Primary Biliary Cholangitis (PBC)

Compiled by
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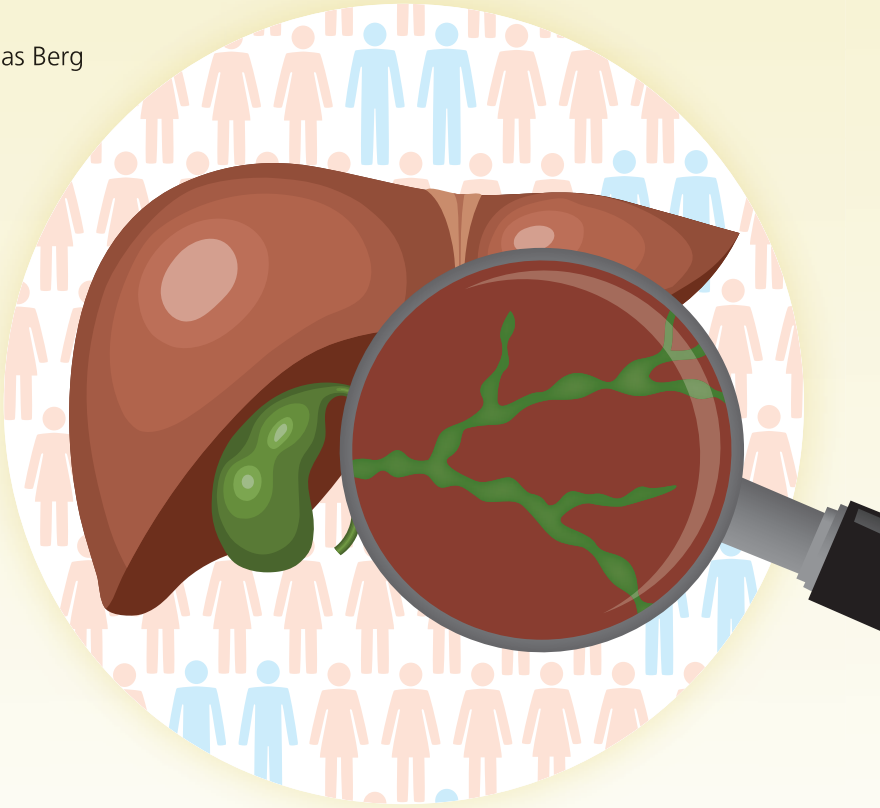

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1 Introduction

Primary biliary cholangitis (PBC, previously known as primary biliary cirrhosis) is an autoimmune cholestatic liver disease that is usually progressive and is characterized by a triad of intrahepatic cholestasis, circulating antimitochondrial antibodies (AMAs), and a pattern of typical histological signs (destructive cholangitis with interlobular bile duct destruction).[1] The disease is thought to be caused by interactions between environmental factors and genetic susceptibility to these external factors.[2-4] The progression of the disease through inflammation and fibrosis is classified into 4 stages (see p. 6–7), although the length of each of these stages is not known. The end stage of PBC is cirrhosis (fig. 1).

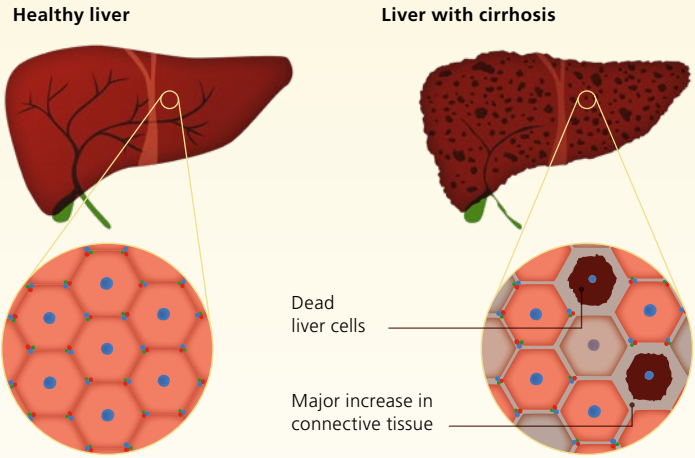


Figure 1: Healthy liver (left) and cirrhotic liver in the end stage of PBC (right)

1.1 Epidemiology

The prevalence of PBC is estimated to be 30 per 100,000 persons in the general population, with an annual incidence of about 1–2 per 100,000.[2,5] This makes PBC a rare disease; 80–90% of patients are female, and the disease usually starts between the ages of 40 and 60. To date, the youngest patient with a confirmed

case of PBC was 12 years old.[6] An increase in the number of PBC cases has been observed in recent years, especially in Europe and the US.[7] It remains unclear whether this increase is due to a genuine rise in prevalence or can be attributed to higher rates of diagnosis. The disease is most common in women in Europe or the US who are above the age of 45 years old (prevalence of approx. 1 per 800).[8]

1.2 Staging

PBC can be classified into 4 stages (stages 1–4) based on typical histological findings (see p. 6–7).

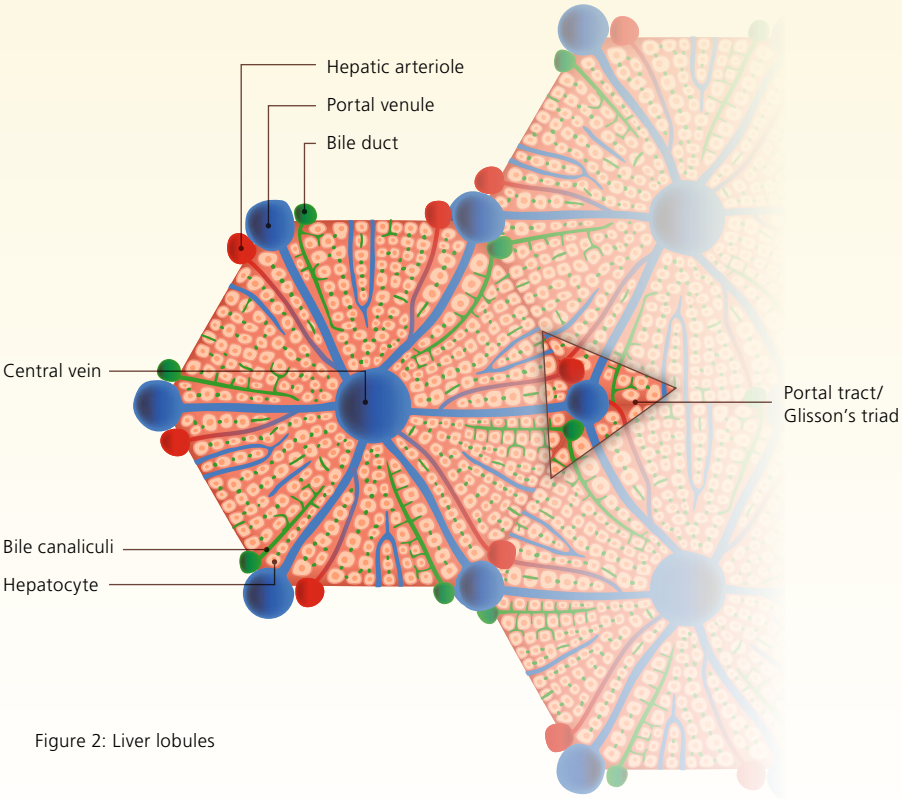
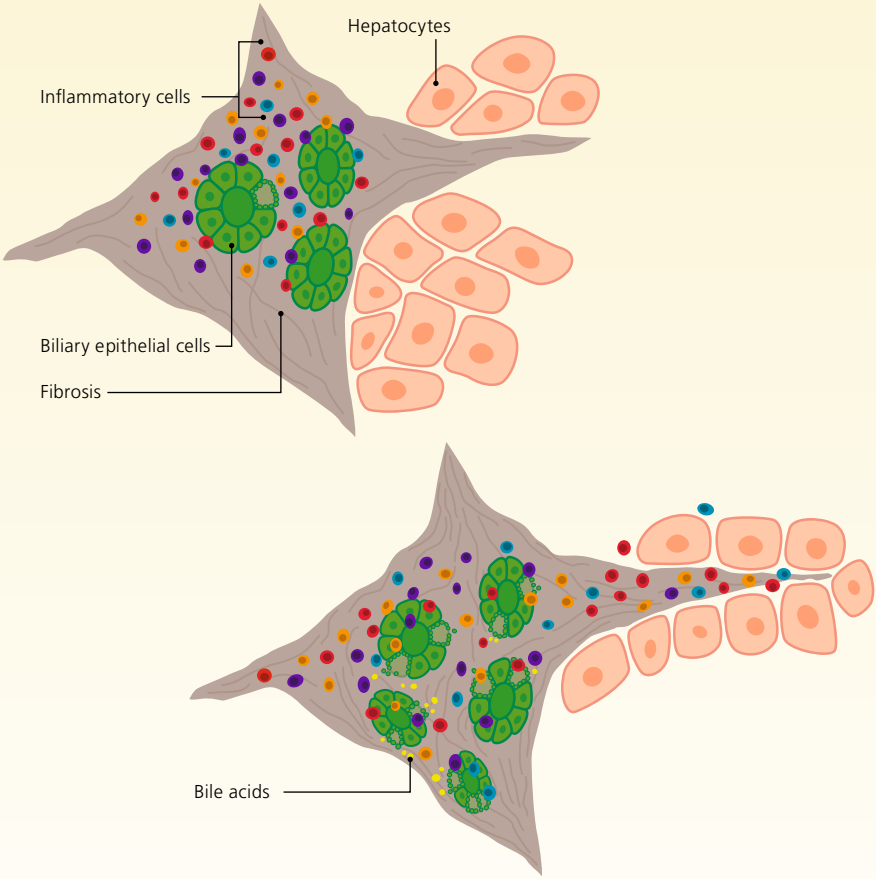


