The PBC Network

Canadian PBC Society

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Canadian Liver Foundation
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Primary biliary cholangitis (PBC)

Living with your diagnosis

Officially endorsed and reviewed by

EASL™
The Home of Hepatology

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About this guide

The European Association for the Study of the Liver (EASL) is a major European Association with international influence, dedicated to the study of the liver and liver disease. EASL promotes research collaborations to help patients all over the world.

We have produced this guide to help patients diagnosed with primary biliary cholangitis (PBC) understand the EASL clinical guidelines for this condition, and to demonstrate the importance of a structured, life-long and personalised approach to their care.

We understand that patients receive health information from many different sources, which can be confusing. In producing this guide, we have added context, description and interpretation to the EASL clinical guidelines to present them from a patient perspective. You may also notice a difference in the way that the EASL guidelines are implemented in your country. This is because the guidelines are designed to be adapted for local healthcare provision.

This guide is solely designed to focus on the different aspects of PBC – if you are seeking information on overlapping conditions such as autoimmune hepatitis, then your local patient organisation should be able to help you.

There is much information to cover so this is more than just a patient information leaflet – we hope that you can use it as a reference document, as you progress through your journey with PBC, to help you discover more about managing and living with your condition.

Contents

1 Summary

Primary biliary cholangitis (PBC) is a liver disease that affects mainly women over 40, and may develop into end-stage biliary cirrhosis (scarring of the liver tissue) without the right treatment.

PBC will usually be diagnosed if your doctor finds that your bile flow is reduced or blocked (cholestasis), and your blood contains a specific type of antibody (antimitochondrial antibodies, or AMA).

There is no cure for PBC, so treatment and management of PBC aim to prevent end-stage liver disease and ease problematic symptoms. Each person will experience PBC differently, so your doctor should analyse your individual condition and risks to provide a personalised care plan.

There are medicines available to slow or stop the progression of PBC. These currently include ursodeoxycholic acid (UDCA, or 'urso') and obeticholic acid (OCA), which are licensed therapies, and also fibrates and corticosteroids (budesonide), which are off-label therapies and are currently undergoing clinical trials.

There are a number of organisations dedicated to understanding and treating liver conditions, as well as specific PBC patient support groups. These offer detailed information on living with PBC, coping with symptoms, and the treatments available to you. These groups can be a valuable source of support and guidance, and we recommend that you contact them at the earliest opportunity.

2 Introduction

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a liver disease that affects mostly women. PBC occurs in adults – the youngest reported case is age 15 – and it is a life-long condition that often worsens over time.

If you have PBC, your doctor will probably have noticed some or all of these changes to your body:

- reduced or blocked bile flow (cholestasis)
- presence of certain antibodies in your blood (AMA or ANA)
- inflammation of small bile ducts in your liver.

We don't know exactly why people develop PBC, but we believe that genetic factors combined with environmental factors could play a role. In Europe, up to 2 people per 100,000 per year are likely to develop PBC, and between 1.9 and 40.2 per 100,000 people are thought to be currently living with the condition.

There is currently no cure for PBC, but there are treatments available to halt the disease progression and ease symptoms that reduce your quality of life. The main symptoms of PBC include:

- itchy skin (pruritus)
- tiredness
- dry mouth (sicca complex)
- abdominal pains.

You may also experience restless legs, sleeplessness, depression, and 'brain fog'.

If you've been diagnosed with PBC then it is vital that you obtain appropriate treatment – this makes a significant difference in slowing the development of the disease and improving your life expectancy.

Each patient will respond differently to treatment, and much depends on:

- your age when the condition developed
- the stage at which you were diagnosed
- if you are male or female
- your blood levels of two specific enzymes – alanine transaminase (ALT) and alkaline phosphatase (ALP) - after 12 months on UDCA.

A personalised, life-long strategy that meets your individual needs will be the most successful approach to treatment.

3 Diagnosing cholestasis

Before diagnosing PBC, your doctor would have noticed a more general liver condition called cholestasis.

Your liver produces bile, a digestive liquid, which travels through bile ducts in your liver to your small intestine. Here, it breaks down toxins and enables your digestive functions to work effectively. Cholestasis is a condition where that bile formation or flow is reduced, meaning that bile cannot flow from your liver to your small intestine. This leads to a build up of bile in your liver, which causes inflammation and scarring.

Symptoms of cholestasis may include fatigue, itchy skin, pain on the right side of your abdomen, and jaundice. However, some people don't experience any symptoms at all. Cholestasis is considered chronic if it has lasted for six months, and is classified as intrahepatic or extrahepatic.

This relates to the different types of bile ducts within your liver; intrahepatic cholestasis is linked with PBC, while extrahepatic cholestasis is linked with a slightly different condition called primary sclerosing cholangitis (PSC).

Because many people with chronic cholestatic liver disease have no symptoms for months, or even years, the condition is often discovered incidentally when a raised level of alkaline phosphatase (ALP) is noticed during routine blood tests. If your doctor suspects cholestasis following a blood test, EASL recommends the following systematic approach to determine whether this is due to PBC or a different liver condition:

1. Take a detailed history and physical examination

Personal history
Your doctor should take detailed notes of your personal, social, travel and family history, as these may provide critical clues when diagnosing unexplained cholestatic liver disease. Conditions associated with PBC include:

- autoimmune Hashimoto's thyroiditis (thyroid inflammation)
- Sjögren disease/sicca complex (dry eyes and mouth)
- coeliac disease (intolerance to gluten)
- systemic sclerosis (an autoimmune disease of the connective tissue).

Drug history
You should tell your doctor about your experience of:

- current and former prescribed medications
- herbal preparations
- alcohol and smoking
- any other kind of drug use (such as anabolic steroids or laxatives)
- long-term exposure to paints, diesel, and other oil products or industrial gases
- previous surgery or blood transfusions
- experience of intensive care or multiple severe injuries.

Physical examination
Your doctor should perform a physical check on your liver and spleen, as well as checking for other symptoms of advanced liver disease, such as:

- yellowing eyes, skin and mucous membranes
- small yellow or white bumps around the eyes (xanthelasma)
- reddening of the palms and soles of the feet
- nail abnormalities
- scratch marks, particularly on the arms and legs, which may be due to itching.

2. Perform an ultrasound scan

Your doctor will perform an ultrasound scan on your abdomen, to rule out other causes such as bile duct obstruction, mass lesions, or gallbladder abnormalities. This will also help them to differentiate between intrahepatic and extrahepatic cholestasis.

3. Perform specific blood tests

Your doctor will then test for ALP and gamma-glutamyl transferase (gamma-GT).

4. Perform extended imaging

Imaging studies (magnetic resonance cholangiopancreatography, or MRCP) may be used to rule out other diseases, or to make further evaluations of your condition once you have been diagnosed with PBC.

5. Take a liver biopsy

If blood tests and extended imaging are not conclusive, your doctor may request a liver biopsy to confirm your diagnosis. This involves using a needle to remove a small piece of your liver tissue for testing.

6. Perform genetic tests

If all other diagnoses have been ruled out, your doctor may order genetic testing from a specialist laboratory. This is to make sure that you do not have one of the other, very rare, liver conditions that are similar to PBC.

4 Diagnosing PBC

Your doctor will have noticed a number of 'markers', from a combination of talking to you, examining you, and assessing your blood test or scan results, that indicate you have PBC.

