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REVIEW

A consensus integrated care pathway for patients with primary biliary cholangitis: a guideline-based approach to clinical care of patients

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ABSTRACT

Introduction: Primary biliary cholangitis (PBC) is an infrequent, immune-mediated cholestatic liver disease, which can lead to liver fibrosis, cirrhosis and complications of end-stage liver disease. The established goals of treatment of PBC are prevention of end-stage liver disease and amelioration of associated symptoms. The European Association for the Study of the Liver (EASL) management guidelines provide extensive recommendations on the diagnosis and management of PBC.

Areas covered: This article describes the development by expert consensus of a 'PBC Integrated Patient Care Pathway' to simplify and standardize the management of PBC for clinicians based on current practice.

Expert opinion: Guideline adoption is potentially poor in practice since most patients with PBC in the community are seen by general gastroenterologists or hepatologists without a special interest in autoimmune liver disease. The PBC Integrated Patient Care Pathway is a best practice tool for clinicians designed to complement the EASL Clinical Practice Guidelines for the diagnosis and management of PBC patients. It gives clinicians a practical decision tree of the key steps in PBC management, thereby providing a simplified framework and an opportunity for more uniform practice that supports the safe and timely adoption of varied models of care provision to patients with PBC.

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1. Introduction

Primary biliary cholangitis (PBC) is a rare, immune-mediated cholestatic liver disease, which can lead to liver fibrosis, cirrhosis and complications of end-stage liver disease if untreated or under-treated [1,2]. Ultimately, it may result in liver transplantation or death [3]. Therefore, efforts to prevent the development of end-stage liver disease are important components of care. Accordingly, the established goals of treatment of PBC are summarized as prevention of end-stage liver disease and amelioration of associated symptoms [1]. The bile acid ursodeoxycholic acid (UDCA) alongside the semi-synthetic bile acid obeticholic acid (OCALIVA®, OCA) are currently the only therapies approved for the treatment of PBC [2]. Other therapies are used off-label (e.g. bezafibrate). In all patients with PBC, treatment should be ideally personalized to the individual's risk and stage of liver disease, alongside associated symptoms. In this way, the heterogeneity of disease presentation, course, and consequence can be recognized and most efficiently impacted on. Over time, the efficacy of care, as related to response to therapy and symptom control, must be continually appraised. Ongoing international collaborative studies confirm that the patients with the best long-term outcome from PBC, are those who have the most improvement in serum liver tests i.e. alkaline phosphatase (ALP) and bilirubin in particular. To reach this goal, many efforts are ongoing globally to develop new therapies, as well as to investigate existing therapies.

Efforts to slow down disease progression focus on offering all patients with PBC first-line therapy with UDCA. In long-term studies, UDCA has been shown to reduce the incidence of liver-related complications and prolong survival in patients with PBC. Patients with intolerance to UDCA or at high-risk of disease progression, as evidenced by inadequate response to UDCA, should be considered for second-line therapy. In this setting, OCA is the only licensed therapy [4]. It is indicated in combination with UDCA in patients who have an inadequate response after UDCA therapy or as monotherapy for those unable to tolerate UDCA [5,6]. Non-licensed therapy with fibrates is also a recognized choice for patients, given the recent randomized controlled trial data from France [7].

The latest guidelines from the European Association for the Study of the Liver (EASL) provide extensive recommendations

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Supplemental data for this article can be accessed here.

Article highlights

- The suggested pathway starts with making a clear diagnosis of PBC based on elevated ALP and the presence of disease-specific autoantibodies in adult patients with cholestasis and no overt alternate systemic disease.
- This is followed by initiation of life-long first-line ursodeoxycholic acid (UDCA) therapy at 13–15 mg/kg/day, alongside baseline clinical assessments.
- Pre-treatment risk of disease progression should be determined and patients at the highest risk of disease progression should be considered for close monitoring and/or early referral for specialist assessment.
- After 12 months of UDCA therapy, all patients should be assessed for biochemical response to treatment.
- A significant proportion of patients (25-50%) do not adequately respond to UDCA and are therefore at increased risk of disease progression.
- Patients with ALP <1.5xULN and normal bilirubin levels and early or no evidence of fibrosis can be considered low risk and maintained on UDCA therapy. Patients with severe uncontrolled pruritus, bilirubin levels >2xULN or decompensated cirrhosis should have further specialist assessment. Patients with an inadequate response to UDCA are at intermediate to high risk of disease progression and should therefore be considered for 2nd line therapy
- The pathway concludes with initiation of 2nd line therapy for which the only licensed therapy is the FXR agonist, obeticholic acid (OCALIVA®, OCA).
- Other reported therapies are used either off-label (e.g. Bezafibrate) or available as clinical trial agents only.
- The development of safe and effective therapies, alone, or in combination, is an evolving area of PBC care, with present significant optimism that in the future patients will access a variety of licensed treatment options.

on the diagnosis and management of PBC [1]. The EASL Clinical Practice Guidelines (CPG) include a considerable amount of information on various PBC topics, and provide 47 recommendations around [1]: the initial diagnosis of PBC [2]; PBC risk stratification [3]; defining inadequate response to treatment [4]; guidance for prognostic tools for PBC in practice [5]; therapies to slow disease progression [6]; PBC in the pregnancy setting [7]; management of PBC with features of autoimmune hepatitis (AIH) [8]; management of symptoms and extrahepatic manifestations [9]; management of complications of liver disease; and [10] organization of clinical care delivery.

