC patients with fatigue a complete diagnostic work-up to exclude alternative causes of fatigue is recommended. Education and counseling on developing coping strategies for patients with PBC is recommended.

Quality of Evidence: Low
Strength of Recommendation: Strong for

Fatigue is a common symptom in PBC, reported in up to 50% of Italian and French patients at diagnosis [120,121], and even more frequently in British patients [122]. It significantly impairs the quality of life of PBC patients and is characterized by the inability to perform daily activities, both mentally and physically [123]. Cognitive dysfunction is also prevalent in a considerable number of patients, further impacting their quality of life [123].

However, fatigue in PBC patients can have other underlying causes such as thyroid dysfunction, anemia, depression, or dia-

betes. Thus, a comprehensive diagnostic workup is recommended to rule out alternative diagnoses that can be appropriately treated.

To date, there is no proven medical treatment for fatigue in PBC patients. The guidelines suggest providing patients with advice on developing coping strategies and avoiding social isolation, as this can exacerbate the effects of fatigue [72].

3.6. Liver transplantation

3.6.1. When should we refer a PBC patient to a liver transplant center?

Recommendation 35: PBC patients with complications of cirrhosis, including HCC, or indicators of advanced disease (progressively increasing bilirubin values, MELD >15, worsening disease-specific prognostic scores) should be referred to a transplant center.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 36: LT can be considered in very selected patients with refractory pruritus causing a significant impact on quality of life. Fatigue is not, per se, an indication for liver transplantation in patients not meeting transplant minimal listing criteria.

Quality of Evidence: Low
Strength of Recommendation: Strong for

Advanced PBC is a well-established indication for liver transplantation (LT) [124] and accounts for about 3,6–9,7 % of transplants in adults [125–127]. The percentage of individuals transplanted for PBC showed a decrease over the last decades in various series [126,128] but the absolute number of transplants seems to remain essentially stable in recent years [125].

Post-transplant results in subjects with PBC are comparable, if not sometimes better [127,129], than observed in other indications with 1-year survival rates reported between 92 and 93 % and 5-year survival between 80 and 9–90 % [128–130].

LT should be considered in PBC similarly to other indications, particularly when the Model for End-stage Liver Disease (MELD) exceeds a value of 15 [131]. Persistent increase in bilirubin values (above 3–5 mg/dl) and the presence of portal hypertension, or other cirrhosis complications, including HCC, should also result in referral to the transplant center [132,133]. Several disease-specific prognostic scores have been developed and validated over the years (Mayo Risk Score [132], UK-PBC Risk Score [18], GLOBE Score [63]) with even better predictive capabilities than MELD [133] but their use in everyday clinical practice as a tool for indication for LT is scarce and shows significant variability across countries and different transplant systems. In addition, no data exist on the potential usefulness of such scores as list prioritization tools.

Refractory pruritus with a significant impact on quality of life may be an indication for transplantation in selected cases when available medical treatments have failed [133]. Given the scarce evidence in the literature to guide LT indication in these cases, they should be discussed in a multidisciplinary manner on a case-by-case basis. Similarly, no literature data are available to define the list priority of patients with such indication, which may vary significantly across transplant centers.

Overall health-related quality of life usually improves after liver transplantation but disease-related symptoms, mainly chronic fatigue, may persist in a non-negligible proportion of subjects, so fatigue is not an indication for LT [123,133].

3.6.2. How can we prevent PBC from recurring after liver transplant?

Recommendation 37: Post-LT PBC recurrence is common and with potential impact on graft and patient survival and must be histologically proven.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recommendation 38: Management of immunosuppressive therapy should follow standard protocols in PBC transplanted recipients.

Quality of Evidence: Low
Strength of Recommendation: Conditional for

Recommendation 39: Prophylactic UDCA therapy should be offered after LT in PBC transplanted subjects.

Quality of Evidence: Moderate
Strength of Recommendation: Strong for

Recurrent PBC has been described with various frequencies ranging between 8,3 % and 46 % [134–139]. The diagnostic criteria used (histologic or biochemical), and the time of observation, inevitably influence the observed frequencies. Diagnosis of disease recurrence requires in-depth histologic investigation because AMA p/ositivity may persist after LT regardless of disease recurrence and laboratory changes may be nonspecific and caused by various post-transplant complications.

Recurrent PBC has been long considered a benign condition with no significant impact on long-term post-LT outcomes [134,140], but more recently it has been reported that disease recurrence is associated with lower graft survival and worse outcomes [130,141].

A role for immunosuppressive regimen after LT has been proposed in PBC recurrence. It has been reported that tacrolimus [130] and mycophenolate [140] may increase the risk of recurrent PBC whereas cyclosporine may be associated with a reduced risk. In a meta-analysis of available retrospective studies, only tacrolimus use was associated with a higher risk of PBC recurrence [140]. It is necessary to consider how multiple additional factors, including recipient age, donor-recipient sex mismatch, and MELD score, have been proposed as potential risk factors for PBC recurrence [140].

There is insufficient evidence to suggest a specific immunosuppressive regimen to prevent PBC recurrence, even considering the general benefits of tacrolimus as the immunosuppressive agent of choice in LT recipients.

UDCA is used in some transplant centers as general graft protective treatment, but this practice is not supported by adequate evidence. In recent years, evidence has emerged for the protective role of UDCA in preventing PBC recurrence and in improving post-transplant outcomes in PBC transplanted subjects [141–143]. UDCA is a safe and inexpensive drug with proven efficacy in PBC and should therefore be offered as post-LT prophylactic treatment in individuals transplanted for that indication.

Conflict of interest

Cristina Rigamonti receives speaking engagements and travel grants from Advanz Pharma, Roche, and Abbvie. Nora Cazzagon receives speaker fees from Intercept and Advanz, and serves on advisory boards for Albireo, IPSEN, and Orphalan, also receiving travel grants from Orphalan and IPSEN. Luigi Muratori has received speaker fees from Advanz. Alessio Gerussi receives speaker fees from Advanz and consults for CAMP4 Therapeutics, Ipsen, and Signant Health. Marco Carbone consults for Ipsen, Advanz, GSK, Albireo, Cymabay, Mayoly, Echosens, and IHEP, and serves on advisory boards for Ipsen, Cymabay, and Dr. Falk.

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