Risk factors

If you experience mucosal infections (especially recurrent urinary infections) or smoke cigarettes, these increase your risk of developing PBC. Your doctor may decide to order blood tests to check for PBC if you have these risk factors in addition to any of the other markers.

Noticeable symptoms

Symptoms of itching or fatigue may alert your doctor to the possibility of PBC.

Blood tests

Your doctor will order blood tests to help them diagnose your condition correctly. If you have PBC, your blood tests are extremely likely to show the following markers:

- AMA (antimitochondrial antibodies) – more than 90% of patients with PBC will have these in their blood results
- Raised ALP – this indicates that there is an injury in the bile ducts

If this is the case, your doctor can very quickly make a diagnosis of PBC. However, if your blood tests are inconclusive for the combination of AMA and ALP, your doctor may look for the following additional markers to help their diagnosis:

- Reduced bile flow levels
- Raised immunoglobulin concentrations, particularly IgM
- Raised transaminase enzymes AST and ALT – these are liver enzymes; raised levels can indicate that inflamed or injured liver cells are leaking higher than normal amounts of these enzymes into your bloodstream
- Raised bilirubin levels – this is a pigment in your blood that produces jaundice (yellow skin and eyes); levels increase as PBC progresses
- Specific ANA (antinuclear antibodies) – around 30% of patients with PBC will have these

Abnormal blood test results can indicate a number of conditions, and should always be interpreted alongside clinical findings by an experienced practitioner to avoid misdiagnosis. However, if your blood tests indicate both AMA and abnormal cholestasis levels (bile flow), then your doctor is likely to diagnose PBC.

Table 1 gives you an overview of the markers that your doctor is looking for.

Imaging

PBC cannot be diagnosed by imaging techniques (scans of your internal organs), but an abdominal ultrasound scan will help your doctor rule out any other causes of your symptoms.

Liver imaging is also useful to identify signs of advanced PBC, which are similar to other chronic liver diseases.

Table 1: Overview of PBC markers

Test	Finding	Suspicion	Diagnosis	Prognosis	Notes
ALP	↑	✓	✓	✓	Values associated with disease progression
AST/ALT	↑	✓		✓	Prominent elevation may be suggestive of PBC with features of AIH
GGT	↑	✓			Reflects cholestatic liver injury
IgM	↑	✓			Elevated values associated with disease
AMA (>1/40)	+		✓		Diagnostic hallmark in over the 90% of patients in correct clinical context
Specific ANA	+		✓		Specific immunofluorescence patterns: Perinuclear rims, nuclear dot, centromere; present in 30%
anti-gp210	+		✓	✓	Specific immunoassays available
anti-sp100	+		✓		Specific immunoassays available
Anti-centromere	+			✓	Associated with portal hypertensive phenotype
Bilirubin	↑			✓	Elevation at late stages; frequently indicative of cirrhosis except in patients with ductopenic non-cirrhotic variant
Platelets	↓			✓	Indicative of cirrhosis
INR	↑			✓	Indicative of cirrhosis
Albumin	↓			✓	Indicative of cirrhosis

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

Categorising PBC

A new staging system for PBC was recently proposed, which will help your doctor to predict how your condition will develop over the next 10 years. In particular, it will help them to predict the development of cirrhosis and associated complications.

This new approach identifies four different stages of PBC by measuring the increase in bile duct damage, and providing a risk score.

Table 2: PBC staging score

Stage	Description
1	No or minimal progression
2	Mild progression
3	Moderate progression
4	Advanced progression, indicating cirrhosis

Liver biopsy

Liver biopsy is not usually necessary to diagnose PBC because blood test results normally give a very clear indication of the condition. However, if your blood tests remain inconclusive then your doctor may order a biopsy to confirm PBC. Table 3 shows the conditions that your doctor will consider, based on your liver biopsy results.

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

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

5 Monitoring your PBC

The goal of PBC treatment is to manage your symptoms, and to prevent your condition from worsening into advanced liver disease.

The progression of PBC is very slow, so it is difficult for your doctor to measure the success or failure of each treatment effectively. Your doctor will perform various tests to predict the way that your condition is likely to develop, and adapt your treatment accordingly. It is impossible to guarantee that their prediction will be completely accurate, but it will be based on scientific evidence. The test results can help your doctor determine two main factors:

- **The stage your condition has reached**
  If you are diagnosed at an early age (below 45 years old) or diagnosed when the disease is already advanced, you may be less likely to respond to medication.
- **If you are responding to UDCA**
  If your blood test levels – such as alkaline phosphatase and bilirubin – show improvement, your condition is more likely to progress slowly, with mild symptoms. If UDCA medication is not effective, you may be more likely to experience complications from PBC.

Based on these factors, your doctor can then make a prediction about how your condition could progress. These tests can also help doctors to classify patients who participate in clinical trials, in order to do better research about PBC.

When will I be tested?

We recommend that your doctor performs the following actions

Before treatment:

- Assess the stage of your condition before treatment begins.

Follow-up appointment:

- Assess the stage of your condition to see if it has changed.
- Make a personalised follow-up plan according to your disease stage and the severity of your symptoms.
- Measure your response to UDCA – this is very important. This is normally checked after 12 months of treatment, but could be after 6 months.

How will I be tested?

Your doctor should order some or all of the following tests, depending on the severity of your condition:

- Blood tests: these should include alkaline phosphatase (ALP) bilirubin, albumin, alanine transaminase (ALT), aspartate aminotrasferase (AST), and platelet count.
- Elastography: also called vibration-controlled transient elastography (VCTE), this will provide a liver stiffness measurement (LSM).
- Liver biopsy: this provides an analysis of your liver tissue, but is not usually recommended if an elastography is available.

Tables 4 and 5 show what your doctor will be looking for in your test results.

If your results show that your PBC is at an early stage, your ALP level is less than 1.5 times the upper limit of the normal range, and your bilirubin level is normal after 1 year of therapy with UDCA, you could expect to live just as long as a healthy person without PBC.

Your doctor may use a risk score to help them analyse your blood test results collectively. You can read more about these at:

GLOBE score:
http://www.globalpbc.com/globe

UK-PBC risk score:
http://www.uk-pbc.com/resources/tools/riskcalculator

Table 4

Tool	Early disease	Advanced disease
Blood serum: bilirubin and albumin	Both normal	At least one abnormal
Elastography: liver stiffness measurement	Less than or equal to 9.6 kPa	More than 9.6 kPa
Liver biopsy (when suitable)	Absent or mild fibrosis	Bridging fibrosis or cirrhosis

Table 5

Tool	Low risk of progression	High risk of progression
Blood serum: bilirubin, albumin, ALP, AST, platelet count	Normal	Abnormal

6 Treatment

There are good treatment options available for PBC and there is also a lot of progress in the development of new options.

UDCA

The recommended treatment for all patients diagnosed with PBC is ursodeoxycholic acid (UDCA, or 'urso'), and your doctor should offer you this immediately. UDCA is a naturally occurring bile acid, found in small quantities in humans and also in certain types of bear. You will be given it in tablet form.

If your condition responds well to UDCA, then you will need to continue taking it for the rest of your life. Don't be tempted to stop taking it if you notice an improvement in your condition. This will be due to the medication, and if you stop taking UDCA then your condition will deteriorate.