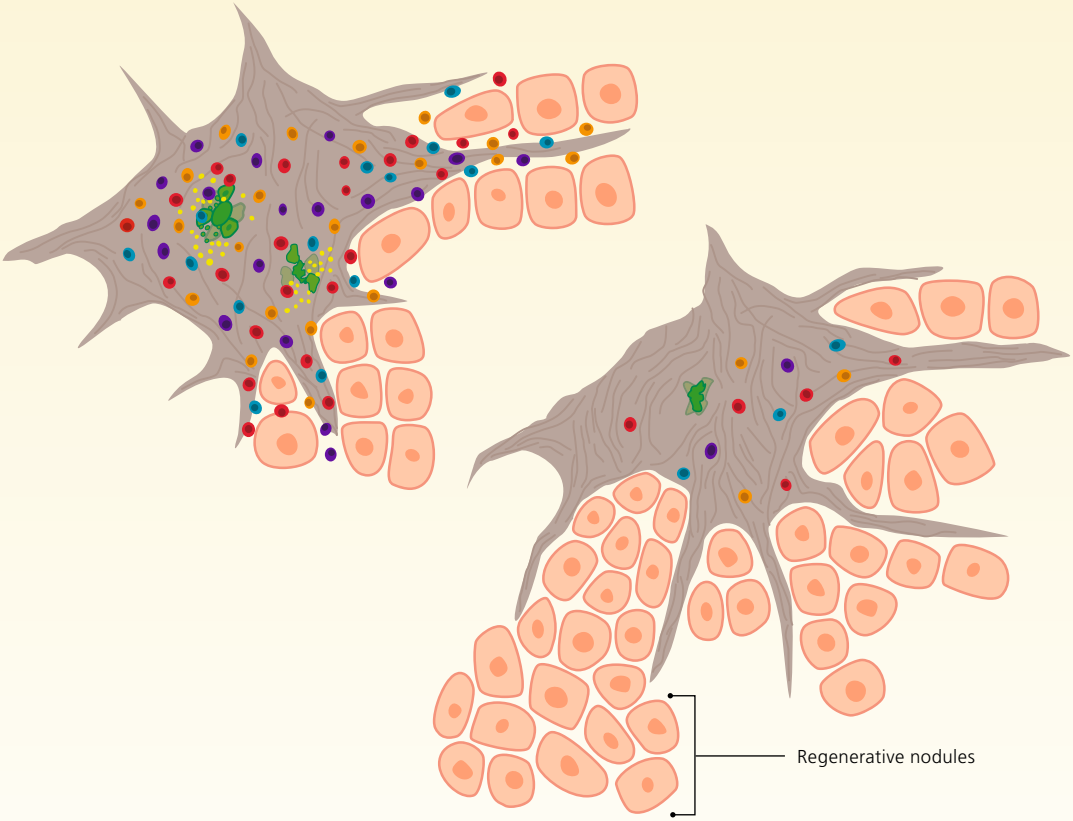
Figure 2: Liver lobules

Stage 1: In this stage, inflammation is confined to the bile ducts and surrounding connective tissue (portal tracts). Inflammatory cells migrate into tissues and destroy the bile ducts.



Stage 2: An increase in the number of bile ducts (ductular proliferation) can be observed by microscopy. These newly formed bile ducts attempt to replace the destroyed bile ducts. The inflammation around the portal tracts is dense and can also spread to the adjacent liver tissue.

Stage 3: Many bile ducts are now destroyed. There is a major increase in the inflammatory infiltrates in the adjacent liver tissue. Liver tissue has an increasingly fibrotic structure, reflecting the incipient cirrhosis.



Stage 4: The disease has reached the cirrhosis stage with extensive fibrosis. Regenerative nodules of various sizes form owing to the high propensity of liver tissue to regenerate. The number of bile ducts decreases greatly (vanishing bile duct syndrome). Intrahepatic vessels are also displaced, leading to portal hypertension.

1.3 Patient life expectancy

PBC typically progresses slowly. The life expectancy of patients with untreated PBC is highly variable and may be as long as many decades depending on inflammatory activity (fig. 3). Nonetheless, about one-quarter of patients will develop liver failure within 10 years.[9] Smoking likely accelerates the course of the disease, and in particular promotes the development of liver fibrosis in a dose-dependent manner.[10] Although no medications can currently cure PBC, they can nonetheless greatly slow or stop the progression of liver damage. Patients whose PBC is detected at a sufficiently early time point and who exhibit complete biochemical response to medical therapy with ursodeoxycholic acid (UDCA; see p. 20) have a normal life expectancy (approx. 75% of patients).[11,12] Liver transplantation can usually cure PBC in eligible patients with cirrhosis and liver failure and/or with hepatocellular carcinoma (HCC).

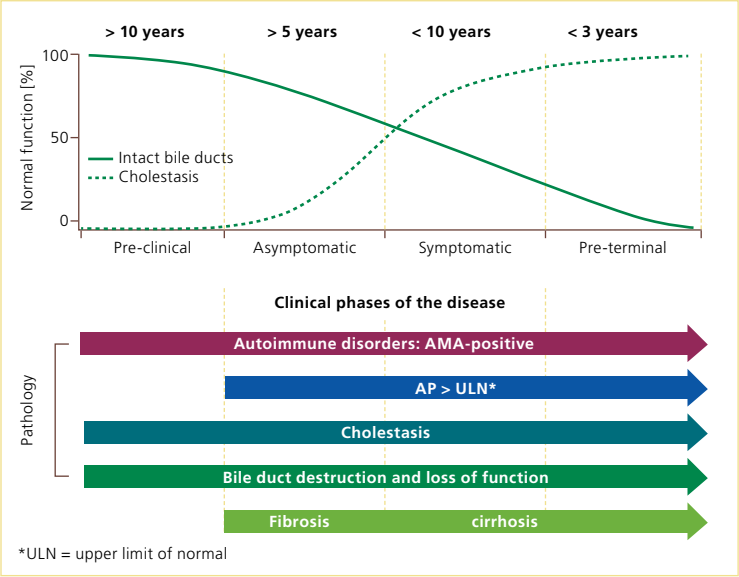


Figure 3: Natural course of PBC (modified from[13])