Guidelines are consensus statements that provide an overview of all the available evidence with recommendations on patient management [8]. Most patients with PBC in the community are seen by general gastroenterologists or hepatologists without a special interest in autoimmune liver disease. Therefore, guideline adoption is recognized to be potentially poor in practice [9], which suggests added value to development by expert consensus of simplified patients care pathways for clinicians. Vanhaecht et al. define a care pathway as 'a complex intervention for the mutual decision-making and organization of care processes for a well-defined group of patients during a well-defined period' [10]. In PBC, care pathways aim to ensure a global minimum standard of care for any patient living with this condition so that the right things are done by the right clinician, to the right patient, in the right way, at the right time. In this way, it is hoped that any inherent complexities associated with guideline details can be overcome and translated into clear messages to allow clinicians with less experience in PBC management to deliver high-quality care. Such efforts focus on consistency with guidelines derived *Clinical Care Standards*, which for PBC include how to [1]: efficiently diagnose PBC [2]; risk-stratify patients correctly [3]; treat appropriately; and [4] alleviate as able any associated symptom burden.

We herein describe our development of a 'PBC Integrated Patient Care Pathway' standardizing the management of PBC based on current practice. The content is based on the EASL Clinical Practice Guidelines and reflects the opinions of the academic authors. The process was supported by Intercept Pharmaceuticals, but without restriction on the guidance provided.

2. Methods

On the basis of existing guidance and practice, 12 specialists with experience in managing PBC working across Europe and Canada were asked to agree on the steps, core content and supporting tools for a proposed Patient Care Pathway. They aimed to move toward a cohesive method of PBC management that was reflective of best-care for patients, and in particular mirrored health delivery models of the European and Canadian region. The group was also asked to agree on the best format for its dissemination. For this purpose, the specialists discussed the information needs of clinicians with varying levels of experience of managing patients with PBC. The group agreed that the pathway should give practical advice on [1]: confirming a diagnosis of PBC [2]; performing baseline clinical and risk assessments [3]; initiating first-line therapy [4]; performing on-treatment risk stratification at the appropriate time point based on response to first-line therapy; and [5] identifying patients who require second-line therapy and/or further assessments. The experts debated the assessments and criteria that should be included, and formed subsequent consensus. A diagram delineating the consensus on management principles most common across different countries was outlined and further developed based on EASL guidelines [1] and clinical experience.

Based on the consensus, a working and writing subgroup of six of the experts further developed and completed the Integrated Patient Care Pathway. As this pathway should provide guidance for the clinicians with less experience in PBC management, the subgroup agreed that it should be limited in depth and detail, focusing on key clinical care decisions for clinicians. Furthermore, the subgroup agreed that any recommendations should be framed in a positive and inclusive tone (i.e., when treatment should be given, rather than when it should not be given).

3. Results

The subgroup reached consensus on a five-part structure and the content for the Integrated Patient Care Pathway based on the EASL Clinical Practice guidelines alongside their clinical experience (Supplementary file 1). The pathway captures the journey most commonly experienced by patients with PBC. It recognizes broad paths followed by patients and provides

added guidance on timing and frequency of investigations, as well as appropriate follow-up frequency, and recommendations for further specialist assessment.

3.1. Confirming a PBC diagnosis

3.1.1. Initial assessment and management

- A diagnosis of PBC should be suspected in adult patients with persistent cholestatic abnormalities in serum biochemistry, particularly elevated ALP, and/or gamma-glutamyltransferase [GGT]; increased bilirubin (conjugated) values and IgM levels can also be seen. These abnormalities in serum biochemistry may or may not be in the context of relevant symptoms such as pruritus, sicca syndrome, arthralgia, or fatigue [1] (Figure 1).
- Other biochemical markers such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may be elevated, indicating liver parenchymal inflammation [1].
- Initial assessment of patients should be based on history, physical examination, laboratory investigations, and abdominal ultrasound (Figure 1).
  - History should carefully exclude drug exposure, and seek the presence of coexistent autoimmune conditions in the patient and family (most commonly thyroid disease, celiac disease, Sjogren's disease, and scleroderma).
  - Physical examination (including skin evaluation) should be used to screen for hepatomegaly, splenomegaly, and extrahepatic signs of advanced liver disease [1] (e.g. xanthelasma and spider thalangectasia), as well as exclude alternate systemic disease processes.
  - Laboratory investigations should exclude common causes of liver disease (e.g. viral, metabolic, and genetic), and should specifically include serum liver biochemistry (ALP, transaminases), specific autoimmune liver disease evaluation: antimitochondrial antibodies (AMA) and/or PBC-specific antinuclear (ANA) antibody, alongside immunoglobulin quantification.
  - Ultrasound should be used to exclude overt obstructive causes of cholestasis [1].
- A secure diagnosis of PBC can be established based on elevated ALP and the presence of disease-specific autoantibodies (most often AMA at a titer of more than 1:40) in adult patients with cholestasis and no likelihood of alternate systemic disease [1] (Figure 1).
- Liver biopsy is rarely required for diagnosis and can be misleading at times, as disease in patients presenting most commonly with early stage can be patchy and nonspecific. Liver biopsy should be considered if disease-specific autoantibodies are absent, or in case of concern over features of autoimmune hepatitis (AIH), or coexistent nonalcoholic fatty liver disease (NAFLD), or other systemic/extrahepatic comorbidities (Figure 1).
- In some series upwards of 8–10% of PBC patients demonstrate features of AIH (Figure 1). The presence of PBC with features of AIH can be approached diagnostically using the 'Paris criteria' [1,11]. This approach attempts to confirm that there are simultaneous characteristic features of PBC and AIH (PBC-AIH 'overlap' syndrome).

PBC equates to at least two of the following:

- ALP ≥2x upper limit of normal (ULN) or GGT >5x ULN;
- AMA titer >1:40;
- Florid bile duct lesion on histology.

