Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases

Keith D. Lindor[1], Christopher L. Bowlus[2], James Boyer[3], Cynthia Levy[4], Marlyn Mayo[5]

From the [1]Arizona State University, Division of Gastroenterology and Hepatology, Mayo Clinic, Phoenix, AZ; [2]University of California Davis, Sacramento, CA; [3]Yale School of Medicine, New Haven, CT; [4]University of Miami, Miami, FL; [5]University of Texas Southwestern Medical Center, Dallas, TX

This guidance has been approved by the AASLD and represents the position of the association.

PURPOSE AND SCOPE OF THE GUIDANCE (Preamble)

This American Association for the Study of Liver Diseases (AASLD) 2018 Practice Guidance on Primary Biliary Cholangitis (PBC) is an update of the PBC guidelines published in 2009. The 2018 updated guidance on PBC includes updates on etiology and diagnosis, role of imaging, clinical manifestations, and treatment of PBC since 2009. The AASLD 2018 PBC Guidance provides a data-supported approach to screening, diagnosis, and clinical management of patients with PBC. It differs from more recent AASLD practice guidelines, which are supported by systematic reviews and a multidisciplinary panel of experts that rates the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development and Evaluation system. In contrast, this guidance was developed by consensus of an expert panel and provides guidance statements based on formal review and analysis of published literature on the topics. The quality (level) of the evidence and the strength of each guidance statement are not rated.

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Intended for use by health care providers, this guidance identifies preferred approaches to the diagnostic and therapeutic aspects of care for patients with PBC. As with clinical practice guidelines, it provides general guidance to optimize the care of the majority of patients and should not replace clinical judgment for a unique patient.

The major changes from the last guideline to this guidance include information about obeticholic acid (OCA) and the adaptation of the guidance format.

Etiology of Primary Biliary Cholangitis (PBC)

PBC is considered an autoimmune disease because of its hallmark serologic signature, antimitochondrial antibody (AMA), and specific bile duct pathology.(1-4) The etiology of PBC is thought to be due to a combination of genetic risk factors and environmental triggers.(5-7)

AMA is a highly disease-specific autoantibody(8) that targets the lipoic acid present on the 2-oxo-acid dehydrogenase complexes located on the inner mitochondrial membrane.(9) In addition to a loss in humoral tolerance, there is an increase of autoreactive cluster of differentiation (CD)$4^{+}$$CD8^{+}$ Pyruvate Dehydrogenase Complex (PDC-E2)-specific T cells in the liver.(10, 11)

In addition to the high concordance among monozygotic twins compared with dizygotic twins with PBC(5), the strong association with human leukocyte antigen alleles, which vary by ethnicity, supports a genetic cause of inherited risk.(12-20) Despite progress, only an estimated 15% of the variability of the disease has been accounted for by genetic studies.(21) Environmental risks have been suggested by several large case-control cohort studies that have found associations with urinary tract infections, reproductive hormone replacement, nail polish, and past cigarette smoking.(22-24) Studies of geographic clustering have suggested environmental exposure and socioeconomic factors as well.(25-28) The interaction between genetic and environmental effects has only begun to be assessed in PBC, with several possible gene-modifying mechanisms being supported.(15, 29)

Specific environmental agents that may lead to the loss of tolerance to (pyruvate dehydrogenase complex PDC-E2) are xenobiotics that may either mimic or modify lipoic acid, such as 2-octynoic acid,

which is common in cosmetics, and 6,8-bis (acetylthio) octanoic acid, a metabolite of acetaminophen. AMA-positive serum from PBC patients strongly cross-reacts with these xenobiotics.(30, 31) Further experimental support for the role of xenobiotics in PBC pathogenesis comes from the ability of xenobiotics to induce a PBC-like pathology, including AMA, in animal models.(32, 33)

The enigma of PBC pathogenesis has been the specific targeting of the biliary epithelial cells in the setting of a ubiquitous autoantigen. The majority of AMA produced by plasmablasts is immunoglobulin A (IgA), which may undergo transcytosis through the biliary epithelium and disrupt mitochondrial function. Alternatively, the specificity of the immune attack may be due to the incomplete proteolysis of pyruvate dehydrogenase complex PDC-E2 and other mitochondrial enzymes during apoptosis of biliary epithelial cells, a unique feature of this cell type.(17, 34) Taken together, the evidence strongly supports the antimitochondrial response as a direct effector of the liver pathology, although other nonautoimmune mechanisms may play a role as well.

