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Introduction

Primary biliary cholangitis (PBC) is a chronic, inflammatory autoimmune disease. Generally, PBC is a progressive disease that, without treatment, can advance to cirrhosis and liver failure, culminating in liver-related death. This newsletter will provide an overview of PBC, discuss the latest advances in diagnosis and treatment recommendations, and answer some commonly asked questions that PBC patients often pose to advanced practice providers (APPs).

The Pathophysiology and Clinical Manifestations of PBC

Although there is a general idea of what causes PBC, there are still some unanswered questions. Like other better-characterized autoimmune diseases, there appear to be at least two distinct requirements for PBC to develop: genetic susceptibility and a triggering event that initiates the autoimmune attack on bile duct cells. This triggering event could be an environmental factor, virus, allergen, chemical, or medication. What exactly causes or triggers the T-cell attack on small bile duct epithelial cells is unknown.[1]

PBC is a Chronic, Progressive Disease

- Factors possibly associated with onset and perpetuation of bile duct injury in PBC

Genetics

Environment

Immune response

Bile duct damage
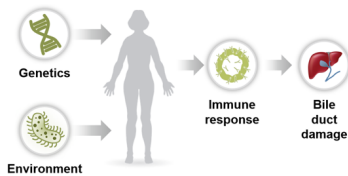
PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis

1. Poupon R et al. *J Hepatol*. 2010;52(5):745-758; 2. Selmi C et al. *Lancet*. 2011;377(9777):1600-1609; 3. Carey EJ et al. *Lancet*. 2015;386(10003):1565-1575.

Although PBC is a progressive disease, it can sometimes be asymptomatic. The natural history of untreated PBC is traditionally described as a gradual progression through four phases: preclinical, asymptomatic, symptomatic, and liver failure (See "Schematic of the Natural History" figure). The proportion of asymptomatic patients who will subsequently develop PBC-related symptoms has been investigated in several studies. All of these studies provide evidence of progressive disease in a substantial proportion of patients, with between 36% and 89% becoming symptomatic during average follow-up periods ranging from 4.5 to 17.8 years and with a median time from diagnosis to the appearance of symptoms between 2 and 4.2 years.[3, 4]

Schematic of the Natural History of PBC[5, 6]
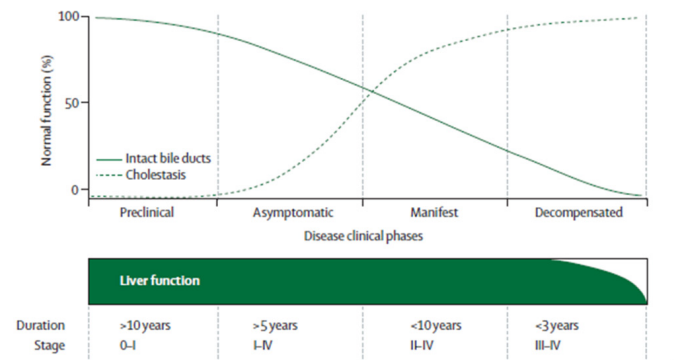
If symptoms are present, the most common are generally bothersome to patients. The impact of PBC on patient functional capacity and well-being may far exceed that typically associated with advanced liver disease. The principal factors underpinning this impaired quality of life (QoL) are multiple and complex, including fatigue, cognitive symptoms, social and emotional dysfunction, sleep disturbance, and depression. Specifically, fatigue and pruritus occur in up to 85% and 70% of PBC patients, respectively.[5, 6]

Without treatment, PBC generally progresses to cirrhosis and eventually liver failure over a period of 10 to 20 years, although its rate of progression can vary substantially among individual patients. Studies of cirrhotic PBC patients indicate that progression to decompensated liver disease (ascites, bleeding, hepatic encephalopathy, and/or hyperbilirubinemia [>6 mg/dL]) occurs at rates of 15 to 25%.[7, 8] Ultimately, PBC accounts for up to 2% of deaths from cirrhosis.[3]

Clinical Features Vary Greatly Between PBC Patients

- **Fatigue**[1,2]
- **Pruritus**[1,2]
- **Concurent autoimmune diseases**[1,2]
- **Reduced bone density**[1,2]
- **Hypercholesterolemia**[1,2]
- **Xanthoma and xanthelasma**[2,3]

PBC can range from asymptomatic and slowly progressive to symptomatic and rapidly evolving.[1]

1. Selmi C et al. *Lancet*. 2011;377(9777):1600-1609; 2. Carey EJ et al. *Lancet*. 2015;386(10003):1565-1575. 3. Lindor KD et al. *Hepatology*. 2009;50(1):291-308.