For AIH, histology is considered essential in the form of moderate or severe interface hepatitis in addition to the following features:

- ALT ≥5x ULN;

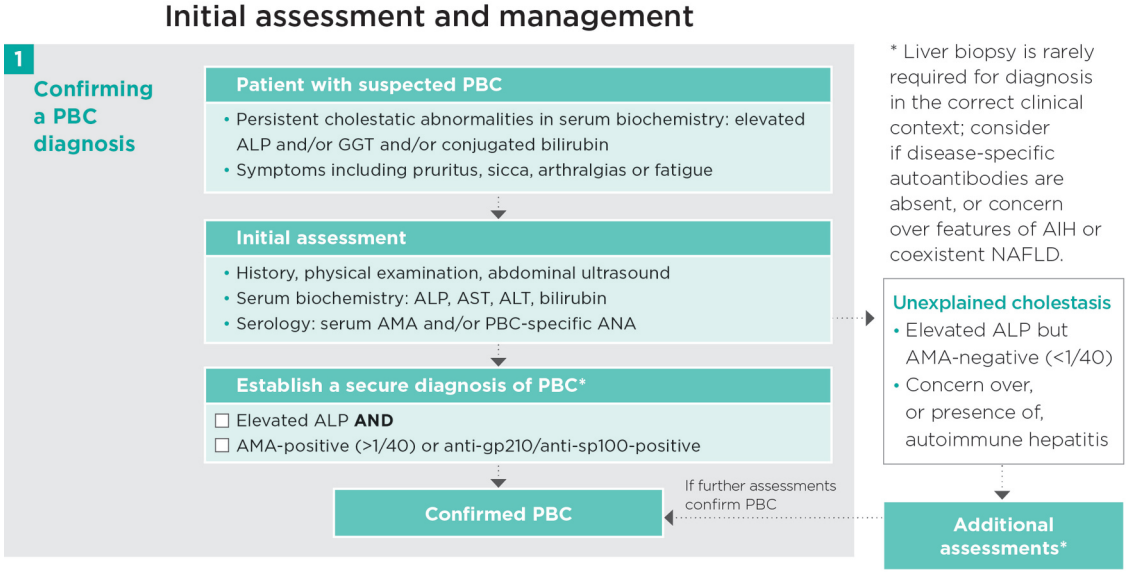

Figure 1. Confirming a PBC diagnosis Abbreviations.

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondiral antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis.

- Serum IgG levels ≥2x ULN or smooth muscle autoantibody positive.

Hyperlipidemia is frequently seen in cholestatic liver disease including PBC and may require further evaluation as to its individual clinical significance in any individual patient.

3.2. Initiating first-line UDCA therapy and performing baseline clinical assessment and risk stratification

3.1.2. Initiation of first-line therapy

- All patients diagnosed with PBC should be offered first-line therapy with oral UDCA in a weight-based manner at a dose of 13–15 mg/kg/day (Figure 2). UDCA should be continued for life if tolerated. UDCA has been shown to improve long-term clinical outcomes.

3.1.3. Performing baseline clinical assessment

- Baseline clinical assessment should be carried out alongside treatment initiation. This assessment 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 (Figure 2).
- A baseline assessment should consider the following (Figure 2):
  - Around 90% of patients diagnosed with PBC are female and the average age at diagnosis is around 50 years [2,12].
  - Early age at diagnosis (e.g. <45 years) is a recognized risk factors for inadequate response to UDCA therapy