UDCA is most effective when dosed according to your weight, so it is crucial that your weight is monitored regularly and the dose adjusted according to any changes. This is extremely important – studies have shown that an incorrect dosage can mean that you don't respond to the tablets, and can even affect your life expectancy. The recommended dosage is 13–15 mg per day, per kilo of weight.

UDCA is available in a number of options, including 150mg, 250mg, 300mg and 500mg. If you find that taking several tablets every day is difficult to maintain, ask your doctor if you can be moved onto a higher, single-dose version.

Obeticholic acid

If your condition does not respond to UDCA, your doctor may recommend that you try obeticholic acid (OCA). This can improve blood levels of ALT and AP in people who have not responded to UDCA alone, and is the only licensed second-line therapy after UDCA. In clinical trials, OCA improved liver biochemistry in the vast majority (87%) of cases, and was found to help almost 50% of patients.

If you need to take OCA, your doctor should prescribe it in combination with UDCA. You may take OCA on its own if you were intolerant to UDCA. If your doctor tells you to stop taking UDCA even though you have no problems with it, you should tell them that the EASL guidelines always recommend combined therapy if tolerated.

You will probably be given an initial dose of 5mg daily, rising to 10mg after six months if you are not experiencing any problems. There is increased risk of itching when taking OCA, but most people find that they can manage this by taking rifampicin.

It is important to remember that, if you have advanced cirrhosis (categorised with a Child-Pugh score of B or C), your liver will be slower at metabolising OCA. Instead of a daily dose, you must take a **much lower dose**, starting with 5mg **once per week**. A higher dose could harm you and even cause liver failure.

Some doctors have offered their patients fibrates or budesonide as a second-line treatment for PBC. It is important to know that neither of these is licensed for treating PBC, and the EASL guidelines currently state that a recommendation for such therapy cannot be made. However, this may change in the near future.

7 PBC and pregnancy

Most women diagnosed with PBC are past childbearing age, but it also affects a minority of younger women. If you have PBC, your condition should not prevent you from having a successful pregnancy, with careful monitoring.

If you are considering having a baby, we recommend that you talk to your PBC doctor about the possible risks, and ask questions on how to manage your condition during pregnancy and after the birth.

Our knowledge of PBC in pregnancy is limited but experts believe that UDCA is safe to use during conception, pregnancy and after the birth. Rifampicin (from the third trimester) and cholestyramine are also considered safe.

In rare cases, where the itch during pregnancy becomes unbearable, a treatment called plasmapheresis may help. This involves taking your blood and filtering it to remove plasma, then returning the remaining cells into your bloodstream.

If your bile flow is heavily reduced or blocked (cholestasis), you will need to take particular care to avoid a deficiency in fat-soluble vitamins (A, D, E and K). Some patients have experienced increased cholestasis during late pregnancy and after giving birth, so it is vital that you receive close monitoring during this period.

Your doctor should recommend an individual programme of pre-pregnancy care. If you have high blood pressure, you will have a higher risk of problems occurring, and should receive additional care and monitoring. The increase in blood pressure due to pregnancy could cause veins and blood vessels to leak or burst, leading to internal bleeding. If this is a risk for you, your doctor should offer a procedure called ‘endoscopy’ during your second trimester to evaluate the condition of your veins.

During this procedure, your doctor will insert a tiny camera on a thin, flexible, lighted tube (endoscope) through your mouth and into your esophagus, stomach and the beginning of your small intestine (duodenum). The images are fed back to a screen where your doctor can assess the situation.

8 Managing your symptoms

It is possible to have PBC without knowing, but many people experience a number of symptoms, which may appear at any time and can affect your daily life.

Symptoms of PBC include:

- itching
- tiredness
- dry mouth, eyes and intimate areas (sicca complex)
- bone and joint pain
- stomach ache
- restless legs.

Treatment for your PBC will not alleviate your symptoms, but these can often be treated and improved if the right guidance is followed. Not all clinics and doctors will have expertise in treating PBC symptoms; this guide offers you advice on how best to manage them.

Please ask your doctor for advice if you experience any symptoms, or if your symptoms change. They may give you a questionnaire to fill in, to get a full picture of how PBC impacts your life.

How to deal with itching

Itching is a common symptom of PBC, although not all patients will have it. Indeed, some people may find that their itching improves while their condition worsens. Itching due to PBC can often be treated and improved, but there is no one-size-fits-all treatment. Instead, your doctor should look at your individual situation.

Your itching could be due to cholestasis, where the bile ducts in your liver are blocked. This could happen due to gallstones, or other complications from your condition. Itching may be especially strong if you have a form of PBC called 'ductopenic variant', where the bile ducts in your liver have disappeared.

There are medications available to help, but they may not be suitable or effective for everyone. Sometimes, a few practical measures can bring relief:

- Emollients and oatmeal extract can soothe dry and inflamed skin.
- Cold baths or showers may help, especially if your itching is triggered by heat.
- If scratching the itch has become an addiction and is damaging your skin, professional psychological advice can help.
- Consider whether food or other allergies could be the cause of your itching, rather than PBC, and ask your doctor to test for these if necessary.

Medications

There are several medications your doctor may prescribe to help with the itching. They all have advantages and disadvantages, and not every drug will work for you. They will usually be prescribed in the order listed below; be prepared to try more than one treatment, until you find the most effective option for you.

a) Bile sequestrants

These medications are often the first that your doctor will prescribe; they work by reducing the bile in your liver, if this is the cause of your itching. Here are some examples:

- Cholestyramine – this should be the first option that you are offered; although it does not work for all patients, most find that they don't have any problems taking it. Side effects that you may experience include bloating and constipation. It may also be affected by other medications you are taking – always discuss this with your doctor.
- Colesevelam – this produces less side effects but its effectiveness is uncertain. Some people feel better when taking it, and tests have shown that it has reduced their bile acid levels. On the other hand, this medicine did not work better than a placebo in a controlled trial.

If you take bile sequestrants, you should be aware that:

- they might stop other drugs from working if you take them at the same time
- you must take them 2 to 4 hours before you take any other drug, such as UDCA or OCA.

Ask your doctor for advice on when exactly to take your medicines.

b) Antibiotics

If bile sequestrants do not help your itching then your doctor may prescribe rifampicin, an antibiotic that treats bacterial infections. It can improve itching in PBC by inhibiting a receptor in your body that is thought to play a role in itching. The recommended dose is 150–300mg daily.

We know from clinical trials that rifampicin really works against itching in PBC, and also in other cholestatic diseases. Unfortunately, it can cause side effects, although not everybody gets them. These are not included in the EASL PBC guidelines, but include nausea, vomiting, diarrhoea, loss of appetite, and high body temperature. You may also find that some of your bodily fluids, such as urine, sweat and tears, change colour to orange-red. Don't let this scare you – this effect is common and looks strange, but should not cause concern. Rifampicin may also lower the amount of vitamin K in your body.

Some patients may experience more serious side effects, such as fewer red blood cells, longer blood clotting, or even liver damage. If you take rifampicin, your doctor will order regular blood tests for monitoring; this should take place after 6 weeks and again after 12 weeks. If this detects any new problems, you may need to stop taking rifampicin and try something else.

c) Oral opiate antagonists

If bile sequestrants and/or rifampicin do not work for you, or produce too many side effects, oral opiate antagonists may be another option. These include naltrexone and nalmefene, which can reduce itching but may also have long-term side effects.

Starting naltrexone on a low dose will help to avoid these side effects, which can be similar to those of opiate withdrawal and feel a bit like flu. You may also be more sensitive to pain.