2 Diagnosis

Before the discovery of AMAs as marker antibodies, PBC was difficult to diagnose and was often not identified until its final stage. There were also no effective treatment options in the past. Hence, the disease was originally termed "primary biliary cirrhosis". In 2015 the disorder was renamed to "primary biliary cholangitis", both to reflect the fact that it is now diagnosed in an early stage (stages 1–2) in most patients and to avoid the stigma associated with the term cirrhosis.[14]

2.1 Medical history and physical examination

PBC can frequently go unnoticed for years, and often becomes suspected following the identification of elevated liver enzyme levels during routine testing. A targeted medical history is key for uncovering valuable clues (table 1). Patients frequently complain of major fatigue, dry mucous membranes in the eyes and mouth, and arthritis-like joint symptoms with morning stiffness of the fingers. Patients may also have mild, moderate, or even severe pruritus which is most prominent at night and on the arms, back, and lower legs. This itching may be intensified by heat (such as in bed) or by dry air (for example when heating an indoor space in winter). Patients should be asked about certain disorders that frequently accompany PBC (see table 3, p. 15). They should also be queried about their medication history, since certain drugs may cause laboratory test results which mimic PBC (e.g. NSAIDs, sulfonamide drugs, anti-epileptics, or herbal remedies such as *Chelidonium majus*, mistletoe, or valerian). Alcohol abuse must also be ruled out.

PBC may also occur after pregnancy, and should be suspected whenever intrahepatic cholestasis of pregnancy does not fully resolve following childbirth.[15]

Factors indicative of PBC
Primarily affects women ages 40 and above, rarely men
Itching (arms, legs, back)
Fatigue, exhaustion, decreased strength
Dry eyes and mucous membranes (sicca syndrome)
Joint symptoms with morning stiffness, especially in the joints at the base of the fingers
Sensation of pressure in right upper abdomen
Fat deposits around the eyelids (xanthelasma)
Yellow pigmentation of the skin and the whites of the eyes (jaundice)
Potential onset of symptoms during pregnancy
Other autoimmune diseases

Table 1

It is usually not possible to detect any abnormalities by physical examination during the initial stages of PBC. Jaundice of the skin or scleral icterus typically do not yet occur, and the liver and spleen are not palpably enlarged. Signs of itching may be visible on the arms and legs. The typical physical signs of PBC are subcutaneous yellowish-gray fat deposits (called xanthelasma), particularly on the eyelids proximal to the nose. Small fatty nodules (xanthomas) may also form on the hands, feet, or buttocks. At advanced stages, the liver is usually palpably enlarged, and patients exhibit jaundice (see table 4, p. 18). In stage 4, the surface of the liver

feels bumpy, and splenomegaly or ascites may develop as a result of portal hypertension. Muscle wasting is also frequently observed, and is most visible on the arms and legs (sarcopenia).

2.2 Laboratory test parameters

PBC can usually be diagnosed using a specific group of laboratory parameters (table 2). Serum tests reveal a typical cholestasis pattern with elevated alkaline phosphatase (AP) and gamma-glutamyl transferase (GGT).[15] The levels of these cholestasis markers correlate with disease activity. Other typical findings are elevated immunoglobulin M (IgM) levels and hypercholesterolemia. If this pattern is observed in lab tests, serum should be tested for AMAs. The PBC-specific AMA-M2 is an antibody targeting the mitochondrial M2 antigen.[16] This antigen is found on the E2 subunit of the pyruvate dehydrogenase complex, which is part of the branched-chain 2-oxo-acid dehydrogenase complex on the inner mitochondrial membrane. AMAs are neither the cause of PBC nor are they responsible for the severity of the disease. Nonetheless, the presence of these antibodies together with elevated AP and GGT levels confirms the diagnosis of PBC even in the absence of clinical symptoms. These antibodies are detected in more than 90% of PBC patients.[16] PBC without AMAs is termed AMA-negative PBC. Antinuclear antibodies (ANAs), which target structures in the cell nucleus (e.g. sp100 [nuclear dots], gp210 [nuclear membrane], or centromeres) in a non-organ-specific manner, are detected in these patients quite often.[15] A diagnosis of AMA-negative PBC should be confirmed by the detection of the typical PBC histology findings after fine-needle biopsy of the liver. Detection of AMAs alone without the typical laboratory pattern of cholestasis is not indicative of PBC: Only 1 in 6 patients with positive AMAs and normal AP levels will develop PBC within a 5-year period.[17]

Levels of the transaminases alanine aminotransferase (ALT) and aspartate aminotransferase (AST) typically exhibit no or only minor elevation in early stages of PBC. Highly elevated ALT is a marker of hepatocyte injury and occurs during the advanced stages of PBC (stages 3–4), and it may also be a sign of an overlap syndrome (also known as a variant syndrome) with autoimmune hepatitis.

Typical laboratory test results during the initial stages of PBC
Elevated AP and GGT
Hypercholesterolemia and high IgM levels
Detection of antimitochondrial antibodies (AMAs)
Normal or slightly elevated transaminase levels (ALT and AST)

Table 2

Elevated serum levels of bilirubin are also typical of later stages (stages 3–4). Patients develop jaundice, which is first visible in the sclera and later across the entire body. Because bilirubin can no longer be adequately eliminated in bile, it is excreted in urine. This confers the urine with a dark color, while stool becomes lighter in color. During the end stage of PBC (stage 4), the synthesis function of the liver gradually deteriorates, which can be detected by a decrease in protein concentration (blood albumin), platelets, and blood clotting factors (prothrombin time).

2.3 Ultrasound and elastography

There are no characteristic features that can be observed using imaging procedures during the initial stages of PBC. It is nonetheless important to perform an ultrasound examination of the liver and bile ducts to rule out other causes of cholestasis (especially extrahepatic cholestasis secondary to choledocholithiasis, cancer, or biliary strictures). If PBC progresses to cirrhosis, the typical ultrasound presentation of cirrhosis can be observed, with small to large bumps on the surface of the liver, heterogeneous parenchyma, enlarged caudate lobe, decreased vascularization, possible reversed portal vein flow, ascites, and splenomegaly.[18]

Several non-invasive elastographic methods have become available in recent years that allow measurement of liver fibrosis, including an ultrasound-based method called Fibroscan (fig. 4).

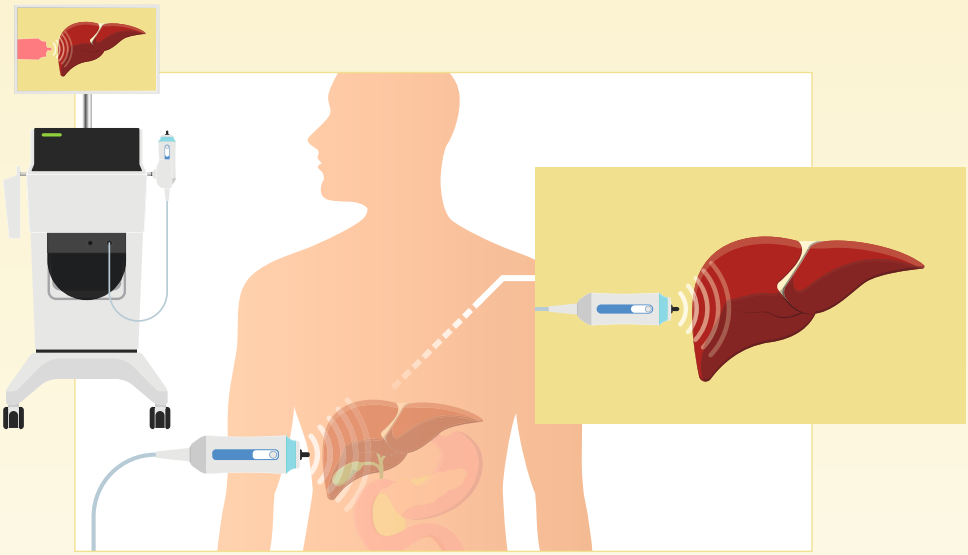


Figure 4: Non-invasive elastography of the liver for measuring stiffness, staging fibrosis, and determining the degree of liver injury