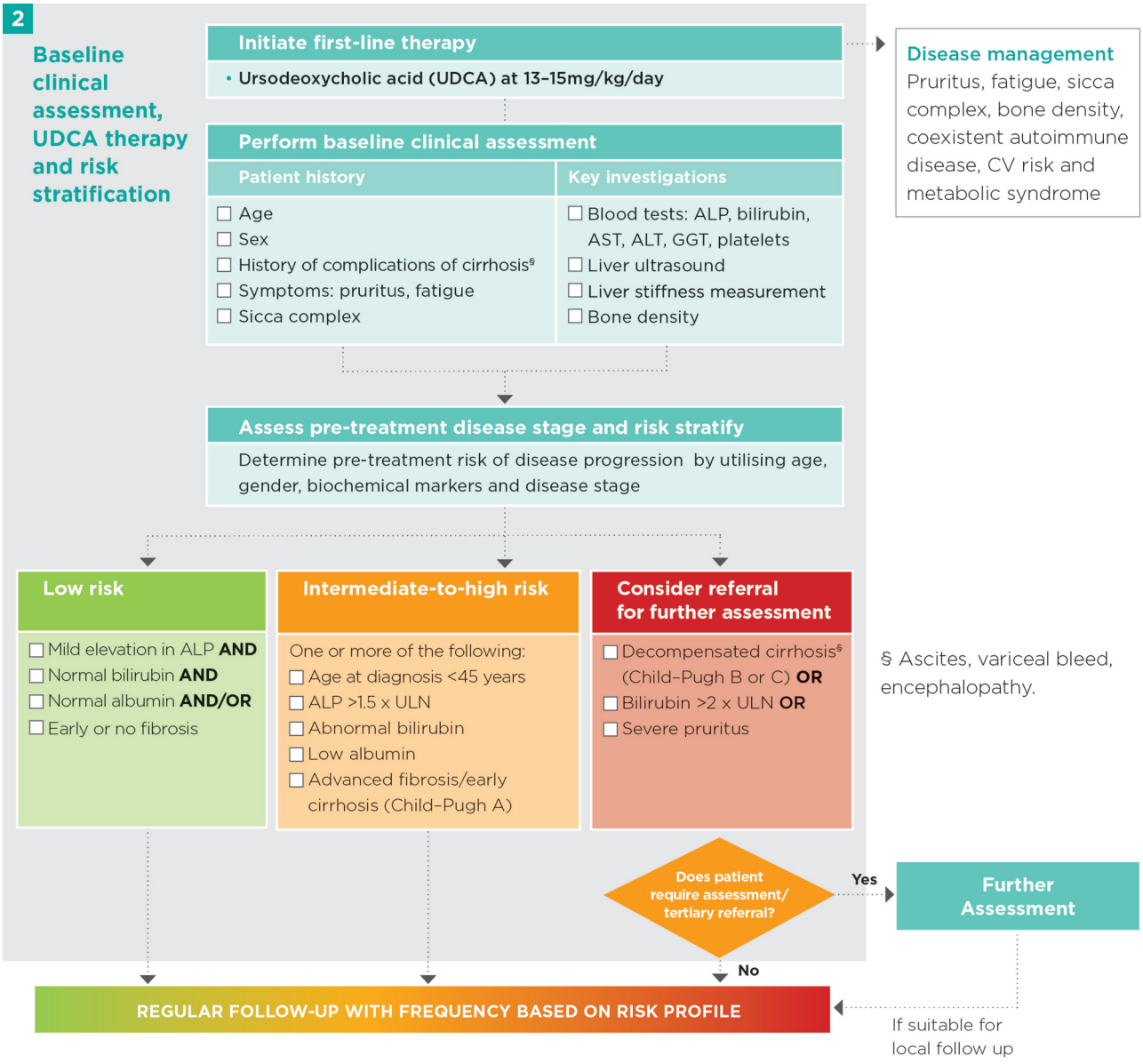

Figure 2. Baseline clinical assessment, UDCA therapy and risk stratification.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CV, cardiovascular; GGT, gamma-glutamyltransferase; PBC, primary biliary cholangitis; UDCA, ursodeoxylcholic acid; ULN, upper limit of normal.

and therefore disease progression. Male patients have been described to have more advanced disease at PBC diagnosis, likely for a late presentation [12]. Hence, particular attention needs to be paid to male patients and all patients diagnosed at a young age, such as before the age of 45 years.

- Patients with an insufficient response to UDCA are at the greatest risk of disease progression, and along with patients with cirrhosis, are at greater risk of liver complications [1]. Liver complications of PBC include the complication of any end-stage liver disease, i.e. esophageal varices and variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatocellular carcinoma [1]. It is therefore important to identify high-risk patients early in the patient care cycle to evaluate them actively for the most appropriate pathway of care, with targeted monitoring.
- The severity of symptoms does not necessarily correlate with the disease stage in PBC. However, severe pruritus can indicate an aggressively ductopenic variant of PBC, which is associated with a poorer prognosis [1].
- Patients with PBC have frequent evidence of osteoporosis with resultant risk of fragility fractures, while osteopenia affects the majority of patients. Therefore, all patients with PBC should have a risk assessment for osteoporosis [2] including measurement of serum levels of vitamin D and bone mineral density.

- The following key investigations should be performed [2]:
  - Blood tests:
    - ALP – as an enzymatic measure of cholestatic injury.
    - Bilirubin – as a biochemical measure of cholestatic injury and liver synthetic function.
    - ALT, AST – as indicators of liver inflammation.
    - Platelets – as an indicator of portal hypertension.
  - Liver ultrasound – to identify overt cirrhosis, ascites, and splenomegaly.
  - Liver stiffness measurement – as a noninvasive marker of liver fibrosis.

3.1.4. Pre-treatment disease staging and risk stratification

- Results from baseline clinical assessment is used to determine patient risk profile and to stage disease (Figure 2).
- Patient presentation and the course of PBC can be diverse; therefore, risk stratification is important to ensure all patients receive a personalized approach to their care.
- The frequency of regular follow-up should be based on symptoms burden and risk profile.
- Pre-treatment risk of disease progression can be determined by age, gender, biochemical markers and disease stage.
  - Patients at low risk of disease progression will tend to present with the following features (Figure 2):
    - Mild elevation in ALP; and
    - Normal bilirubin; and
    - Normal albumin; and/or
    - Early or no fibrosis.
  - Patients at intermediate-to-high risk of disease progression will have one or more of the following criteria [1] (Figure 2):
    - Age at diagnosis <45 years; or
    - ALP >1.5x ULN; or
    - Abnormal bilirubin; or
    - Low albumin; or
    - Advanced fibrosis/early cirrhosis (Child-Pugh A).
  - The following patients with the following should be considered at high risk and prioritized for early referral for further specialist assessment:
    - Decompensated cirrhosis (Child-Pugh B or C, ascites, variceal bleeding); or
    - Compensated cirrhosis with evidence of clinically significant portal hypertension; or
    - Bilirubin >2x ULN; or
    - Severe pruritus.

3.1.5. Symptom management

- Pruritus is a common burden for patients living with PBC:
  - Approximately 70% of patients experience pruritus at some point during their disease, with a point prevalence of over 50% [13].
  - Pruritus is reported as persistent by 30% of patients, and severe by 15% [2].
  - Importantly, pruritus in PBC can significantly impact quality of life [1].
- The severity of pruritus (no pruritus; mild pruritus; or moderate-to-severe pruritus) and its impact on the patient's quality of life should be determined and treatment given to control pruritus prior to initiation of PBC therapy.
- **Mild pruritus** can be self-managed using emollients and cold baths/showers, hydrating the skin immediately after a bath or shower, using an unscented moisturizer, wearing loose light clothes made from natural fibers, such as cotton, to avoid skin irritation from friction, maintaining a low room temperature where possible (especially in the bedroom) and avoiding hot environments and dry conditions
  - Anti-pruritic drug treatment should be considered if the patient's quality of life is affected.
- **Moderate-to-severe pruritus** should be treated using a stepwise approach. The approach is as outlined in current EASL Clinical Practice guidelines:
  - **Step 1**: Cholestyramine is classically recommended as a first-line therapy to treat pruritus [1]. However, its effect on the absorption of other drugs including OCA and UDCA should be considered.
  - **Step 2**: Rifampicin is recommended as second-line treatment of pruritus, usually at a dose of 150 to 300 mg daily [1]. Patients commencing treatment require blood test (ALT, AST, bilirubin) monitoring 2–

4 weeks after initiation and then every 6 to 12 weeks and following any dose change, because of potential hepatotoxicity [1]. Attention should be paid to drug interaction since rifampicin is a Cytochrome P450 inducer.
    - **Step 3**: Oral opiate antagonists (naltrexone and nalmefene) can be used as third-line therapy as they can reduce the itching sensation. Naltrexone should be started at a low dose to 12.5 mg/day to avoid opiate withdrawal-like reactions in the first few days of treatment. Patients should be monitored closely for signs of long-term tolerability and opiate withdrawal-like reactions [1].
    - Recently, the use of off-label bezafibrate for pruritus has been described with patient benefit reported from many centers [14].
- **For patients with treatment-resistant pruritus**, liver transplant may be necessary.