Experimental treatments

Experimental medical treatments

Several other medicines have been found to help individual patients with itching, but a lack of convincing data from large trials means that EASL does not officially recommend them.

- Selective serotonin reuptake inhibitors (SSRIs), such as sertraline, were found to improve itching in a small controlled trial and patients felt better than those who received a placebo. We don't know exactly how SSRIs work against PBC itching, but it's possible that they reduce itch signals in the brain, so that the itching feeling is reduced. SSRIs can also cause a dry mouth, which is a frequent symptom of PBC.
- Gabapentin (an anticonvulsant drug used in epilepsy) and anti-histamines have also been used, but more research needs to be done before they can be recommended by EASL. Gabapentin did not work better than a placebo in a controlled trial, yet some patients feel it has helped them. Similarly, some patients have felt that the calming and numbing effect of anti-histamines have provided relief from itching.

Experimental physical treatments

Physical methods have also been used to treat PBC-related itching, although EASL does not make an official recommendation for any of them.

- Ultraviolet (UV) light therapy and liver dialysis have helped individual patients.
- Liver dialysis has improved very strong itching, even when other treatments not work. However, the itching can return so you may need to repeat the procedure.

Liver transplant

Transplanting the liver is a last resort against unbearable itching, when everything else has failed. A liver transplant is normally reserved for patients with advanced liver disease, who are at risk of liver failure. However, exceptions can be made for individual patients if all other itching treatments, even therapeutic trials, have failed. Patients have found that the itching can rapidly disappear, often within the first 24 hours after the liver transplant.

How to deal with fatigue

Fatigue is a common symptom of PBC; more than half of patients feel tired and exhausted. About one in five PBC patients experience fatigue so extreme that their quality of life really suffers.

To improve this, your doctor should investigate other reasons for fatigue and treat them, if possible. These can include:

- lack of red blood cells (anaemia)
- low thyroid function (hypothyroidism)
- disturbed sleep (for example, because of itching).

Your doctor should also advise you on coping strategies that you can use to avoid isolation and depression, as these can also cause extreme fatigue.

How to deal with dryness (sicca complex)

You may experience dry eyes, a dry mouth, swallowing problems or dryness of the vagina. These are called 'sicca syndrome', and there are treatments that can help. You should tell your doctor if you suffer from any of these symptoms.

Many people find artificial tears and artificial saliva to be effective. If these are not enough, you can try stronger medications such as pilocarpine or cevimeline. These drugs are known as 'muscarinic receptor agonists'.

If your mouth is very dry, you are more likely to develop tooth decay. Good oral hygiene, such as brushing and flossing your teeth regularly, is important, as well as regular visits to the dentist. You may also have a higher risk of fungal infections in your mouth (known as oral candidiasis, or thrush). Please inform your doctor if you see changes in your mouth such as:

- cracks at the corners of your mouth
- an unpleasant taste in your mouth
- a sore tongue or sore gums
- difficulty eating and drinking.

Vaginal moisturisers are widely available to help against dryness of the vagina. Oestrogen creams can also be used; these are safe for your liver, but please check with your doctor or gynaecologist if you should use them.

If these tips don't work for you, there are other options that you can follow up. Specific guidelines on how to manage sicca symptoms are available, and your doctor may also refer you to a specialist who can help.

Other symptoms

You may also experience a symptom called 'Raynaud's phenomenon' - one in four PBC patients has reported this. This causes your fingers and toes (and sometimes your nose and ears) to feel very sensitive to cold because the arteries cannot cope with the cold, and suddenly contract. As a result, your fingers and toes turn white, then blue, and finally red when the blood flow returns. You may also have unpleasant feelings such as pain, burning or tingling.

If this is only mild, you may find it sufficient to keep warm – wear gloves, use hand warmers and avoid cold environments. If you have stronger Raynaud symptoms, your doctor may prescribe a type of medicine called 'vasodilators', which work against the artery contraction. Some patients experience very severe symptoms, including ulcers on their fingers or other extremities. About one in twelve PBC patients experience CREST syndrome, which affects the connective tissue in a number of their organs. Symptoms of CREST may include:

- calcifications under the skin
- Raynaud's phenomenon
- dilated arteries
- thicker and tighter skin
- skin ulcers
- problems swallowing food.

If you have these symptoms, please ask your hepatologist for advice, or for referral to a specialist rheumatology consultant.

9 Managing complications

PBC can lead to a number of complications. Your doctor can help you manage these in a variety of ways.

Osteoporosis

Osteoporosis is a bone disease that occurs when the body loses too much bone, makes too little bone, or both. As a result, bones become weak and may break from a fall or, in serious cases, from sneezing or minor bumps.

Osteoporosis is a common complication in patients with PBC. You can help to prevent and treat osteoporosis by ensuring you have a good diet, take some weight-bearing exercise, and stop smoking. Your doctor may consider giving you calcium supplements (if you have no history of renal stones) and vitamin D. Several trials have demonstrated that bisphosphonates (drugs that prevent or slow down bone thinning), especially weekly alendronate and monthly ibandronate, are effective in increasing bone mass in patients with PBC.

Reduced vitamin absorption

Patients with PBC, particularly those with prolonged jaundice, can struggle to absorb fat-soluble vitamins (vitamins A, D, E and K). Your doctor may recommend that you take a supplement, but this should be considered on an individual basis.

Hyperlipidaemia

When the concentration of triglycerides or cholesterol in your blood is too high, it is called ‘hyperlipidaemia’. Hyperlipidaemia is normally linked to an increased risk of cardiovascular disease, such as heart attack and angina, stroke, and narrow blood vessels in the legs. But it can also appear because of cholestasis, as part of your PBC, so it does not necessarily mean that your cardiovascular risk is increased.

If you have PBC alongside low HDL cholesterol and high LDL cholesterol levels, we recommend that you take cholesterol-lowering medication as part of a personalised plan.

Veins

Patients with PBC may develop a type of high blood pressure known as ‘portal hypertension’. This affects your hepatic portal system, which is the part of your vein network that directs blood from your intestines to your liver. Portal hypertension is often caused by scar tissue (cirrhosis) that forms in your liver due to inflammation.

You are more at risk of portal hypertension if your blood tests show low albumin, elevated bilirubin, and/or elevated INR ('international normalised ratio' – a measurement of blood clotting). Men are also more likely to experience portal hypertension than women.

If you have portal hypertension, you may also develop enlarged or swollen veins in the lower part of your esophagus (the tube connecting your throat to your stomach).

Your doctor should check for this by using a procedure called upper gastrointestinal endoscopy. This means that your doctor will insert a thin, flexible, lighted tube (endoscope) through your mouth and into your esophagus, stomach and the beginning of your small intestine (duodenum).

These veins are often treated with medication to reduce pressure in your veins, or by wrapping the veins with an elastic band to prevent them from bleeding. This treatment can take place during your endoscopy. If your veins are bleeding, your doctor may treat this with a tiny balloon, which is inserted into the bleeding vein and inflated, or a self-expandable metal tube.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a cancer that starts in the liver cells, and is one of the most serious complications of PBC. It is more likely to occur in men. There are several non-surgical treatment options for HCC:

- Ablative therapies – treatments that destroy the cancer cells, such as radiofrequency ablation, ethanol injections or cryotherapy
- Embolisation – a injection to block the blood supply to the cancerous cells in the liver (trans-arterial embolisation, or TAE), which can also be performed in conjunction with chemotherapy (trans-arterial chemoembolisation, or TACE).