Natural History

PBC is a chronic cholestatic disease with a progressive course that may extend over many decades. The rate of progression varies greatly among individual patients. Over the past decades, there have been many changes in the diagnosis and management of PBC. More patients are being recognized with earlier-stage disease, and many of these patients respond well to medical therapy. In both Europe and North America, the number of liver transplants for PBC is falling.(35, 36) However, the overall prevalence of the disease is increasing.(37)

Patterns of Clinical Disease and Natural History in the Pre-Ursodeoxycholic Acid (UDCA) Era

The overall prevalence of AMA positivity in various populations is not well known. It is estimated that 0.5% of the general population in Italy are AMA positive.(38) In a study from Japan, 11 of 1714 people (0.64%) were AMA positive.(39)

AMA may be detectable in serum when patients are symptom free and liver tests are normal.(40) Long-term follow-up of 229 AMA-positive individuals for up to 7 years found that the 5-year incidence of PBC was 16%. In a smaller study, the median time from the first positive AMA test to persistently abnormal liver tests was 6 years, with a range between 1 and 19 years; none of these patients developed cirrhosis during the follow-up.(41) The overall prevalence of clinical disease in various populations has been difficult to estimate due to the rarity of the disease. Estimates vary between 19 and 402 cases of PBC per million.(3) A recent paper showed an overall prevalence of 290 per million, with a prevalence of 430 per million in women and 110 per million in men as opposed to other studies suggesting a 9:1 ratio of women to men.(42) PBC may affect all races and ethnicities, with most data collected from the Caucasian population.

The prevalence of AMA positivity in first-degree relatives (FDRs) of PBC patients is increased compared with controls (13.1% and 1%, respectively). Greater prevalence of AMA was found in female FDRs of PBC probands (sisters [20.7%], mothers [15.1%], and daughters [9.8%]) than in male FDRs (brothers [7.8%], fathers [3.7%], and sons [0 %]).(43)

Asymptomatic versus Symptomatic PBC: The proportion of asymptomatic patients (which has been variably defined) who will subsequently develop PBC-related symptoms has been investigated in several series from the United Kingdom, North America, and Sweden.(44-49) 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, with the median time from diagnosis to the appearance of symptoms between 2 and 4.2 years.(45, 48-50)

In the absence of UDCA therapy, patients have a significantly shortened survival compared with a healthy population regardless of symptoms.(48, 49) The 10-year survival of asymptomatic patients in three series ranged from 50% to 70%, whereas the median duration of survival for symptomatic patients ranged from 5 to 8 years from the onset of symptoms.(45, 48-50)

In an early study of 279 patients from the United States,(50) followed for 24 years, the median survival of symptomatic patients was 7.5 years, much shorter than the median survival of 16 years for asymptomatic patients. This marked difference in survival was not found in the study from northeast England, a finding possibly explained by an excess of deaths unrelated to liver disease in older asymptomatic patients or possibly because referrals to subspecialists were made only when patients became symptomatic.(51)

Disease Progression

Histologic stages have been found to predict survival.(50, 52) The rate of histologic progression has been assessed in three large groups of patients in the absence of a therapeutically effective agent.(52-54) The median time to develop extensive fibrosis (≥F3) was 2 years. After 4 years, the probability of remaining in the early stage of PBC was 29% (confidence interval [CI], 15%-52%), while cirrhosis was diagnosed in 50% of patients who initially had only interface hepatitis without fibrosis. Only a minority (20%) of patients who were precirrhotic showed histologic stability. On average, the histologic stage progressed by 1 stage every 1.5 years.(54)

The development of decompensated liver disease (ascites, bleeding, hepatic encephalopathy, or hyperbilirubinemia [>6 mg/dL]) during a follow-up of 5 years has been estimated to be 15% in a large community-based study of 770 patients in northeast England(48) and 25% of the 236 patients enrolled in a European clinical trial of azathioprine.(52) About half of the patients in both studies were cirrhotic at entry.

The rate of development of esophageal varices and its impact on survival were evaluated in a prospective study of 256 patients (28% of whom had cirrhosis) observed for a median time of 5.6 years.(55) A total of 31% of patients developed esophageal varices. After the development of varices, the 3-year survival was 59%, whereas after a first bleeding episode, it was 46%.

Natural History in the UDCA Era (Circa 1990)

UDCA was the first and only drug approved for the treatment of patients with PBC in the United States until 2016, when (obeticholic acid) was approved by the Food and Drug Administration. Several randomized trials, combined analyses, and long-term observational studies have shown that UDCA not only improves biochemical indices but also delays histologic progression and improves survival without transplantation.(53, 56-67) Accordingly, UDCA is the initial drug of choice for PBC therapy.