This method allows the extent of liver damage to be assessed even at early stages of PBC, and can also be of predictive value.[19] The stiffness of liver tissue is reported in the unit of kilopascal (kPa). A healthy liver has a stiffness of 5.5 ± 1.6 kPa.[20] Values of ≥ 13 kPa must be assumed to denote cirrhosis.[21] Values of > 9.6 kPa have been linked to increased mortality and the requirement for liver transplantation in patients with PBC.[15,19]

2.4 Liver biopsy

Ultrasound-guided fine needle biopsy of the liver is no longer generally recommended for confirmation of a diagnosis of PBC. If the laboratory test results are clear, a liver biopsy should be skipped in order to avoid the potential complications (especially bleeding). It is currently possible to reliably evaluate the stage of PBC (especially the degree of fibrosis) using non-invasive techniques (such as elastography). However, biopsy remains an option if AMA-negative PBC is greatly suspected, to rule out concurrent autoimmune hepatitis if transaminase levels are greatly elevated

even in early stages, and to confirm the diagnosis in patients who do not respond to treatment.[15]

2.5 Genetic testing

Genome-wide association studies (GWAS) have identified a number of genes which are associated with an increased risk of developing PBC when mutated. This particularly includes genes involved in regulating the immune response, such as STAT4, NFκB1, or CXCR5.[22] While individual susceptibility to PBC thus appears to have a genetic underpinning, the disease is not triggered by any one specific mutation. It is thus not (yet) possible to use a genetic test to detect or predict the likelihood of developing PBC. A study from Iceland reported that the hereditary risk of PBC is significantly higher for first-degree to third-degree relatives of PBC patients (9.1-fold, 3.6-fold, and 2.6-fold higher, respectively) and somewhat higher for fourth- and fifth-degree relatives (1.7-fold and 1.4-fold higher, respectively).[23] Nonetheless, the absolute risk appears to be low even for first-degree relatives with positive AMAs, meaning routine family screening for PBC is not necessary based on current research.[24]

3 Concomitant disorders and complications

There are a large number of potential concomitant disorders and complications of PBC that typically exert a major impact on patients' quality of life.

Autoimmune diseases that can accompany PBC	
Common	Sjögren's syndrome (sicca syndrome)
	Hashimoto's thyroiditis
	Scleroderma
	Autoimmune hepatitis
	Raynaud's disease
Less common	Myasthenia gravis
	Addison's disease
	Pernicious anemia
	Rheumatoid arthritis
	Celiac disease (gluten-sensitive enteropathy)
	Inflammatory bowel disease
	Pemphigus vulgaris
	Restless legs syndrome

Table 3

3.1 Concomitant autoimmune diseases

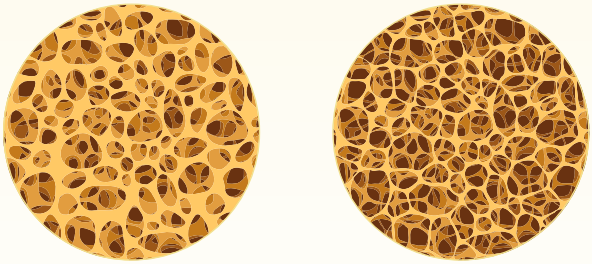
Up to 50% of PBC patients also have autoimmune disorders (table 3).[25] These include sicca syndrome of the major moisture-producing glands (e.g. tear ducts, salivary glands). The dry mucous membranes render patients more susceptible to cavities or fungal infections and they may report difficulty swallowing. The decrease

in the production of tears causes a sensation of having a foreign object in the eyes, together with burning, redness, sensitivity to light, swollen eyelids, and an inability to tolerate contact lenses. Dry eyes pose a risk of infection since tears contain antimicrobial substances.

PBC patients also frequently suffer from concurrent Hashimoto's thyroiditis, which involves autoimmune destruction of thyroid tissue leading to hypothyroidism. Approximately one-quarter of PBC patients suffer from Raynaud's disease, especially in the fingers and toes, while a smaller percentage of patients experience restless legs syndrome.

Osteoporosis and vitamin deficiencies

Osteoporosis is a common concomitant disorder or complication of PBC. It is not fully clear how osteoporosis develops during PBC. Cholestasis and the resulting bile acid deficiency in the small intestine may lower the uptake of some nutrients, including the fat-soluble vitamins (A, D, E, K). Vitamin D plays an important role in bone turnover. Because PBC primarily afflicts women over the age of 40, who are already at a higher risk of osteoporosis due to menopause, it is difficult to clearly differentiate between these causes. Osteoporosis can be quantified by X-ray examination (DEXA).[26]



Normal Osteoporosis

Vitamin A deficiency may promote night blindness, whereas vitamin K is essential for the production of vitamin K-dependent coagulation factors by the liver. As these vitamin deficiencies are only mild in most cases, they cause few complications and do not require treatment.[15]

Bile acid deficiency in the small intestine also impairs the production of micelles for the absorption of fat, which may result in fatty stools (steatorrhea) in some patients.

3.2 Complications of cirrhosis

The overall clinical presentation of PBC-related cirrhosis (table 4 and fig. 5) does not differ from that of cirrhosis due to other causes. Portal hypertension forces the use of portocaval anastomoses as collateral circulation and may result in major bleeding in some patients. Of particular clinical importance is collateral circulation through the submucosal veins of the small curvature of the stomach and the distal esophagus (leading to the formation of esophageal/gastric varices), through the rectal venous plexus (leading to the formation of anorectal varices), and through the paraumbilical veins (leading to the formation of caput medusae).[27] Hypertension-mediated dilation of the veins of the gastric mucosa can also lead to portal hypertensive gastropathy, which may also result in acute gastrointestinal bleeding. Portal hypertension is also the cause of ascites. The increase in intra-abdominal pressure also frequently causes visceral hernias, particularly in the umbilical region. The reduced synthesis function of the liver results in decreased production of proteins and coagulation factors. These low levels of protein may lead to edema and an increased risk of bleeding. Acute deterioration of a patient's condition with hepatorenal syndrome or the development of hepatic encephalopathy (or worsening of existing hepatic encephalopathy) are commonly due to bacterial infections such as spontaneous bacterial peritonitis or due to variceal bleeding.

Clinical signs of cirrhosis
Skin changes due to disease • Scleral icterus and jaundice • Spider angioma • Palmar and plantar erythema • White nails or Terry's nails • Glossy lips and smooth tongue • Atrophic skin with "paper money" skin • Dupuytren's contracture of the finger tendons • Angular cheilitis
Ascites, lower leg edema, sarcopenia
Hematoma even after trivial injuries
Loss of chest hair and gynecomastia in men
Hepatic encephalopathy

Table 4

3.3 Hepatocellular carcinoma

PBC patients have a significant risk of developing hepatocellular carcinoma (HCC), especially patients with stage 4 disease. Approximately 3 in every 1,000 patients with (advanced) PBC develop HCC; with a higher risk among men and among patients who do not adequately respond to first-line medical therapy (see below).[28,29] HCC screening (liver ultrasound, measurement of alpha-fetoprotein [AFP]) is thus recommended every 6 months for patients with stage 4 PBC.[30]