3.2. Assessing response to first-line therapy

- A significant proportion of patients (25–50%) do not achieve a sufficient response from UDCA first line therapy to confidently prevent progressive liver disease [1].
- A 12-month period is conventionally used to assess biochemical response to UDCA. ALP and bilirubin are the two best individual variables that can be used to predict PBC prognosis.
- Several dichotomous prognostic tools (e.g. Paris-I, Paris-II, Toronto, Barcelona) are used to assess response to first-line therapy.
- The Paris-II criteria is recognized as a simple and widely applied approach for management [1] of patients with an early stage of disease. At one year of UDCA therapy, a patient is defined as having an inadequate response to UDCA therapy if any of the following Paris II criteria are identified:
    - ALP >1.5x ULN; or
    - AST >1.5x ULN; or
    - Bilirubin >1 mg/dl.
- After 12 months of UDCA treatment, patients defined as having an:
    - **Adequate response to UDCA**: are at low risk of disease progression and so should be maintained on UDCA, and assessed for their response to UDCA every 6–12 months (Figure 3). Periodicity depends on many factors such as the patient, disease severity, symptom burden, comorbidities, and home-to-hospital distance.
- **Inadequate response to UDCA**: are at 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.
- Most of the biochemical response criteria have been validated as predicting long-term disease progression at 12 months from UDCA initiation. However, it has also been demonstrated that evaluation at 6 months may be equally discriminatory [1,15]. Patients deemed to be at intermediate-to-high risk of disease progression at the start of treatment should be evaluated at 6 months.
- The medium- and long-term prognosis can be assessed by using quantitative scoring systems computed from continuous parameters (e.g. UK PBC and GLOBE scores) [1]. They allow the quantification of the risk of events or the survival, respectively, at specific time points and therefore can aid management decision.
- Elastography can be used yearly to assess liver stiffness and fibrosis (Figure 3). Bedside transient elastography is increasingly available as a surrogate marker for the detection of cirrhosis or severe fibrosis [1]. Progressive increases in liver stiffness are associated with an increased risk of disease progression. It has also been demonstrated that liver stiffness measurements (as measured by elastography) of greater than 9.6 kPa are associated with a 5-fold increased risk of liver decompensation, transplantation or death [3]. However, the ability of elastography to predict disease progression in PBC requires further validation [1].

3.3. Performing on-treatment risk stratification

Assessment of risk of progression based on treatment response

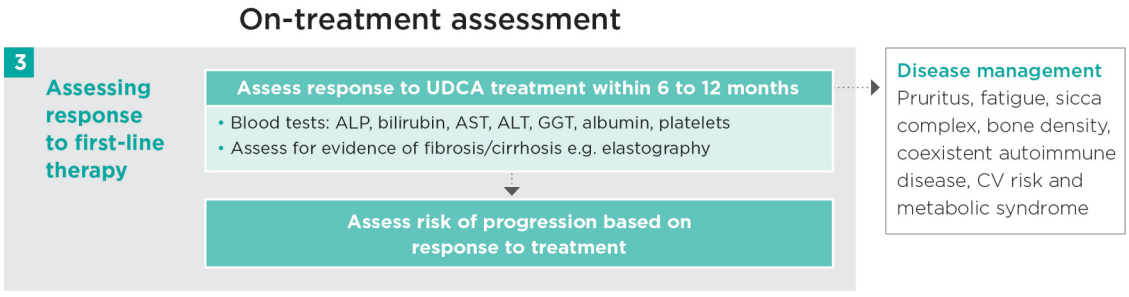

Figure 3. Assessing response to first-line therapy.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CV, cardiovascular; GGT, gamma-glutamyltransferase; UDCA, ursodeoxylcholic acid.

- Response to treatment should be evaluated and ongoing risk stratification should continue through the patients' journey. Risk assessment should be based on biochemistry and any evidence of fibrosis or signs of decompensation (Figure 4).
- Clinicians in charge of treatment should consider the following aspects of care:
  - Is the biochemical response to treatment adequate?
  - Has the patient got evidence of progressive fibrosis?
  - Have they got evidence of rising bilirubin or early jaundice?
  - Do they need other therapies?
  - Do they need input from a more specialist PBC clinic to help make sure they are getting optimal access to care, symptom management and trials if needed?

3.4. Identifying patients who require second-line therapy and initiating second-line therapy

- Since PBC is a heterogeneous disease and UDCA is not sufficiently beneficial for all patients. Patients with an insufficient response to UDCA are at higher risk of disease progression [1]. Therefore, these patients should be considered for second-line therapy.
- Some patients may not tolerate UDCA despite reintroduction with reduced dose and slow uptitration. Such patients should also be offered alternative therapy, with recognition that OCA is also indicated as monotherapy for patients intolerant of UDCA. The use of OCA in Child-Pugh B and C liver disease is not likely to be beneficial where transplant is the best intervention if indicated. It is highly unlikely that the risk-benefit assessment would ever favor its use.