In an early study, the rate of histologic progression to cirrhosis was significantly lower in the UDCA group than in the control group (13% versus 49%).(56) In a trial involving 192 patients, UDCA therapy significantly delayed histologic stage progression after a median follow-up of 3.4 years.(60) In a French study of UDCA, the risk of progression per year from stages I-II to stages III-IV was 7% ± 2% with UDCA and 34% ± 9% with placebo.(53) Predictive factors for cirrhosis developing included serum bilirubin greater than 1 mg/dL and moderate to severe lymphocytic piecemeal necrosis on the liver biopsy.(68)

The effect of UDCA therapy on the development of esophageal varices was addressed in a prospective study of 180 patients who received UDCA versus placebo and were observed for up to 4 years;(69) a total of 139 patients had no varices, and 41 had varices at baseline. After 4 years, the risk of developing varices was 16% for the UDCA-treated patients and 58% for those receiving the placebo. However, UDCA did not reduce the rate of bleeding, which was low in both groups.

Survival

Prognostic Models: Early natural history models evolved in the pre-UDCA era. The first PBC-specific model was proposed by Roll et al. in 1983 (the Yale model) based on a retrospective study of 280 patients observed over a period of 19 years. Age, serum bilirubin, hepatomegaly, and advanced fibrosis or cirrhosis were independent risk factors for a poorer prognosis. However, this model required liver biopsy, limiting its usefulness.(50) In 1985, Christensen et al. presented a European model also requiring liver

biopsy.(70) Once the Mayo model was introduced by Dickson, prognosis could be estimated without the need for biopsy.(71)

Following the introduction of UDCA therapy, a series of models—which are summarized in recent reviews(72, 73) and most of which were based on alkaline phosphatase (ALP) responses to treatment—ensued. The two most recent prognostic models, the GLOBE score and the UK-PBC score, are based on larger sample sizes obtained from and derived from multiple centers. The GLOBE score was developed from a retrospective cohort of 2,488 UDCA-treated patients and validated by a second cohort of 1,631 European and North American patients.(74) The score included the following five variables: serum bilirubin, albumin, ALP, platelet count after 1 year of treatment (http://www.globalpbc.com/globe), and age at start of therapy. Patients with a score >0.30 had a shorter transplantation-free survival than an age- and sex-matched healthy population. The UK-PBC score involved a cohort of 3165 patients and found that serum ALP, amino transferases, and bilirubin after 12 months of therapy—as well as albumin and platelets at baseline—predicted the risk of a liver transplant or liver-related death occurring within 5, 10, or 15 years.(75) Both the GLOBE and UK-PBC scores are superior to prior models although validation in other ethnic groups and populations is needed.

***Other predictions of prognosis*:** The bilirubin level is the best predictor of survival and is the most important component in all mathematical models of prognosis in PBC.(71, 76) Serum ALP less than twice the upper limit of normal with treatment is a reliable predictor of treatment response.(77-79) Transient elastography is emerging as a technique to assess prognosis and treatment response as well.(80)

Diagnosis of PBC

The diagnosis of PBC should be suspected in the setting of chronic cholestasis after exclusion of other causes of liver disease, particularly in a middle-aged female with an unexplained elevation of serum ALP. The diagnosis is largely confirmed with tests for AMA. A liver biopsy can be used to further substantiate the diagnosis but is rarely needed.(81)

Liver Biochemical Tests

Most patients with PBC have abnormal liver tests including elevations of ALP, mild elevations of aminotransferase (alanine aminotransferase or aspartate aminotransferase) activity, and increased levels of immunoglobulins (mainly IgM). Some patients with PBC may have high alanine aminotransferase or aspartate aminotransferase activities associated with hyper-γ-globulinemia (elevated IgG). The magnitude of biochemical test elevations are loosely related to the severity of the disease.(70, 82, 83) In patients without cirrhosis, the degree of elevation in ALP is strongly related to the severity of ductopenia and inflammation; the increase in aminotransferase activity and IgG levels mainly reflects the degree of periportal and lobular necrosis and inflammation; and hyperbilirubinemia reflects the severity of ductopenia and biliary piecemeal necrosis. A rise in serum bilirubin, γ-globulins, and hyaluronic acid together with a fall in serum albumin and platelet count are the early indicators of the development of cirrhosis and portal hypertension.(82, 83) As in other cholestatic diseases, serum cholesterol levels are often elevated.(84) Individual serum bile acid levels can be elevated but are not routinely determined.