Surgical therapies are also available, and HCC can be treated by removing the affected part of your liver – this procedure is known as a 'liver resection'. However, if the damage to your liver is such that none of the options above are suitable, then you are likely to be offered a liver transplant.

Liver transplant

Your doctor may suggest a liver transplant if they notice complications that involve scarring of the liver (cirrhosis), high levels of bilirubin, jaundice, itching, or fatigue.

Having a liver transplant does not guarantee that you will be free of PBC – around 20 per cent of patients who have received a transplant go on to experience PBC again in their new liver. This is called recurrent PBC.

After a liver transplant you will be prescribed medication to suppress your immune system (tacrolimus), in order to lower the risk of the new liver being rejected by your body. Tacrolimus has been associated with an increased rate of recurring PBC after transplant, but there is not enough data available for us to recommend one medication over another.

Taking UDCA will lower your liver enzymes, and may reduce your risk of recurrent PBC, but again there is not enough evidence for us to make a firm recommendation for its use after transplant.

Your risk of osteoporosis increases after a liver transplant, so your doctor should check carefully for this and help you to manage this.

10 Delivering your care

PBC is very complex for clinicians to manage, as their care programme must meet the needs of patients with very different levels of symptoms and risk.

Who will manage my care?

The nature and risk profile of your condition will determine who is responsible for managing your care. This could range from primary care physicians to tertiary/transplant-centre experts. As a minimum, the person managing your care should offer you an assessment every year that looks at your symptoms and treatment needs. This should develop into a structured, life-long, follow-up process that is tailored to your personal experience of the condition.

Standards of care

Your doctor should follow these treatment standards, which have been approved internationally:

- All patients with suspected PBC should have an abdominal ultrasound as part of their baseline treatment, to exclude alternate reasons for cholestasis.
- UDCA (at 13–15 mg/kg/day) should be the first-line treatment for all patients with PBC.
- Blood test results, taken after one year of UDCA therapy, should be used to categorise individual risk of the disease progressing.
- All patients should be asked about their symptoms (particularly itching, sicca complex and fatigue) to assess the impact on their quality of life, and to ensure appropriate investigation and treatment.
- To improve the opportunities for patients to receive a liver transplant if necessary, any tests that show evidence of bilirubin, or bleeding veins, a build up of fluid in the abdomen, or ‘brain fog’, should be discussed with a hepatologist linked to a transplant programme.
- All patients with PBC should have a risk assessment for osteoporosis, with treatment and follow-up according to the guidelines in your country.
- If patients have PBC combined with features of autoimmune hepatitis (AIH), this is unusual and a liver biopsy is recommended for diagnosis.

Patient support groups

We strongly recommend contacting your local patient support groups, who can offer you more information about PBC and the treatment options available to you. They can also provide invaluable support and counselling to help you in living with your condition. Your doctor can provide details of these, or you can find them by searching online.

11 Conclusion

PBC is a liver condition that prevents bile flowing freely from the liver to the intestine, and particularly affects women over the age of 40. There is no cure for PBC and it will worsen without treatment, resulting in end-stage liver disease that requires a transplant. However, there are treatments available to manage symptoms and slow down the disease progression.

Your doctor will probably diagnose PBC based on blood tests and scans, but a biopsy may be necessary if other tests are inconclusive. Your doctor should also assess your individual risk of disease progression, both at the point of diagnosis and during treatment. Although most patients with PBC are past childbearing age, your condition should not prevent you from having a successful pregnancy, with careful monitoring.

You should be prescribed UDCA medication as a first-line treatment, with the dose based on your weight. If you do not respond well to UDCA, there is now a licensed second-line drug (OCA) available for you to try, as well as several new and repurposed drugs undergoing clinical trials.

PBC can cause various symptoms, such as itching, dry mouth and fatigue, and your doctor should provide treatment to manage these. Your doctor should take a life-long approach to your care, with regular monitoring to ensure you receive the best possible treatment as your condition develops.

Glossary

Adverse event

Any unexpected medical occurrence experienced by a patient who has been administered a pharmaceutical product. The occurrence does not necessarily have to have a causal relationship with this treatment.

Autoimmune Hashimoto's thyroiditis

Also called Hashimoto's disease, Hashimoto's thyroiditis is an autoimmune disease – a disorder in which the immune system turns against the body's own thyroid and causes an inflammation.

Autoimmune hepatitis (AIH)

A chronic disease characterised by inflammation of the liver caused by antibodies or lymphocytes produced against substances naturally present in the liver cells.

Alkaline phosphatase (ALP)

Alkaline phosphatase (ALP) is a simple blood marker that shows how well the bile ducts in your liver work. It can be used to monitor response to therapy.

It can also serve as a diagnostic biomarker. The first indicator of primary biliary cirrhosis (PBC) may be elevated ALP levels, as measured by routine blood tests. In PBC, elevated ALP is an indication of continual bile duct destruction, which leads to inflammation and damage. ALP is also produced in the bones, and levels may be elevated due to bone disease or fractures.

Antimitochondrial antibodies (AMA)

Between 95 and 98% of patients with primary biliary cirrhosis (PBC) have autoantibodies (antibodies to self) in their blood that react with the inner lining of mitochondria. These autoantibodies are called antimitochondrial antibodies (AMA).

Mitochondria are the energy factories present inside all cells, not just the cells of the liver or bile ducts. The mitochondria use the oxygen carried in the blood from the lungs as a fuel to generate energy. AMA bind to protein antigens that are contained in multienzyme complexes (packages of enzymes) within the inner lining of the mitochondria. These multienzyme complexes produce key chemical reactions necessary for life. The complexes are referred to as multienzyme because they are made up of multiple enzyme units.

Antinuclear antibodies (ANA)

Antinuclear antibodies (ANAs, also known as antinuclear factor or ANF) are autoantibodies that bind to contents of the cell nucleus. In normal individuals, the immune system produces antibodies to foreign proteins (antigens) but not to human proteins (autoantigens). In some individuals, antibodies to human antigens are produced. ANA levels can also be elevated in cases of autoimmune hepatitis.

Autoimmune diseases

An autoimmune disease is a disorder where the body's natural defence mechanisms attack the body's own cells like a foreign body such as a virus or bacteria. PBC is an autoimmune disease, which causes the body to attack its own bile ducts in the liver. Other autoimmune liver diseases are AIH (autoimmune hepatitis), PSC (primary sclerosing cholangitis) and IgG4-associated autoimmune diseases.

Bile acids

Bile acids have long been known to facilitate digestion and absorption of lipids in the small intestine as well as regulate cholesterol homeostasis. Over the last decade, however, it has become clear that bile acids are not simply digestive detergents, and that they are the body's primary route for breaking down cholesterol. Bile acids are now recognised as hormones involved in the regulation of various metabolic processes. Through activation of various signaling pathways, bile acids regulate not only their own synthesis and enterohepatic circulation, but also triglyceride, cholesterol, glucose, and energy homeostasis. Bile acid accumulation due to cholestasis contributes to progressive liver damage, leading to fibrosis and cirrhosis.

Bile ducts

The duct that conveys bile from the liver and the gall bladder to the duodenum. The bile ducts play an important role in keeping the liver healthy. Bile ducts are tubes that carry bile from the liver to the small intestine to help with digestion. PBC damages bile ducts and causes bile to get trapped in the liver. Bile build-up can be toxic and can damage the liver tissue.