3.4.1. Initiation of second-line therapy

- OCA is currently the only licensed therapy for patients with PBC who are intolerant or inadequately responding to UDCA [4] (Figure 5). The EASL guidelines provide other options for second-line therapy including unlicensed therapies such as fibrates, which may also be considered for other reasons. Enrollment into clinical trials is a further option for patients to consider.
- Symptoms, mainly pruritus, should be assessed and managed before initiating treatment with second-line therapy. OCA treatment may exacerbate preexisting pruritus; most patients, however, tolerate therapy well if pruritus is well controlled prior to starting treatment.
- The use of second-line therapies can be enhanced by consultation with expert PBC clinical centers. This offers the opportunity for individualized review of patient management, and guidance for treatment considerations,

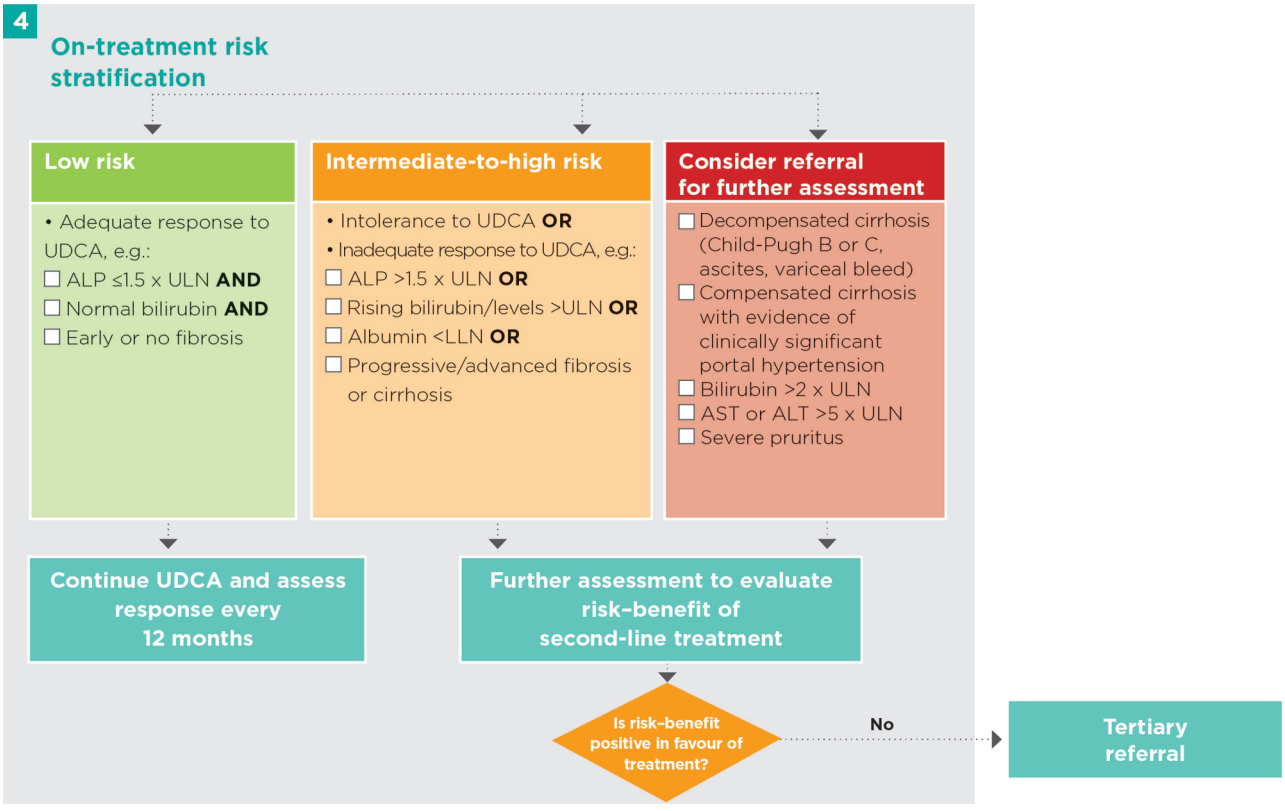

Figure 4. On-treatment risk stratification.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LLN, lower limit of normal; UDCA, ursodeoxylcholic acid; ULN, upper limit of normal.

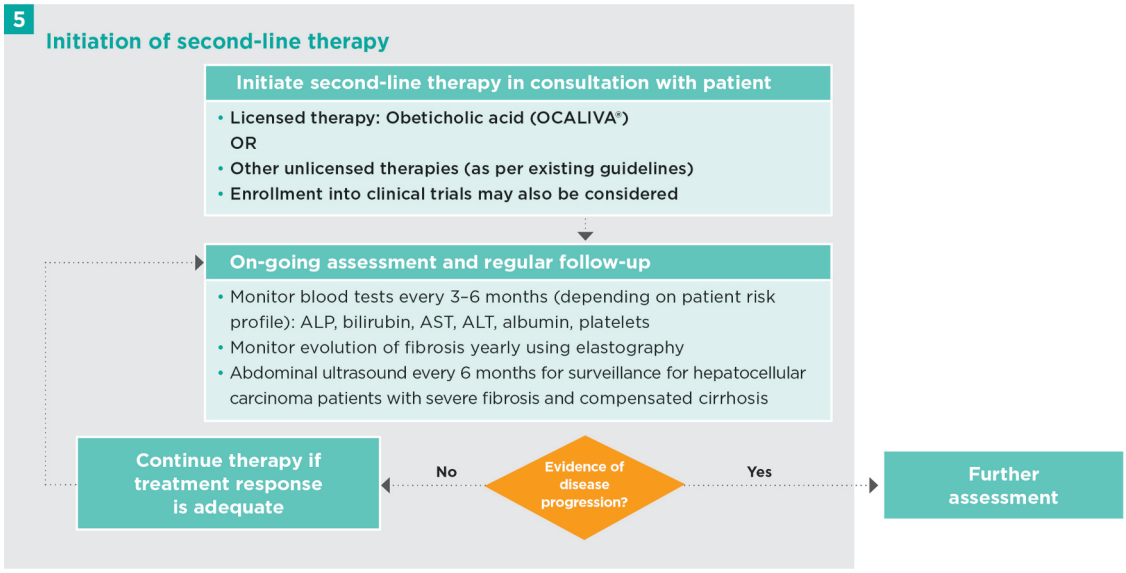

Figure 5. Initiation of second-line therapy.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

which continue to evolve based on clinical trial data, as well as case-series.