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Diagnosis, Staging, and Monitoring

Recently, the Chronic Liver Disease Foundation (CLDF) published an updated expert consensus document on PBC, which provided updates on staging and the use of noninvasive testing methods (NITs), and a treatment algorithm to provide evidence-based and practical tools for clinicians who manage PBC, with the ultimate goal of improving long-term outcomes for patients with this chronic liver disease.[9] This information is summarized here.

The diagnosis of PBC can be puzzling for the practicing clinician. Often, the diagnosis is made based on the presence of symptoms, but the disease can remain asymptomatic for years. Nonetheless, taking a good patient history is essential.

Take a Good Patient History

- Symptom burden[1,2]
  - Pruritus
  - Fatigue
  - Sicca syndrome: dry eyes/mouth/vagina
  - Abdominal pain
  - Arthralgias
  - Remember, some patients remain asymptomatic
- Relevant medical history[1]
  - Autoimmunity (personal or family)
  - Smoking
  - Recurrent urinary tract infection
  - Pruritus during pregnancy

1. Hirschfield GM et al. *Best Pract Res Clin Gastroenterol*. 2011;25:701-712; 2. Trivedi PJ et al. *Aliment Pharmacol Ther*. 2012;36:517-533.

The hallmark of PBC is the presence of anti-mitochondrial antibodies (AMAs). These antibodies target different components, mainly enzymes, in the mitochondria. Anti-mitochondrial antibodies in sera can be identified with a specificity of 98% for the disease in 90–95% of patients with PBC. Furthermore, AMAs may be detectable in sera when patients are symptom free and liver tests are normal. Additional laboratory tests may be helpful but not essential. PBC should be suspected in patients with chronic elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin with or without PBC-specific symptoms, such as pruritus or fatigue.

Interpreting AMA, ANA, and Immunoglobulin Testing in PBC

- AMA
  - Positive in >90% of patients with PBC, depending on the assay[1]
  - In the correct context, AMA reactivity with an elevated ALP and no significant elevation in AST is associated with a >95% PPV of histologic PBC[2]
- Antinuclear antibodies (ANA)
  - Two ANA immunofluorescent patterns are specific to PBC: multiple nuclear dots and perinuclear/rim-like membranous[3]
  - Automated ANA assays will likely not detect these reactivities
  - Laboratories should perform immunofluorescence if enzyme-linked immunosorbent assay (ELISA)-based assays for gp210 and sp100 are not available
- Immunoglobulins
  - Elevated IgM is a sensitive but non-specific characteristic of PBC[1]
  - Elevated IgG is primarily observed in autoimmune hepatitis (AIH)[1]

Abbreviations: AIH, autoimmune hepatitis: ALP, alkaline phosphatase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IgM, immunoglobulin M; PBC, primary biliary cholangitis; PPV, positive predictive value; PSC, primary sclerosing cholangitis.
1. Trivedi PJ et al. *Aliment Pharmacol Ther*. 2012;36:517-533; 2. Zein CO et al. *Clin Gastroenterol Hepatol*. 2003;1:89-95; Zeman MV, Hirschfield GM. *Can J Gastroenterol*. 2010;24:225-231.

The CLDF consensus document recommends the following scenarios are supportive of the diagnosis of PBC.

Criteria for the Diagnosis of PBC[9]

- **Scenario 1:** Chronic elevation of ALP with a positive AMA (immunofluorescent assay titer > 1:40 or enzyme immuno assay (EIA) > 25 units) in the absence of other liver and systematic diseases
- **Scenario 2:** Chronic elevation of ALP with a negative AMA but positive PBC-specific ANA (sp-100, gp-210) tests or a reticular ANA pattern
- **Scenario 3:** Chronic elevation of ALP with negative AMA and ANA tests but a liver biopsy showing nonsuppurative cholangitis and destruction of the interlobular bile ducts

Once the diagnosis is confirmed, PBC should be **staged.**[9]

- **Baseline assessment** of confirmed PBC should include:
  - Chronic elevations in liver enzymes and/or bilirubin
  - The presence of PBC-specific symptoms
  - A physical exam that indicates hepatomegaly, splenomegaly, and/or extrahepatic signs of advanced liver disease
- **Imaging-based NITs** should be utilized in early-stage disease to identify PBC patients with advanced fibrosis and an increased risk of hepatic decompensation in the future
  - TE > 10 kPa and an MRE >4.3 kPa are considered acceptable to identify advanced fibrosis