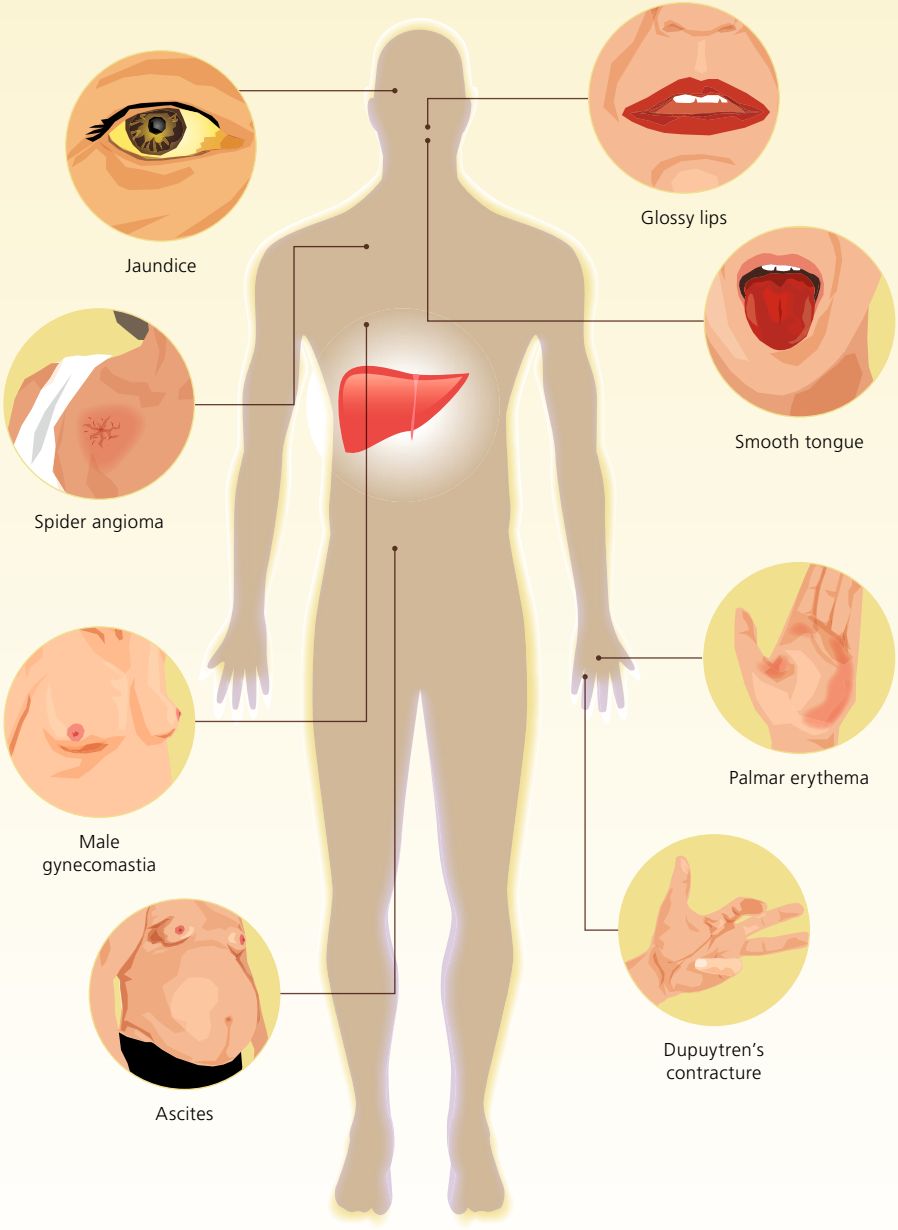


Figure 5: Clinical signs of cirrhosis

4 Treatment

The goal of treatment is to slow or, ideally, to stop progression of PBC. Extrahepatic manifestations and other symptoms should also be incorporated into a treatment plan, since these can greatly impact patients' quality of life.

4.1 Risk factors for inadequate response to treatment

Before PBC treatment is initiated, the risk of incomplete response to first-line treatment with ursodeoxycholic acid (UDCA) should be evaluated for all patients so that they can be referred to specialized clinics with a wider range of treatment options as early as possible. The risk factors for poor response to UDCA treatment and a greater risk of unfavorable disease outcomes primarily include young patient age at first PBC-related visit (< 45 years old), male sex, high bilirubin levels, and low albumin levels.[31,32] Calculating the aspartate aminotransferase to platelet ratio index (APRI) may be a useful parameter for predicting the likelihood of response to UDCA.[33] Patients with positive ANA autoantibodies (sp100 and gp210) also tend to have worse disease outcomes, although determination of ANA levels is of lesser importance in clinical practice.[34]

4.2 Treatment of PBC

Medical treatment (table 6) must be initiated immediately after diagnosis. The first element of medical treatment is the bile acid UDCA, which is present at only low concentrations (1–3% of natural bile acids) in humans and is enriched with treatment.[35] UDCA stimulates biliary secretion by hepatocytes through post-translational modifications whose effects include altering the density of membrane transporters. UDCA also stimulates the secretion of chloride and bicarbonate anions by cholangiocytes, producing a bicarbonate "umbrella" which protects the cholangiocytes from the cytotoxic effects of bile acids (fig. 6).[36,37] PBC likely causes major damage to these protective mechanisms.

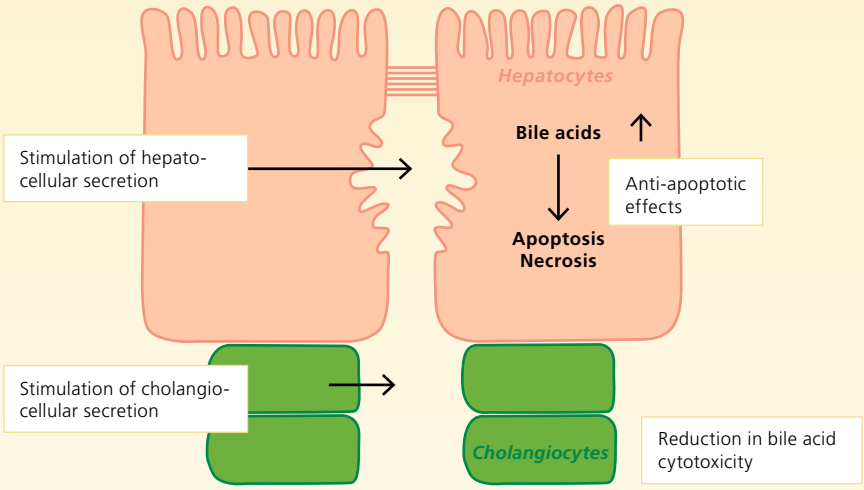


Figure 6: Model of potential mechanisms and sites of UDCA activity in cholestatic liver diseases. The relative contributions of each of these mechanisms to the anticholestatic effects of UDCA is not known (modified from[37])

The recommended dose of UDCA is 13–15 mg/kg body weight per day.[15] The drug can be taken in 2 doses across the day or as a single dose in the evening. Treatment should not be interrupted and should continue indefinitely.

While UDCA may cause diarrhea, it is usually well-tolerated without any clinically relevant adverse effects even with long-term use. Based on current research, initiating or continuing UDCA treatment at the recommended daily dose during pregnancy and breast-feeding is both possible and recommended.[38]

Up to 75% of patients respond well to treatment with UDCA, which is associated with an improvement or normalization of laboratory parameters.[39] UDCA greatly reduces the risk of cirrhosis and extends the time until liver transplantation is required.[40] When PBC is diagnosed at an early stage and AP and ALT levels normalize with UDCA therapy, patients' long-term survival becomes comparable to that of the general population.[41]

A number of scoring systems have been developed to evaluate treatment response after 6 to 12 months. These tests use specific laboratory parameters (especially AP, bilirubin, and albumin) to define response and incomplete response to UDCA (e.g. using Paris I or Paris II criteria; see table 5 for prognosis based on selected scores).[15] The GLOBE score developed by the Global PBC Study Group (https://www.globalpbc.com/globe) and the UK-PBC score by the UK-PBC consortium (http://www.uk-pbc.com) represent further developments of these simple scoring systems that can be continuously measured and which incorporate the disease stage as well as biochemical response. Even patients with incomplete response to UDCA experience improved survival compared with untreated patients.[42,43]

Patients with incomplete response to UDCA should be referred to a specialized clinic for further treatment with combination regimens. The possibility of concurrent autoimmune hepatitis should also be taken into consideration for patients who respond inadequately to UDCA (see overlap syndrome). A combination regimen is indicated only if there are no signs of an overlap syndrome. One promising alternative is the combination of UDCA plus the synthetic bile acid analogue obeticholic acid (OCA), which was approved in Germany in December 2016 for patients with PBC who do not adequately respond to UDCA. After entering hepatocytes and cholangiocytes, OCA activates the nuclear farnesoid X receptor (FXR), which in turn activates the transcription of numerous genes whose protein products play important roles in the synthesis, transport, secretion, and detoxification of bile acids. These effects bolster the bicarbonate umbrella, preventing the unimpeded entry of potentially toxic bile acids into the cholangiocytes.[37,47] Approximately half of patients with no or inadequate response to an initial regimen of UDCA respond to this combination.[48] This regimen starts with 5 mg of OCA once daily, which can be increased to 10 mg daily after 6 months in patients with inadequate response.[15] However, caution is warranted: In patients with known advanced cirrhosis (Child-Pugh class B or C), OCA may only be started at a much lower dosage (1x 5 mg/week) and then only with close monitoring of liver parameters, as there is a risk of liver failure with this drug.[49] Depending on how well it is tolerated, the dose may be increased up to 2x 10 mg/week in order to achieve optimal response.