Biliary

Relating to bile or the bile duct.

Bilirubin

Elevated serum bilirubin is a marker of advanced liver disease including PBC and an early indicator of cirrhosis and portal hypertension.

Usually, initial bilirubin levels remain normal in PBC for several years. Elevated serum bilirubin levels occur in advanced stages of PBC.

A serum bilirubin level higher than 1 mg/dL (17 µmol/L) is a predictive factor for developing cirrhosis. A total serum bilirubin level exceeding 2 mg/dL (34 µmol/L) is associated with a late stage of PBC.

Biopsy

A liver biopsy is a medical test commonly performed by a hepatologist, gastroenterologist or another trained surgeon involving extraction of sample cells or tissues for examination to determine the presence or extent of a disease. Liver biopsy may be used to confirm staging during the diagnosis of PBC.

Cholangitis

Inflammation of the bile ducts in the liver.

Choleresis

The flow of bile from the liver especially when increased above a previous or normal level.

Cholestasis

Cessation or reduction of the flow of bile, typically resulting from obstruction within the larger bile ducts or gall bladder (more fully extrahepatic cholestasis) or from factors affecting bile efflux or flow within the liver (more fully intrahepatic cholestasis).

Cirrhosis

A chronic disease of the liver marked by degeneration of cells, inflammation, and fibrous thickening of tissue. It is typically a result of long-term chronic liver diseases.

Fatigue

Fatigue (either physical, mental or both) is a frequent symptom in many liver diseases. It may be difficult for the patient to describe, and words like lethargic, exhausted and tired may be used. Up to 85% of patients with PBC experience fatigue during the course of the disease.

Fibrosis

The thickening and scarring of connective tissue, usually as a result of injury.

Farnesoid X Receptor (FXR)

FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. OCALIVA (obeticholic acid) is a farnesoid X receptor (FXR) agonist.

Jaundice

A medical condition with yellowing of the skin or whites of the eyes, arising from excess of the pigment bilirubin and typically caused by obstruction of the bile duct, by liver disease, or by excessive breakdown of red blood cells.

Liver (organ)

A large lobed glandular organ in the abdomen of vertebrates, involved in many metabolic processes.

The liver is dark reddish brown in color and is divided into two main lobes which are further subdivided into approximately 100,000 small lobes, or lobules. About 60% of the liver is made up of liver cells called hepatocytes, which absorb nutrients and detoxify and remove harmful substances from the blood. A hepatocyte has an average lifespan of 150 days. There are approximately 202,000 hepatocytes in every milligram of a person's liver tissue. The liver receives its blood supply via the hepatic artery and portal vein.

Liver failure

The damage caused by cirrhosis, severe acute hepatitis, or intoxication may not be reversible and can eventually become so extensive that the liver stops functioning. This is called liver failure. Cirrhosis can be fatal if the liver fails. However, it usually takes years for the cirrhosis to reach this stage and treatment can help slow its progression.

Mechanism of action

Mechanism of action describes the process by which a molecule, such as a drug, functions to produce a pharmacological effect. A drug's mechanism of action may refer to its effects on for example cell growth, or its interaction with its direct biomolecular target, for example a protein or nucleic acid.

Non-alcoholic fatty liver (NAFL)

If a person has excess fat in their liver, but no inflammation or liver damage, this condition is called 'fatty liver', or NAFL. It resembles alcoholic liver disease, but occurs in people who drink little or no alcohol. A fatty liver is not normal, but by itself it probably causes little harm or permanent damage.

Non-alcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is a general term for several forms of fatty liver diseases, which range from bland fatty liver (NAFL) to more non-alcoholic steatohepatitis (NASH), to advanced liver disease such as cirrhosis and/or liver cancer

If fat is suspected based on blood test results or scans of the liver, this problem is called non-alcoholic fatty liver disease (NAFLD). If a liver biopsy is performed in this case, it will show that some people have NASH while others have simple fatty liver (NAFL).

Non-alcoholic steatohepatitis (NASH)

Non-alcoholic steatohepatitis, or NASH, is a a more severe form of non-alcoholic fatty liver (NAFL). The major feature in NASH is fat in the liver, along with inflammation and damage. Most people with NASH feel well and are not aware that they have a liver problem. Nevertheless, NASH can be severe and can lead to cirrhosis, in which the liver can be permanently damaged and scarred and is no longer able to work properly. NASH may also cause liver cancer even when there is no cirrhosis.

Both NASH and NAFLD are becoming more common, possibly because of the greater number of people with obesity. Obesity also contributes to diabetes and high blood cholesterol, which can further complicate the health of someone with NASH.

Non-viral vs. viral liver diseases

Viral liver diseases are caused by a virus; non-viral liver diseases are not. Other reasons for liver disease may be autoimmune, metabolic, toxic or genetic. For some non-viral liver diseases, including autoimmune diseases such as PBC, the cause is unknown. Viral liver diseases include Hepatitis A, B, C, D and E.

Non-viral liver diseases include PBC, autoimmune hepatitis, non- alcoholic steatohepatitis (NASH), and haemochromatosis.

Nuclear receptor

Nuclear hormone receptors belong to a certain class of proteins that, when bound to specific sequences of DNA, serve as on-off switches for transcription within the cell nucleus. These switches control the development and differentiation of skin, bone and behavioural centres in the brain, as well as the continual regulation of reproductive tissues.

FXR belongs to a subclass of metabolic receptors within the nuclear receptor (NR) family and is identified as a nuclear receptor for bile acids.

Obeticholic acid

A selective FXR agonist, obeticholic acid, given orally, binds to the farnesoid X receptor (FXR), a nuclear receptor found in the nucleus of liver and intestine cells. FXR is a key regulator of bile acid metabolic pathways. Obeticholic acid increases bile flow from the liver and suppresses bile acid production in the liver, thus reducing the exposure of the liver to toxic levels of bile acids.

Primary biliary cholangitis (PBC)

Primary biliary cholangitis (PBC) is a chronic autoimmune disease and a rare liver disease that affects the bile ducts in the liver. If left untreated, it can progress to hepatic fibrosis, cirrhosis, liver failure, and death unless a patient receives a liver transplant.

While PBC is rare, it is the most common cholestatic liver disease and typically strikes women in the prime of life. PBC is typically diagnosed in people between 35 and 60 years of age. An estimated 90 percent of people with PBC are women. Although a population-based approach to the detection of cases has little feasibility for PBC because of its rarity, the disease has been found to be most frequent in northern Europe and North America.

The majority of patients are asymptomatic at diagnosis, but become symptomatic within 10 years, and the estimates for developing symptoms at 5 and 20 years are 50% and 95%, respectively. Pruritus, or itching, and fatigue are the most common symptoms reported by patients with PBC; however, these symptoms do not correlate with disease severity or clinical outcomes.

PBC is diagnosed primarily based on two biomarkers in the blood:

- An abnormal elevation of alkaline phosphatase (ALP) levels
- The presence of antimitochondrial antibodies (AMA), which are observed in approximately 90-95% of people with PBC

Although not required, a liver biopsy can be used to further substantiate the diagnosis, if needed.

The progression of PBC can vary significantly, with some patients progressing to liver failure over a period of years and others remaining asymptomatic for more than a decade. It is important to note that liver function can begin to deteriorate in people with PBC prior to the onset of symptoms.