3.4.2. Ongoing assessment and regular follow-up

- Blood tests should be monitored every 3–6 months depending on the patient's risk profile: ALP, bilirubin, transaminases, albumin and platelets (Figure 5).
- Elastography should be considered yearly (or every 2 years in patients with adequate response to UDCA) to monitor the evolution of fibrosis (Figure 5).
- In patients with severe fibrosis and compensated cirrhosis, abdominal ultrasound should be done every 6 months for surveillance for hepatocellular carcinoma [16] (Figure 5).
- Other parameters often assessed during the follow-up include lipid profile and creatine kinase.
- Second-line therapy should be continued if patient is tolerating therapy and treatment response is adequate without any evidence of disease progression.
- In all patients, PBC management includes monitoring in an ongoing manner the risk-benefit ratio of treatment. Such monitoring is particularly relevant in patients with cirrhosis and those undergoing any second-line therapy. When initiating a second-line therapy, clinicians should determine clearly with the patient the goals of therapy. Follow-up monitoring is usually aligned with standard of care, but it may be relevant for some patients with cirrhosis to have more frequent monitoring e.g. up to monthly blood assessments. Overall, assessment is generally based on laboratory markers, imaging and elastography. If disease progression is noted, or insufficient improvement in biochemical markers of disease activity occurs, discussion with the patient is required to reevaluate risk-benefit. In this way clinicians can ensure that ongoing therapy choices remain appropriate.

Any patient with evidence of disease progression despite second-line therapy should be referred for additional specialist assessment if not already in a PBC specific clinic (Figure 5). Dose adjustment or temporary drug holidays may be appropriate whilst a specialist input is sought.

4. Discussion

While PBC diagnosis and the initiation of first-line therapy should be relatively straightforward for all clinicians, the heterogeneous course of the disease means that hepatologists and gastroenterologists who do not manage a significant PBC patient load may lack the experience required to recognize the patient whose clinical path is not classic and is therefore at a higher risk of disease progression. Risk stratification to identify patients at risk of disease progression, as well as the timing for initiation of second-line therapy are challenges frequently faced in clinical practice. The fact that no single widely agreed, definition of inadequate response to UDCA is available, adds to the challenge of managing this complex disease. The EASL guidelines provide a comprehensive evidenced-based resource for the management of PBC patients, however it was not designed to be a practical step by step guide to patient management.

To overcome such issues, this consensus Patient Care Pathway for the management of PBC was evolved, refined and delivered by a group of expert PBC clinicians, with recognition of the EASL guidelines of 2017, as well as clinical practice. Therefore, the pathway builds on recently published guidelines to support patient care and is in intent an exemplar for clinicians involved in the care of patients with PBC.

In its presentation, the PBC Integrated Patient Care Pathway is simple, directive and a patient-directional tool available to guide clinicians with varying levels of expertise and experience in PBC management. Importantly, the pathway highlights that simple risk stratification (low, intermediate, high) is essential and clinicians with less experience in PBC management can be guided how to deliver it. Risk assessment after PBC diagnosis helps to identify patients at high and low risk of disease progression. The PBC Care Pathway provides easy to use criteria for clinicians to determine levels of risk of PBC progression [17]. Risk assessment should begin at diagnosis based on clinical criteria and investigation results, including biochemistry and imaging. Pre-treatment risk stratification allows the determination of the level of follow-up care required following UDCA treatment initiation. Ongoing risk stratification allows the clinicians to recognize inadequate response to UDCA therapy and to implement a second-line therapy. Where the patients are insufficient responders to UDCA, they should be considered for other therapies. The guidelines recommend that the patients are considered for licensed therapies (OCA) [1]. Beyond licensed therapies, the risk-benefit of unlicensed therapies such as bezafibrate [7,18] need to be considered, as this molecule could be a better therapeutic option for patients with significant pruritus. Clinical trial opportunities may be available. It is vital that clinicians recognize when a patient is at high risk of disease progression and should travel beyond the services locally available; this care pathway explicitly attempts to give a unified answer to this.

The expert group wanted all clinicians treating PBC to be able to risk-stratify PBC patients correctly into low-, medium- and high-risk groups that lead to different management decisions. The group acknowledged that ALP thresholds in defining inadequate response to UDCA were currently potentially ambiguous and not consistent. No consensus criteria were described for inadequate response to UDCA therapy, but Paris-II, Toronto and Barcelona criteria were all mentioned as acceptable for routine clinical practice. Hence, the group recommended that all clinicians use a local scoring system – either one of an individual's preference, or one used by their reimbursement organization – as implementing even the simplest scoring system (e.g. Paris II or Toronto) is better than not implementing one at all.

Finally, the group recommended that clinicians managing PBC patients should have a low threshold for recognizing and referring patients with advanced disease (e.g. portal hypertension) for further expert assessment.

5. Conclusion

The PBC Integrated Patient Care Pathway is a best practice tool for all those caring for patients with PBC. Designed to complement the EASL Clinical Practice Guidelines for the diagnosis and management of PBC patients, it offers clinicians the ability to ensure high quality, optimal patient care using a practical decision tree of the key steps in PBC management. Also, it provides an opportunity for more uniform practice, and supports the safe and timely adoption of varied models of care provision to patients with PBC, which go beyond classical clinician-lead only management. Ultimately, the goal of the care pathway is to provide a simplified framework that can be adapted in line with local clinical practice and implemented widely to ensure that PBC care is integrated, consistent and coordinated.