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Monitoring for the progression of fibrosis is important even in early-stage PBC.[10] Bilirubin levels >0.6 × upper limit of normal (ULN) and any elevation of ALP above the ULN are important indicators of prognosis.[9]
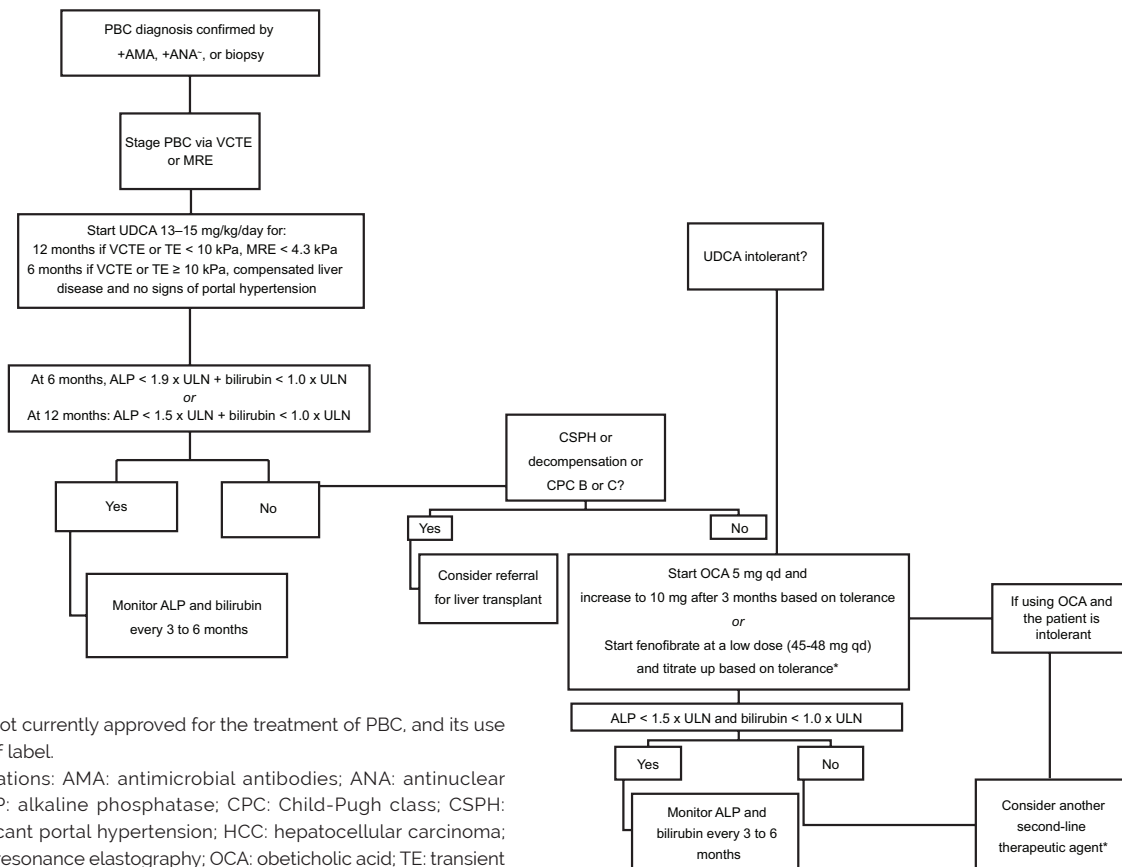
Treatment

Treatment options for PBC include ursodeoxycholic acid (UDCA) and obeticholic acid (OCA). UDCA and OCA do not treat the symptoms of PBC, such as fatigue and pruritus, but can slow disease progression and reduce the need for liver transplantation. A large international meta-analysis that included 4,845 PBC patients demonstrated that UDCA significantly improved transplant-free survival at 5, 10, and 15 years compared to nontreated individuals (90%, 78%, and 66% vs. 79%, 59%, and 32%, respectively).[11] Therefore, once PBC is diagnosed and staged per the recommendations above, treatment is recommended. UDCA is the first-line treatment

for PBC, but a large percentage of patients will not respond. PBC patients with an inadequate response to or intolerance of UDCA should be considered for second-line therapy with OCA.