Primary liver diseases

A primary disease is one that starts spontaneously and without obvious cause. PBC is a primary liver disease.

Progressive liver diseases

A progressive disease is one that gets worse over time. PBC is a progressive liver disease.

Pruritus

Pruritus is defined as an unpleasant sensation that provokes the desire to scratch. Pruritus can affect patients with PBC regardless of cholestasis or stage of disease.

Systemic sclerosis

Systemic sclerosis, also called systemic scleroderma or diffuse scleroderma, is an autoimmune disease of the connective tissue. It is characterised by thickening of the skin caused by accumulation of collagen, and by injuries to small arteries.

Ursodeoxycholic acid (UDCA)

Ursodeoxycholic acid (UDCA) is one of the secondary bile acids, which are metabolic by-products of intestinal bacteria. UDCA has been the standard of care for treatment of PBC for nearly 20 years. UDCA's primary mechanism involves diluting the bile acid pool by replacing/displacing toxic concentrations of bile acid.

Questions to ask your doctor

We have put together a list of questions that you may wish to ask your doctor, to help you find out as much as possible about the options for treating and managing your condition.

General questions

1. What are my blood test results? Do they include alkaline phosphatase, bilirubin, albumin, ALT, AST and platelet count, and show units (such as µmol/L or g/L) and reference ranges?
2. What are the results of other diagnostic tools, such as ultrasound, liver stiffness measurement (LSM) or biopsy?
3. Are you using a risk score? If so, which one, and what are the results?
4. What disease stage am I on?
5. What is my prognosis?
6. You will probably be prescribed UDCA. Make sure to ask your doctor:
    a. How much is my dose?
    b. When and how many times per day should I take it?
    c. What are the normal side effects I don't need to worry about?
    d. What are dangerous side effects that might require medical attention?
    e. If I take other medicines, do I have to take them at different times?
7. When is my next appointment?
8. Any other question you might think of.

Questions at your follow-up appointment

9. Has my disease stage or prognosis changed since my last visit?
10. How am I responding to UDCA?
    a. Is it working?
    b. Do I need to adjust the dose?
    c. If not, should I consider adding other medicines to UDCA? Which? Or should I switch to a different therapy?

Questions about UDCA

11. Is my dosage prescribed according to my weight, at between 13–15mg per kg of weight per day?
12. I am struggling with multiple tablets. Can I be prescribed a stronger, single-dose version?
13. How often will you check the results of the treatment?
14. I don't feel well:
    a. Could this have anything to do with my medicine, or is another reason more likely?
    b. Can you check if my dosage is insufficient, or too high?
    c. Can we reduce/increase the dosage and see what happens?
15. I have lost weight: can I reduce the dosage?

16. I have gained weight: should we increase the dosage?
17. If you discover I have an allergy to the additives in the tablet form of UDCA, is there a liquid version I can take?

Questions about OCA

18. UDCA did not work for me. Can I try to add OCA to my treatment?
19. Is OCA available in our country, and will it be covered by my health insurance?
20. I have heard that it is possible to be prescribed OCA even though it is not registered or covered by health insurance in our country. Is this scheme available to me, and how can I be considered for it?
21. You have prescribed OCA and told me to stop taking UDCA, even though I am not intolerant to UDCA. Can you explain why you are stopping my UDCA treatment?
22. At which dose should I take OCA?
23. I heard that OCA must be given at a lower dose if people have severe liver disease. Does this apply to me, too?
24. What can I do if I suffer from side effects such as itching?

Questions about pregnancy and PBC

25. Does my pregnancy care need to take place at the hospital where I am treated for PBC, or can I see a local midwife?
    a. Is there contact between you and the gynecologist/midwife?
    b. If not: can I ask the gynecologist/midwife to contact you?
    If yes: who is in the lead?
26. Do I need extra blood controls during the pregnancy? And after birth?
27. Is there a possibility that my child will have PBC?
28. Can I have a home birth or is it better to deliver in the hospital?
29. If I don't want to take medication during my pregnancy, how will this affect my condition?

Recommendations

Recommendation 1 [Chapter 3]
EASL recommends taking a detailed history and physical examination when evaluating patients with biochemical tests that suggest cholestatic liver disease.

Recommendation 2 [Chapter 3]
EASL recommends ultrasound as the first-line noninvasive imaging procedure, in order to differentiate intra- from extrahepatic cholestasis.

Recommendation 3 [Chapter 3]
EASL recommends performing serologic screening for AMA and PBC-specific-ANA by immunofluorescence in all patients with unexplained cholestasis.

Recommendation 4 [Chapter 3]
EASL recommends imaging by MRCP in patients with unexplained cholestasis. EUS can be an alternative to MRCP for evaluation of distal biliary disease.

Recommendation 5 [Chapter 3]
EASL recommends considering liver biopsy after serologic screening and extended imaging, in patients with ongoing unexplained intrahepatic cholestasis.

Recommendation 6 [Chapter 3]
EASL recommends considering genetic tests for inherited cholestatic syndromes in patients where clinically appropriate.

Recommendation 7 [Chapter 4]
EASL recommends that in adult patients with cholestasis and no likelihood of systemic disease, a diagnosis of PBC can be made based on elevated ALP and the presence of AMA at a titre of 1:40.

Recommendation 8 [Chapter 4]
EASL recommends that in the correct context, a diagnosis of AMA negative PBC can be made in patients with cholestasis and specific ANA immunofluorescence (nuclear dots or perinuclear rims) or ELISA results (sp100, gp210).

Recommendation 9 [Chapter 4]
EASL recommends against liver biopsy for the diagnosis of PBC, unless PBC-specific antibodies are absent, coexistent AIH or NASH is suspected, or other (usually systemic) co-morbidities are present.

Recommendation 10 [Chapter 4]
AMA reactivity alone is not sufficient to diagnose PBC. EASL recommends following-up patients with normal serum liver tests who are AMA positive with annual biochemical reassessment for the presence of liver disease.

Recommendation 11 [Chapter 6]
EASL recommends that therapy in PBC should aim to prevent end-stage complications of liver disease and manage associated symptoms.

Recommendation 12 [Chapter 6]
EASL recommends evaluating all patients for their risk of developing progressive PBC.

Recommendation 13 [Chapter 6]
EASL recommends recognition that patients at greatest risk of complications from PBC are those with inadequate biochemical response to therapy, and cirrhosis.

Recommendation 14 [Chapter 6]
EASL recommends actively recognising that the strongest risk factors for inadequate biochemical response to therapy are early age at diagnosis (e.g. <45), and advanced stage at presentation.

Recommendation 15 [Chapter 6]
EASL recommends evaluating all patients for their stage of disease using a combination of non-invasive tests (bilirubin, alkaline phosphatase, AST, albumin, platelet count, and elastography) at baseline, and during follow-up.

Recommendation 16 [Chapter 6]
EASL recommends that elevated serum bilirubin and ALP can be used as surrogate markers of outcome for patients with PBC, and routine biochemistry and haematology indices should underpin the clinical approaches to stratify individual risk of disease progression.

Recommendation 17 [Chapter 6]
EASL recommends recognising that the transplant-free survival for early-stage patients with ALP \1.5xULN and a normal bilirubin after one year of therapy with UDCA, is not significantly different to a control healthy population.