6. Expert opinion

PBC is a chronic autoimmune liver disease with a prevalence of around 1 in 1,000 in women over the age of 40 years old. Diagnosis is usually made in primary care, while the disease management is shared with secondary care gastroenterologists/hepatologists for the majority of patients. Tertiary care for specialist input, including transplantation and trials, remains important albeit not universally necessary. At presentation, diagnosis is generally confirmed immunologically, and stage of disease is determined using noninvasive methods. For some patients, liver biopsy assessment is useful, but largely treatment is initiated based on laboratory testing. Disease care focuses on ameliorating the consequences of chronic cholestatic liver injury as well as making efforts to optimize the quality of life of the patient. Given the chronicity of PBC, its management must focus on a long-term vision of avoiding complications of cirrhosis in as many patients as possible. Lessons on management rely on a variety of evidence sources that span randomized controlled trials, international disease registries, and single-center experiences. These collective resources have improved PBC diagnosis, have refined approaches to disease staging and risk stratification, and have optimized treatment choices. Although liver transplantation can be relevant to some patients, optimized care can result in prevention of end-stage disease for the majority of patients. Although the available therapeutic options became more numerous, allowing improvement of symptoms, some residual challenges remain related to how patients with a rare disease can advocate and ensure optimized management.

PBC being a relatively rare disease, reliance on individual expertise based on the number of patients managed, can be limited for treating clinicians. To help all patients to benefit from the latest updates in the management of PBC, it is therefore of utility to develop clinical care pathways. Such pathways augment more detailed treatment guidelines by providing a simplified journey, with appropriate educational guidance, upon which a clinician can anchor the care of any individual patient.

The PBC care pathway described in this article provides an innovative starting point for a more uniform approach to PBC management, that is patient-centered, comprehensive, accessible and appropriately flexible to be individualized as needed. Adoption of such a care pathway offers the opportunity to subsequently evaluate impact through targeted service evaluations. These evaluations can be clinic-based or based on the practice of a wide array of clinicians in a defined geographic region. This sets the scene well for the future of PBC care, give the interest that remains in developing newer therapies beyond the two currently licensed agents (UDCA and OCA), and off-label therapies (namely bezafibrate).

In general, care pathway can become a dynamic document that has the opportunity to be improved over time to reflect evolving best-in-practice approaches. For PBC, this will likely reflect further therapies to change the natural progressive aspect of the disease, alongside improved approaches to symptoms control. Ultimately, the quality and quantity of life of patients with PBC can be positively enhanced thankfully to such pathways, which provide a solid foundation for the current and future medical practice.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. EASL Clinical Practice Guidelines. The diagnosis and management of patients with primary biliary cholangitis. European association for the study of the liver. clinical practice guidelines. J Hepatol. 671: 145–172. 2017; Epub 2017 Apr 18
   •• **This document includes European guidelines for the diagnosis and management of patients with primary biliary cholangitis.**
2. Hirschfield GM, Dyson JK, Alexander GJM, et al. The British society of gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. Gut. 2018;67(9):1568–1594.
   •• **This document describes British guidelines for the management and treatment of patients with primary biliary cholangitis.**
3. Corpechot C, Carrat F, Poujol-Robert A, et al. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. Hepatology. 2012 Jun 5;56 (1):198–208.
4. European Medicine Agency (EMA). OCALIVA. obeticholic acid. 2019. online. [cited 2019 Feb 12]. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/ocaliva
   •• **This report includes European public assessment of obeticholic acid.**
5. Levy C. Evolving role of obeticholic acid in primary biliary cholangitis. Hepatology. 2018 2018 Apr 1;67(5):1666–1668. . Epub
   •• **Review of the role of obeticholic acid in the treatment of primary biliary cholangitis.**
6. OCALIVA® SmPC. 2018; Online. [cited 2019 May 3]. Available at: https://www.ema.europa.eu/documents/product-information/ocaliva-epar-product-information_en.pdf
   •• **This document summarizes the characteristics of obeticholic acid in the treatment of primary biliary cholangitis.**
7. Corpechot C, Chazouillères O, Rousseau A, et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. N Engl J Med. 2018;378(23):2171–2181.
   • **A double-blind, placebo-controlled, phase 3 study assessing the efficacy, and safety of bezafibrate in patients with primary biliary cholangitis.**
8. Graham ID, Harrison MB. Evaluation and adaptation of clinical practice guidelines. Evidence-Based Nursing.2018;8:68–72.
9. Fischer F, Lange K, Klose K, et al. Barriers and strategies in guideline implementation-a scoping review. Healthcare (Basel). 2016;4(3):36. PMID: 27417624; PMCID: PMC5041037.
10. Vanhaecht K, De Witte K, Sermeus W The impact of clinical pathways on the organisation of care processes. PhD dissertation, Belgium: KU Leuven; 2007.
11. Chazouillères O, Wendum D, Serfaty L, et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology. 1998;28(2):296–301.
12. Carbone M, Mells GF, Pells G, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. Gastroenterology. 2013;144(3):560–569. e7; quiz e13-4.
13. Hönig S, Herder B, Kautz A, et al. Pruritus strongly reduces quality of life in PBC patients – real life data from a large national survey. J Hepatol. 2018;68(S216):S216. THU–198.

14. de Vries E, Bolier R, Goet J, et al. Fibrates for Itch (FITCH) in fibrosing cholangiopathies: a double-blind, randomized, placebo-controlled trial. Gastroenterology. 2021;160(3):734–743. e6.
15. Zhang L-N, Shi T-Y, Shi X-H, et al., Early biochemical response to ursodeoxycholic acid and long-term prognosis of primary biliary cirrhosis: results of a 14-year cohort study. Hepatology. 2013;58(1): 264–327.
- **A prospective study analyzing the biochemical response to ursodeoxycholic acid in primary biliary cirrhosis as a predictor of long-term outcome.**
16. El-Serag HB, Davila JA. Surveillance for hepatocellular carcinoma: in whom and how? Therap Adv Gastroenterol. 2011;4 (1):5–10.
17. Primary biliary cholangitis in motion meeting. EMJ Hepatol. 2018;6 (Suppl 1):2–15.
18. Honda A, Tanaka A, Kaneko T, et al. Japan PBC study group. bezafibrate improves GLOBE and UK-PBC scores and long-term outcomes in patients with primary biliary cholangitis. Hepatology. 2019;70(6):2035–2046.