Prognosis of PBC based on response to UDCA treatment		
Score	**Response**	**Incomplete response**
Paris I[11]	90% 10-year transplant-free survival	51% 10-year transplant-free survival
Paris II[44]	100% 10-year transplant-free survival	87% 10-year transplant-free survival
Rotterdam[45]	81% 10-year transplant-free survival	56% 10-year transplant-free survival
Barcelona[46]	95% 10-year transplant-free survival	55% 10-year transplant-free survival

Table 5

OCA is typically tolerated well by patients without known advanced cirrhosis. The primary adverse effect is the potential to trigger or exacerbate pruritus, which may require dose reduction or discontinuation altogether.

The data for combination therapies with UDCA plus a fibrate drug (e.g. bezafibrate) is particularly positive for patients with pruritus, even though not yet approved for PBC (off-label). This combination not only results in lower levels of cholestasis parameters, but also likely improves disease prognosis,[50-52] although conclusive data on long-term outcomes remains lacking. Possible adverse effects include myositis, elevated creatinine levels, or less commonly nausea and dizziness.

Topical steroids (budesonide) in combination with UDCA may be tested in patients with high disease activity and no response to OCA or fibrates, especially if laboratory tests indicate the possibility of concomitant autoimmune hepatitis (see overlap syndrome).[15]

Medical treatment of PBC
• **Ursodeoxycholic acid (UDCA)** 13–15 mg/kg body weight daily – Start of treatment: immediately after diagnosis – Duration: lifelong
In patients with inadequate response to UDCA:
• **Combination therapy with obeticholic acid (OCA)** 1x 5 mg daily with potential dose increase to 10 mg/day after 6 months – Duration: lifelong – Caution: The safety of OCA has not been adequately studied in cirrhosis patients. Maximum starting dose of 1x 5 mg per WEEK!
• **Off-label** Bezafibrate or possibly budesonide (in patients without cirrhosis)[50,54]

Table 6

Despite several positive studies, the effectiveness of budesonide at treating PBC in patients without autoimmune hepatitis remains controversial.[53-57] Hence, budesonide is not approved for the treatment of PBC in the absence of autoimmune hepatitis. Due to the increased risk of osteoporosis, steroid treatment requires prophylactic measures to prevent osteoporosis. Budesonide should not be administered to patients with known cirrhosis.

Management of common symptoms and complications

Managing the symptoms of PBC – some of which may be excruciating, such as pruritus or fatigue – and complications such as osteoporosis or sicca syndrome typically require a great deal of patience and persistence by both the physician and the patient. Effective treatment requires systematic documentation of patients' symptoms, which should be repeated at regular intervals. The PBC-40 questionnaire has proven to be a useful tool in clinical practice (www.gihep.com/pbc40/).

Treatment of pruritus
Cholestyramine
Bezafibrate
Rifampicin
Oral opioid antagonists (naltrexone, nalmefene)
Selective serotonin reuptake inhibitors (e.g. sertraline)
Very rarely: plasmapheresis, albumin dialysis, nasobiliary drainage, phototherapy
Combination of all attempted treatments

Table 7

A number of medications are available to treat pruritus (table 7).[15] Skin should be kept moist using natural skin care products (e.g. oatmeal-based products). A cold shower may (temporarily) alleviate itching, since pruritus is frequently exacerbated by warmth. A comprehensive allergy test should be performed to rule out other possible causes of the itching. In extreme cases, alternative forms of treatment may be attempted at specialized centers, including albumin dialysis or plasmapheresis, an endoscopic tube to drain bile via the nose (nasobiliary drainage), or whole-body UVB light treatment (phototherapy). If none of these treatment attempts work, the option of liver transplantation should be discussed. Itching typically subsides after transplantation,[58] often within the first 24 hours based on reports from clinical practice.

Fatigue is difficult to treat, and no medications are available for this purpose. Studies have shown that social isolation and loneliness exacerbate fatigue.[59] It is crucial that other potential causes of fatigue and exhaustion are ruled out (e.g. hypothyroidism, sleep disorder caused by itching, taking beta blockers). Regular, light physical activity may counteract the symptoms of fatigue. In contrast to itching, fatigue usually persists after liver transplantation.

Artificial tears or saliva and/or muscarinic receptor agonists such as pilocarpine may be used to treat dry eyes or dry oral mucosa related to sicca syndrome. If the eyes are severely affected, other medical and interventional treatment options are available.[15,60] It is important to notify patients about the elevated risk of caries and the need to maintain oral hygiene. If the vaginal region is also affected, the patient should be referred to a gynecologist for further care.

A balanced diet combined with regular outdoor exercise are crucial for preventing osteoporosis, which frequently occurs early in the course of PBC (table 8).[15] Bone density must be measured (by DEXA) at the time of PBC diagnosis and no later than every 2 years thereafter. Calcium and vitamin D supplementation should only be initiated in patients with indications of a corresponding deficiency (low serum vitamin D levels, inadequate nutritional status, known malabsorption, T-score < -1.5).[15] Bisphosphonates (e.g. alendronate 1x 70 mg/week) should be prescribed for patients with a T-score < -1.5 depending on their age and comorbidities (such as type 1 diabetes).[61]

Treatment of osteoporosis due to PBC
Outdoor exercise and balanced diet
Supplementation with vitamin D (800–2,000 IU per day) and calcium (1,000 mg per day) only in deficient patients, caution: Calcium is contraindicated in patients with kidney stones[62]
Bone formation-promoting drugs such as bisphosphonates

Table 8

4.3 Liver transplantation

Should patients develop jaundice, complications of portal hypertension, or HCC during the course of PBC, the option of liver transplantation should be evaluated. The Model for End-stage Liver Disease (MELD) score frequently does not adequately reflect the severity and prognosis of the disease, meaning it may be advisable to register a patient on a transplant list even with a MELD score of < 15 points,[63] which is the usual threshold. Survival rates are typically very high after transplantation.[64] PBC recurrence after transplantation has been reported in 11% to 42% of cases.[65] Continuation of UDCA therapy likely lowers the risk of disease recurrence, although no conclusive studies are available on this question.[66] The risk of PBC recurrence is likely lower with cyclosporine-based immunosuppression than with tacrolimus.[67] A liver biopsy is required to diagnose recurrence after transplantation. AMA autoantibodies remain positive after transplantation even without disease recurrence.

5 PBC and autoimmune hepatitis

Approximately 8–10% of patients with PBC also exhibit concomitant signs of autoimmune hepatitis (AIH).[15,68]

The two disorders may also occur sequentially, even with an interval of years, and thus follow-up laboratory tests should be performed no later than every 6 months. A PBC-AIH overlap or variant syndrome must be kept in mind for patients showing PBC-typical alterations and at least two of the following criteria:[15]

1. AP > 2x ULN (upper limit of normal) or GGT > 5x ULN,

2. AMA > 1:40,

3. histological evidence of bile duct lesions.