Autoantibodies

Among PBC patients, AMA is found in 95%.(85) Antinuclear antibody and anti-smooth muscle antibody are found in nearly half.(85) In approximately 5% to 10% of the patients, AMA is absent or present only in low titer (≤1/80), when immunofluorescent techniques are used. The presence or absence of AMA, rather than the magnitude of antibody level, is most important in diagnosis. In some patients, antinuclear antibodies, particularly anti-glycoprotein 210 (anti-gp210) and/or anti-sp100, are present and may correlate with prognosis;(86) in some other AMA-negative patients, antibodies against the major M2 components (pyruvate dehydrogenase complex,(PDC-E2), 2-oxo-glutaric acid dehydrogenase complex) are present using enzyme-linked immunosorbent assay or Western blotting techniques. There are five common strategies for detecting AMA in clinical practice, including indirect immunofluorescence,

immunoblotting, enzyme immunoassay, Luminex beads assay, and enzyme inhibition assay. The indirect immunofluorescence method has the lowest sensitivity, with over 15% of AMA-negative sera by indirect immunofluorescence showing reactivity to MIT3, a combination of 3 mitochondrial antigens.(87) In addition, nearly all AMA-negative PBC patients have PBC-specific antinuclear antibodies, including sp100 and gp210, which are present in over 30% of PBC patients negative for AMA by indirect immunofluorescence. More recently, anti-kelch-like 12 and anti-hexokinase 1 have been found in 35% and 22% of AMA-negative PBC patients, respectively, but these are not yet widely available.(88)

There are weak correlations between the values obtained with these various methods; however, the methods agree well on whether AMA is positive or negative. A previously mentioned study of 229 individuals without an established diagnosis of PBC followed subjects for up to 7 years and found a 5-year incidence rate of PBC of 16%. The overall conclusion from this study was that only 1 in 6 patients with a positive AMA and normal ALP will develop PBC after 5 years. If liver tests are initially normal, following these patients at 2- to 3-year intervals until age 65 seems reasonable, but there are no data regarding this.(40)

Histology

Liver biopsy is no longer required for diagnosis in most patients. Histologically, PBC is characterized by chronic, nonsuppurative cholangitis that mainly affects interlobular and septal bile ducts. When focal lesions show intense inflammatory changes and necrosis around bile ducts, the term "florid duct lesion" is often used. The inflammatory infiltrate is in close contact with the basal membrane of cholangiocytes undergoing necrosis and consists of plasma cells, macrophages, and polymorphonuclear cells (especially eosinophils). In some cases, epithelioid granulomas are present, more often in the early stage of disease.(85) There are few (if any) arterial lesions. In contrast, portal venules are often compressed and occluded by the inflammatory reaction. Terminal hepatic venules are often retained in their central location with progression of fibrosis and sometimes even in cirrhosis. Bile duct paucity or ductopenia is usually defined as when fewer than 50% of portal tracts contain bile ducts.

The size of the liver biopsy specimen is important. The probability of observing cholangitis and bile duct destruction increases with the number of portal tracts because of the typical patchy distribution of the lesions. At least 10 to 15 portal tracts should be present, and multiple sections should be reviewed to adequately appreciate or rule out cholangitis and ductopenia. These findings would include periportal and/or periseptal copper deposition, periportal and/or periseptal feathery degeneration with or without Mallory-Denk bodies, and cholestatic rosettes. Actual bile stasis is not appreciated until decompensated liver disease has occurred.

Histologic lesions are classically divided into four stages (Fig 1). Stage I is characterized by portal inflammation with or without florid bile duct lesions. In this stage, inflammation remains confined to the portal triads. Disease progression is characterized by the gradual increase of periportal lesions extending into the hepatic parenchyma, referred to as interface hepatitis (stage II). Periportal regions become focally irregular, and the lesion is characterized by cellular necrosis or apoptosis, separation of hepatocytes by inflammatory cells, and macrophages. There are two main types of interface hepatitis. The first is lymphocytic piecemeal necrosis, the association of hepatocellular necrosis or apoptosis with lymphohistiocytic cells. This is similar to the lesion found in autoimmune hepatitis (AIH). Second is biliary piecemeal necrosis, which is marked by a striking ductular reaction—sometimes referred to as ductular proliferation—and is accompanied by edema, neutrophil infiltration, periductular fibrosis, and necrotic hepatocytes, the latter associated with cholestasis. Studies of French PBC patients have shown that severity of interface hepatitis is highly predictive of development of extensive fibrosis.(67, 89) Stage III is characterized by a distortion of the hepatic architecture with numerous fibrous septa. Cirrhosis with the existence of regenerative nodules defines stage IV. Nakanuma et al. recently introduced a system that assesses bile duct loss, fibrosis, and cholestasis to develop a 4-stage model.(90) Nodular regenerative hyperplasia is a known complication of PBC and should be differentiated from cirrhosis; it may also contribute to portal hypertension in noncirrhotic patients.(91)

With the high disease specificity of a positive AMA test, the role of liver biopsy to diagnose PBC is questionable when ALP activity is ≥1.5 times normal and aspartate aminotransferase values are <5

times normal.(81) Liver biopsy may be occasionally recommended in AMA-negative patients and to exclude other concomitant diseases such as AIH and nonalcoholic steatohepatitis, as discussed later in the Special Cases section.