The CLDF expert consensus document on PBC proposes a treatment algorithm for the first- and second-line treatment of PBC. This algorithm includes new guidance-informed suggestions for staging PBC. The second portion of the algorithm, which will be discussed here, focuses on earlier assessment of lower thresholds to gauge UDCA response after the initiation of therapy, the potential for earlier initiation of second-line therapy with OCA at lower ALP or bilirubin levels, OCA avoidance in patients with cirrhosis complicated by portal hypertension or liver decompensation, the safety and durability of response of long-term OCA therapy and the off-label use of fibrates.[9]

Updated Algorithm for the Treatment of PBC[9]

~sp100 gp210

*Fenofibrate is not currently approved for the treatment of PBC, and its use is considered off label.

Figure abbreviations: AMA: antimicrobial antibodies; ANA: antinuclear antibodies; ALP: alkaline phosphatase; CPC: Child-Pugh class; CSPH: clinically significant portal hypertension; HCC: hepatocellular carcinoma; MRE: magnetic resonance elastography; OCA: obeticholic acid; TE: transient elastography; UDCA: ursodeoxycholic acid; VCTE: vibration-controlled transient elastography

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Recommendations for First-Line Treatment with UDCA[9]

- **Patients with a lower stage of fibrosis** (vibration controlled transient elastography (VCTE) or transient elastography (TE) < 10 kPa, magnetic resonance elastography (MRE) < 4.3 kPa) may continue UDCA monotherapy for 12 months prior to determining response (ALP < 1.5 x ULN and bilirubin < 1 x ULN) and the need for second-line therapy.

- For **patients with a more advanced fibrosis stage** (VCTE or TE > 10 kPa), compensated liver disease, and no signs of portal hypertension, response (ALP < 1.5 x UNL and bilirubin < 1 x ULN) and the need for second-line treatment should be assessed at 6 months. Based on recent data, clinicians may consider more stringent criteria (ALP < ULN and bilirubin < 0.6 mg/dL) to assess response in patients with more advanced disease.

Second-Line Treatment with OCA[9]

- PBC patients with an **inadequate response to or intolerance of UDCA** should be considered for second-line therapy with OCA.

- **OCA therapy should not be used** in patients with thrombocytopenia (i.e., with a platelet count < 120 x 109/L, ascites, esophageal varices, hepatic encephalopathy, variceal bleeding) or evidence of hepatic synthetic dysfunction or reduced liver function (i.e., prolonged prothrombin time, elevated serum bilirubin, reduced serum albumin) and should be stopped if any of these develop while on treatment.

- Providers should continue to consider second-line therapies in patients with cirrhosis if their liver function is normal and there are no signs of portal hypertension.

Second-Line Treatment with Off-Label Fenofibrate[9]

- **Fenofibrate** could be considered as an **off-label** alternative second-line therapy in the appropriate patient at a low dose of 45–48 mg per day and titrated up as tolerated

- Bezafibrate is not available in the US

If the patient has not responded to the first second-line option (OCA or fibrate) after three to six months of therapy or the patient is unable to tolerate the selected second-line treatment, then the other second-line option should be considered.[9]

APP Answers to Questions Frequently Asked by PBC Patients

APPs play a key role in developing open and trusting relationships with patients and, as such, often encounter questions. The following questions have been identified as those most frequently asked and are answered here by Andrea Gossard, APRN, CNP.

Will my children get PBC?

Children of individuals with PBC are at an increased risk of developing PBC; however, the disease remains rare. As such, first-degree family members with the condition are not common. It is reasonable to assess for PBC in offspring with blood work (liver enzymes, anti-mitochondrial antibody) at approximately 35 to 40 years-of-age because we have effective therapeutic options.

What are the symptoms of more advanced disease?

The symptoms of more advanced disease may include fluid retention in the ankles and abdomen, gastrointestinal bleeding, and perhaps confusion. Fatigue and itching can occur at any time during the course of the disease.

Is there an effective treatment for PBC?

Treatment options include UDCA and OCA. Although a single treatment option may be beneficial, for some patients, additional treatment with a second agent is needed to improve liver tests to a satisfactory level. Fenofibrate is sometimes added as well, although this is not an Food and Drug Administration (FDA)-approved therapy for PBC.

How do I manage the itching?

Itching can be a very challenging symptom for many patients. Typically, first-line therapy consists of cholestyramine taken two or three times daily. If this is not helpful, the use of rifampin, naltrexone, or sertraline may be considered.

Will I require a liver transplant?

Although there are effective treatments for PBC, some patients will progress to advanced-stage disease and may require liver transplantation. Regular visits with your provider are an important part of monitoring for disease progression.

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