In addition, two of the following conditions must also be fulfilled:

1. ALT > 5x ULN,

2. IgG serum level > 2x ULN or SMAs (smooth muscle antibodies) positive,

3. histological evidence of moderate to severe hepatitis.

The detection of autoantibodies typical of AIH alone without clear ALT activity is generally not an indication of an overlap syndrome.

Treatment with UDCA can be attempted for patients with an overlap syndrome with low-grade hepatitis activity.[5] This intervention alone can achieve complete biochemical response in many patients. For patients with moderate or high disease activity or whose transaminase levels do not normalize with UDCA, a combination of UDCA plus a steroid (e.g. prednisolone) is recommended.[15] Initial studies suggest that the topical steroid budesonide (with high first-pass metabolism) is as effective as prednisolone in patients without cirrhosis, yet has a lower risk of adverse effects such as osteoporosis. However, no long-term results have been reported to date.[5,69]

Once transaminase levels have normalized, the immunosuppressant azathioprine should be added, and the steroid should be tapered and then discontinued. It is usually necessary to continue the combination with azathioprine (possibly at a reduced dose) and UDCA indefinitely. In rare cases, azathioprine can be successfully discontinued many years later. Other immunosuppressants (e.g. mycophenolate mofetil) are available for patients who do not tolerate azathioprine.

6 Summary

- Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease which is usually progressive.
- It starts in the small intrahepatic bile ducts but can transit to the liver tissue, which gradually leads to cirrhosis.
- It is now possible to detect the disease at early stages thanks to improved laboratory diagnostic tests.
- The primary medication used to treat PBC is ursodeoxycholic acid (sometimes in combination with obeticholic acid or bezafibrate). Treatment is initiated immediately after diagnosis and continued indefinitely.
- Ursodeoxycholic acid improves laboratory parameters and life expectancy in the majority of patients. Patients whose PBC is diagnosed at an early stage and who respond well to treatment have a normal life expectancy.
- Topical steroids (budesonide) may be attempted for patients with high disease activity who do not respond to obeticholic acid or fibrate drugs. A confirmed overlap syndrome is treated with a combination of PBC therapy plus steroids (induction) and azathioprine (maintenance of remission).
- Patients should be evaluated for liver transplantation if they develop jaundice or in the event of cirrhosis complications, hepatocellular carcinoma or unmanageable pruritus.
- Patients' prognosis after liver transplantation is generally very good, although some patients do experience a recurrence of PBC.

References

1. Purohit T, Cappell MS. Primary biliary cirrhosis: Pathophysiology, clinical presentation and therapy. World J Hepatol. 2015;7(7):926–41.
2. Griffiths L, Dyson JK, Jones DE. The new epidemiology of primary biliary cirrhosis. Semin Liver Dis. 2014;34(3):318–28.
3. Probert PM, Leitch AC, Dunn MP, Meyer SK, Palmer JM, Abdelghany TM, et al. Identification of a xenobiotic as a potential environmental trigger in primary biliary cholangitis. J Hepatol. 2018;69(5):1123–35.
4. Tanaka T, Zhang W, Sun Y, Shuai Z, Chida AS, Kenny TP, et al. Autoreactive monoclonal antibodies from patients with primary biliary cholangitis recognize environmental xenobiotics. Hepatology. 2017;66(3):885–95.
5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol. 2015;63(4):971–1004.
6. Kitic I, Boskovic A, Stankovic I, Prokic D. Twelve-year-old girl with primary biliary cirrhosis. Case Rep Pediatr. 2012;2012:937150.
7. Boonstra K, Kunst AE, Stadhouders PH, Tuynman HA, Poen AC, van Nieuwkerk KM, et al. Rising incidence and prevalence of primary biliary cirrhosis: a large population-based study. Liver Int. 2014;34(6):e31–8.
8. Hirschfield GM, Dyson JK, Alexander GJM, Chapman MH, Collier J, Hubscher S, et al. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. Gut. 2018;67(9):1568–94.
9. Prince M, Chetwynd A, Newman W, Metcalf JV, James OFW. Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: Follow-up for up to 28 years. Gastroenterology. 2002;123(4):1044–51.
10. Corpechot C, Gaouar F, Chretien Y, Johanet C, Chazouilleres O, Poupon R. Smoking as an independent risk factor of liver fibrosis in primary biliary cirrhosis. J Hepatol. 2012;56(1):218–24.
11. Corpechot C, Abenavoli L, Rabahi N, Chretien Y, Andreani T, Johanet C, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008;48(3):871–7.
12. Kaps L, Grambihler A, Yemane B, Nagel M, Labenz C, Ploch P, et al. Symptom burden and treatment response in patients with primary biliary cholangitis (PBC). Dig Dis Sci. 2020;65(10):3006–13.
13. Selmi C, Bowlus CL, Gershwin ME, Coppel RL. Primary biliary cirrhosis. Lancet. 2011;377(9777):1600–9.
14. Beuers U, Gershwin ME, Gish RG, Invernizzi P, Jones DE, Lindor K, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Clin Res Hepatol Gastroenterol. 2015;39(5):e57–9.
15. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67(1):145–72.

16. Vergani D, Alvarez F, Bianchi FB, Cancado EL, Mackay IR, Manns MP, et al. Liver autoimmune serology: a consensus statement from the committee for autoimmune serology of the International Autoimmune Hepatitis Group. J Hepatol. 2004;41(4):677–83.

17. Dahlqvist G, Gaouar F, Carrat F, Meurisse S, Chazouilleres O, Poupon R, et al. Large-scale characterization study of patients with antimitochondrial antibodies but nonestablished primary biliary cholangitis. Hepatology. 2017;65(1):152–63.

18. Procopet B, Berzigotti A. Diagnosis of cirrhosis and portal hypertension: imaging, non-invasive markers of fibrosis and liver biopsy. Gastroenterol Rep (Oxf). 2017;5(2):79–89.

19. Corpechot C, Carrat F, Poujol-Robert A, Gaouar F, Wendum D, Chazouilleres O, et al. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. Hepatology. 2012;56(1):198–208.

20. Roulot D, Czernichow S, Le Clesiau H, Costes JL, Vergnaud AC, Beaugrand M. Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome. J Hepatol. 2008;48(4):606–13.

21. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology. 2008;134(4):960–74.

22. Gulamhusein AF, Juran BD, Lazaridis KN. Genome-wide association studies in primary biliary cirrhosis. Semin Liver Dis. 2015;35(4):392–401.

23. Ornolfsson KT, Olafsson S, Bergmann OM, Gershwin ME, Bjornsson ES. Using the Icelandic genealogical database to define the familial risk of primary biliary cholangitis. Hepatology. 2018;68(1):166–71.

24. Gulamhusein AF, Juran BD, Atkinson EJ, McCauley B, Schlicht E, Lazaridis KN. Low incidence of primary biliary cirrhosis (PBC) in the first-degree relatives of PBC probands after 8 years of follow-up. Liver Int. 2016;36(9):1378–82.

25. Floreani A, Franceschet I, Cazzagon N. Primary biliary cirrhosis: overlaps with other autoimmune disorders. Semin Liver Dis. 2014;34(3):352–60.

26. DVO. Prophylaxe, Diagnostik und Therapie der Osteoporose bei postmenopausalen Frauen und Männern. AWMF-Reg.Nr.: 183/001. Stuttgart: Schattauer Verlag; 2017.

27. Pillai AK, Andring B, Patel A, Trimmer C, Kalva SP. Portal hypertension: a review of portosystemic collateral pathways and endovascular interventions. Clin Radiol. 2015;70(10):1047–59.

28. Trivedi PJ, Lammers WJ, van Buuren HR, Pares A, Floreani A, Janssen HL, et al. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. Gut. 2016;65(2):321–9.

29. Kuiper EM, Hansen BE, Adang RP, van Nieuwkerk CM, Timmer R, Drenth JP, et al. Relatively high risk for hepatocellular carcinoma in patients with primary biliary cirrhosis not responding to ursodeoxycholic acid. Eur J Gastroenterol Hepatol. 2010;22(12):1495–502.

30. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908–43.

31. Carbone M, Mells GF, Pells G, Dawwas MF, Newton JL, Heneghan MA, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. Gastroenterology. 2013;144(3):560–9.e7.

32. ter Borg PC, Schalm SW, Hansen BE, van Buuren HR. Prognosis of ursodeoxycholic acid-treated patients with primary biliary cirrhosis. Results of a 10-yr cohort study involving 297 patients. Am J Gastroenterol. 2006;101(9):2044–50.

33. Trivedi PJ, Bruns T, Cheung A, Li KK, Kittler C, Kumagi T, et al. Optimising risk stratification in primary biliary cirrhosis: AST/platelet ratio index predicts outcome independent of ursodeoxycholic acid response. J Hepatol. 2014;60(6):1249–58.

34. Wesierska-Gadek J, Penner E, Battezzati PM, Selmi C, Zuin M, Hitchman E, et al. Correlation of initial autoantibody profile and clinical outcome in primary biliary cirrhosis. Hepatology. 2006;43(5):1135–44.

35. Dilger K, Hohenester S, Winkler-Budenhofer U, Bastiaansen BA, Schaap FG, Rust C, et al. Effect of ursodeoxycholic acid on bile acid profiles and intestinal detoxification machinery in primary biliary cirrhosis and health. J Hepatol 2012;57(1):133–40.

36. Beuers U. Drug Insight: mechanisms and sites of action of ursodeoxycholic acid in cholestasis. Nat Clin Pract Gastroenterol Hepatol. 2006;3(6):318–28.

37. Beuers U, Trauner M, Jansen P, Poupon R. New paradigms in the treatment of hepatic cholestasis: From UDCA to FXR, PXR and beyond. J Hepatol. 2015;62(1 Suppl):S25–37.

38. de Vries E, Beuers U. Ursodeoxycholic acid in pregnancy? J Hepatol. 2019;71(6):1237–45.

39. Corpechot C, Carrat F, Bonnand AM, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. Hepatology. 2000;32(6):1196–9.

40. Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology. 1997;113(3):884–90.

41. Corpechot C, Carrat F, Bahr A, Chretien Y, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. Gastroenterology. 2005;128(2):297–303.

42. Harms MH, Janssen QP, Adam R, Duvoux C, Mirza D, Hidalgo E, et al. Trends in liver transplantation for primary biliary cholangitis in Europe over the past three decades. Aliment Pharmacol Ther. 2019;49(3):285–95.

43. Harms MH, van Buuren HR, Corpechot C, Thorburn D, Janssen HLA, Lindor KD, et al. Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. J Hepatol. 2019;71(2):357–65.

44. Corpechot C, Chazouilleres O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. J Hepatol. 2011;55(6):1361–7.

45. Kuiper EM, Hansen BE, de Vries RA, den Ouden-Muller JW, van Ditzhuijsen TJ, Haagsma EB, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. Gastroenterology. 2009;136(4):1281–7.

46. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. Gastroenterology. 2006;130(3):715–20.

47. Levy C. Evolving role of obeticholic acid in primary biliary cholangitis. Hepatology. 2018;67(5):1666–8.

48. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med. 2016;375(7):631–43.

49. Bowlus CL. Obeticholic acid for the treatment of primary biliary cholangitis in adult patients: clinical utility and patient selection. Hepat Med. 2016;8:89–95.

50. Honda A, Tanaka A, Kaneko T, Komori A, Abe M, Inao M, et al. Bezafibrate improves GLOBE and UK-PBC scores and long-term outcomes in patients with primary biliary cholangitis. Hepatology. 2019;70(6):2035–46.

51. de Vries E, Bolier R, Goet J, Pares A, Verbeek J, de Vree M, et al. Fibrates for itch (FITCH) in fibrosing cholangiopathies: A double-blind, randomized, placebo-controlled trial. Gastroenterology. 2021;160(3):734–43.e6.

52. Hosonuma K, Sato K, Yamazaki Y, Yanagisawa M, Hashizume H, Horiguchi N, et al. A prospective randomized controlled study of long-term combination therapy using ursodeoxycholic acid and bezafibrate in patients with primary biliary cirrhosis and dyslipidemia. Am J Gastroenterol. 2015;110(3):423–31.

53. Angulo P, Batts KP, Jorgensen RA, LaRusso NA, Lindor KD. Oral budesonide in the treatment of primary sclerosing cholangitis. Am J Gastroenterol. 2000;95(9):2333–7.

54. Hempfling W, Grunhage F, Dilger K, Reichel C, Beuers U, Sauerbruch T. Pharmacokinetics and pharmacodynamic action of budesonide in early- and late-stage primary biliary cirrhosis. Hepatology. 2003;38(1):196–202.

55. Leuschner M, Maier KP, Schlichting J, Strahl S, Herrmann G, Dahm HH, et al. Oral budesonide and ursodeoxycholic acid for treatment of primary biliary cirrhosis: Results of a prospective double-blind trial. Gastroenterology. 1999;117(4):918–25.

56. Rautiainen H, Kärkkäinen P, Karvonen AL, Nurmi H, Pikkarainen P, Nuutinen H, et al. Budesonide combined with UDCA to improve liver histology in primary biliary cirrhosis: A three-year randomized trial. Hepatology. 2005;41(4):747–52.

57. Hirschfield GM, Beuers U, Kupcinskas L, Ott P, Bergquist A, Färkkilä M, et al. A placebo-controlled randomised trial of budesonide for PBC following an insufficient response to UDCA. J Hepatol. 2021;74(2):321–9.

58. Gross CR, Malinchoc M, Kim WR, Evans RW, Wiesner RH, Petz JL, et al. Quality of life before and after liver transplantation for cholestatic liver disease. Hepatology. 1999;29(2):356–64.

59. Jopson L, Jones DE. Fatigue in primary biliary cirrhosis: prevalence, pathogenesis and management. Dig Dis. 2015;33 Suppl 2:109–14.

60. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology. 2019;69(1):394–419.

61. Pfeil A, Lehmann G, Lange U. Update DVO-Leitlinie 2017 „Prophylaxe, Diagnostik und Therapie der Osteoporose bei postmenopausalen Frauen und Männern“: Was ändert sich, was bleibt unverändert für den Rheumatologen? [Update DVO guidelines 2017 on “Prophylaxis, diagnostics and treatment of osteoporosis in postmenopausal women and men”: What is new, what remains for rheumatologists?]. Z Rheumatol. 2018;77(9):759–63.

62. Strassburg CP, Beckebaum S, Geier A, Gotthardt D, Klein R, Melter M, et al. S2k Leitlinie Autoimmune Lebererkrankungen [Practice guideline autoimmune liver diseases - AWMF-Reg. No. 021-27]. Z Gastroenterol. 2017;55(11):1135–226.

63. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant. 2005;5(2):307–13.

64. Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol. 2012;57(3):675–88.

65. Visseren T, Darwish Murad S. Recurrence of primary sclerosing cholangitis, primary biliary cholangitis and auto-immune hepatitis after liver transplantation. Best Pract Res Clin Gastroenterol. 2017;31(2):187–98.

66. Bosch A, Dumortier J, Maucort-Boulch D, Scoazec JY, Wendum D, Conti F, et al. Preventive administration of UDCA after liver transplantation for primary biliary cirrhosis is associated with a lower risk of disease recurrence. J Hepatol. 2015;63(6):1449–58.

67. Montano-Loza AJ, Hansen BE, Corpechot C, Roccarina D, Thorburn D, Trivedi P, et al. Factors associated with recurrence of primary biliary cholangitis after liver transplantation and effects on graft and patient survival. Gastroenterology. 2019;156(1):96–107.e1.

68. Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrumpf E, et al. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol. 2011;54(2):374–85.

69. Manns MP, Woynarowski M, Kreisel W, Lurie Y, Rust C, Zuckerman E, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology. 2010;139(4):1198–206.

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