Recommendation 18 [Chapter 6]
EASL recommends using elastography and risk scores (such as the GLOBE and UK-PBC score) for patients with PBC, to help better define the individual risk of development of complications of advanced liver disease in the future.

Recommendation 19 [Chapter 7]
EASL recommends oral UDCA at 13–15 mg/kg/day as the first-line pharmacotherapy for all patients with PBC. UDCA is usually continued for life.

Recommendation 20 [Chapter 7]
In a phase III study, evidence of biochemical efficacy of oral OCA has been demonstrated in patients with ALP >1.67xULN and/or bilirubin elevated <2xULN. Oral OCA has been conditionally approved for patients with PBC in combination with UDCA for those with an inadequate response to UDCA, or as monotherapy in those intolerant to UDCA. EASL suggests considering its use in such patients (initial dose 5 mg; dose titration to 10 mg according to tolerability at six months).

Recommendation 21 [Chapter 7]
Data from phase III randomised trials for budesonide (in non-cirrhotic patients), and bezafibrate, both in combination with UDCA, are not yet published; EASL suggests currently a recommendation for therapy cannot be made.

Recommendation 22 [Chapter 8]
EASL recommends expert consultation for all pregnant patients to guide therapy, noting that pregnancy is typically well tolerated in non-cirrhotic patients with PBC. EASL recommends the continued use of UDCA in pregnancy, even though supporting data are limited. Pruritus management is important and may require specialist advice, noting that rifampicin has been used by experts during the third trimester.

Recommendation 23 [Chapter 8]
Pregnancy in patients with cirrhosis carries a higher risk of maternal and foetal complications. EASL recommends offering patients pre-conception counselling and relevant specialist monitoring.

Recommendation 24
Patients with PBC may present with additional features of AIH in around 10% of cases, most often simultaneously, but sometimes sequentially even years after diagnosis of PBC. EASL recommend that a liver biopsy is mandatory in confirming the features of AIH, and should be considered in patients with disproportionate elevations in ALT and/or IgG.

Recommendation 25
Patients with PBC and typical features of AIH may benefit from immunosuppressive treatment in addition to UDCA. EASL suggests immunosuppressive treatment in patients with severe interface hepatitis, and consideration in patients with moderate interface hepatitis. EASL suggests counselling for patients to inform them of the side effect profile of immunosuppressive treatments.

Recommendation 26 [Chapter 9]
EASL recommends the evaluation of all patients for the presence of symptoms, particularly pruritus, sicca complex and fatigue. Whilst end-stage liver disease is associated with progressive symptom burden, severity of symptoms does not necessarily correlate with stage of disease in PBC.

Recommendation 27 [Chapter 9]
EASL recommends treating pruritus using a step wise approach. Patients with severe pruritus may have an aggressively ductopenic variant of PBC, with a poor prognosis. EASL recommends the referral of these patients to an expert centre.

Recommendation 28 [Chapter 9]
Given its favourable safety profile, EASL recommends cholestyramine as the first-line therapy for pruritus, despite its limitations. Attention should be paid to avoid interaction with other medications as a result of its anionic binding resin properties.

Recommendation 29 [Chapter 9]
EASL recommends rifampicin as a second-line therapy for pruritus, usually at a dose of 150 mg–300 mg daily. EASL recommends monitoring serum liver tests after initial use (at 6 and 12 weeks following drug initiation) and following dose increase, because of potential hepatotoxicity The agent should be stopped if toxicity is observed.

Recommendation 30 [Chapter 9]
EASL recommends seeking and treating associated and alternate causes of fatigue, particularly anaemia, hypothyroidism and sleep disturbance.

Recommendation 31 [Chapter 9]
EASL suggests advising patients with fatigue (which in some may be debilitating) on developing coping strategies, including the avoidance of social isolation, which can compound effects of fatigue.

Recommendation 32 [Chapter 9]
Sicca symptoms can be significant and reduce patient QoL; where appropriate EASL recommends considering patients for referral to expert clinicians.

Recommendation 33 [Chapter 9]
EASL recommends referring patients with symptoms resistant to medical therapy for specialist management, regardless of disease severity.

Recommendation 34 [Chapter 10]
EASL recommends considering the risk for osteoporosis in all patients with PBC.

Recommendation 35 [Chapter 10]
As part of evaluating the risk of osteoporosis, EASL recommends considering the use of DEXA to assess bone mineral density at presentation and at follow-up where indicated.

Recommendation 36 [Chapter 10]
EASL suggests supplementing patients with PBC with calcium and vitamin D, according to local practice.

Recommendation 37 [Chapter 10]
Bisphosphonates are safe and effective treatments for patients with PBC and significantly elevated fracture risk from osteoporosis but EASL recommends caution when using them in patients with varices. EASL recommends therapy initiation following specific osteoporosis guidelines.

Recommendation 38 [Chapter 10]
Fat-soluble vitamin malabsorption can occur in patients with PBC, particularly those with prolonged jaundice. EASL suggests that supplementation should be considered on an individual basis.

Recommendation 39 [Chapter 10]
Hyperlipidemia is a feature of cholestasis, for which there is no substantial evidence to support an elevated cardiovascular risk in patients with PBC. In the subgroup of patients with PBC and metabolic syndrome (with high cholesterol, low HDL cholesterol and high LDL cholesterol levels), EASL suggests considering a pharmacologic approach with cholesterol-lowering agents on a case-by-case basis; treatment is not contraindicated.

Recommendation 40 [Chapter 10]
EASL suggests that the Baveno-VI guidelines for screening and management of varices apply equally to patients with PBC.

Recommendation 41 [Chapter 10]
EASL suggests that in patients with suspected cirrhosis, HCC surveillance according to EASL guidelines is indicated.

Recommendation 42 [Chapter 10]
EASL recommends considering patients for transplant assessment when they present with complications of cirrhosis, markers of disease severity (e.g. persistent elevated bilirubin values [50 µmol/L or 3 mg/dl] or MELD > 15), or severe medically resistant pruritus. EASL recommends that listing for transplantation should follow local (usually national) guidelines.

Recommendation 43 [Chapter 10]
EASL suggests that in patients with proven or likely recurrent PBC post liver transplant, the use of UDCA is safe and can improve liver biochemistry.

Recommendation 44 [Chapter 11]
EASL recommends that all patients with PBC should have structured life-long follow-up, recognising that patients have different disease courses, and may require varied levels of attention.

Recommendation 45 [Chapter 11]
EASL suggests the development of a Care Pathway for PBC based on these guidelines, following its approval.

Recommendation 46 [Chapter 11]
EASL suggests that clinicians caring for patients with PBC should use standardised clinical audit tools to document and improve the quality of care delivered to patients.

Recommendation 47 [Chapter 11]
EASL suggests that patients with PBC should be informed of the support available from patient support groups, including access to patient education material.

Authors

This guide has been developed with help from the following organisations:

Deutsche Leberhilfe e.V.	Germany
The Finnish Kidney and Liver Association	Finland
Forening for autoimmune leversykdommer (FAL)	Norway
Hepatitis Hilfe Österreich	Austria
Leberhilfe Projekt gUG	Germany
Leverforeningen	Denmark
Save Liver Association for Patients	Macedonia
Dutch Liver Patients Association	Netherlands
PBC Sverige	Sweden
Rarissimas	Portugal
The PBC Foundation (UK) Ltd	UK

Review by:

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Canadian PBC Society	Canada
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