Role of Imaging

Expert noninvasive imaging of the liver and biliary tree is mandatory in all patients with biochemical evidence of cholestasis. If the diagnosis is uncertain, then cholangiography may be necessary, preferentially with noninvasive magnetic resonance imaging or endoscopically, to exclude primary sclerosing cholangitis or other biliary tract diseases. Transient elastography(80) is a noninvasive tool that has shown a high degree of accuracy in diagnosing advanced fibrosis in patients with PBC.(92) Over a 5-year period, on-treatment liver stiffness appears stable in most noncirrhotic PBC patients, whereas it significantly increases in patients with cirrhosis. Progression of liver stiffness in PBC is predictive of poor outcome(80, 93), and successful medical therapies have been associated with improvement in liver stiffness.(94) The role of serial measurements as an endpoint is being evaluated as is the value of magnetic resonance elastography.

Diagnostic Approach

The diagnosis of PBC is generally based on the presence of at least two of the following criteria:

a) Biochemical evidence of cholestasis with elevation of ALP activity;
b) Presence of AMA;
c) Histopathologic evidence of nonsuppurative cholangitis and destruction of small or medium-sized bile ducts if a biopsy is performed.

The differential diagnosis includes a cholestatic drug reaction, biliary obstruction, sarcoidosis, AIH, and primary sclerosing cholangitis.

Guidance Statements: Diagnosis

1. ***The diagnosis of PBC can be established when two of the following three criteria are met:***
    - ***Biochemical evidence of cholestasis based on ALP elevation.***
    - ***Presence of AMA, or other PBC-specific autoantibodies, including sp100 or gp210, if AMA is negative.***
    - ***Histologic evidence of non-suppurative destructive cholangitis and destruction of interlobular bile ducts.***

Clinical Manifestations of PBC

Symptoms

The major symptoms of PBC are fatigue and itching. There is not a good correlation between these symptoms and stage of disease, although patients with more advanced disease generally have more symptoms.

Fatigue: Fatigue is the most common symptom in PBC; it has been found in 50% to 78% of patients and has a significant negative impact on quality of life.(95, 96) Severe fatigue may be associated with decreased overall survival.(97) The etiology of the fatigue in PBC is unknown, but in some it may be associated with orthostatic hypotension, daytime sleepiness, cognitive defects, or impaired recovery of muscle from acidosis.(98) Fatigue from PBC is relatively constant or slowly progressive over time.(99)

Pruritus: Early studies reported that pruritus (itching) occurs in 20% to 70% of patients with PBC. It is now less common because of the growing number of patients with PBC who are diagnosed in the early, asymptomatic phase.(100-102) Patients report itching as local or diffuse and often exacerbated by contact with clothing, heat, or pregnancy. It has a circadian rhythm and is worse in the evenings. The clinical course of itching in PBC often fluctuates, with periods of relative exacerbation and improvement. Paradoxically, pruritus has been reported to wane in very advanced liver disease.(101)

The origin of pruritus in PBC is still unknown.(103, 104) However, several important mediators in the pathophysiology of cholestatic pruritus, which provide opportunities for therapeutic intervention, have been identified, including lysophosphatidic acid,(105) endogenous opioids, and bile acids. Lysophosphatidic acid is a lipid-signaling molecule that is elevated in many (but not all) cholestatic patients with itch. Lysophosphatidic acid injected into mice causes itch in a dose-dependent manner, compared with vehicle. Activity of autotaxin, the enzyme that produces lysophosphatidic acid, correlates with itch intensity in PBC patients with pruritus. (105) Endogenous opioids are also increased in many patients with PBC pruritus (and some without pruritus).(106) Opioids such as morphine and heroin commonly cause the side effect of pruritus, and cholestatic itch has been ameliorated by opiate antagonists.(107) Some component of bile that accumulates in serum has long been suspected to contribute to pruritus. This is supported by therapeutic efficacy of biliary drainage or plasma filtering procedures. The lack of correlation of serum bile acid levels with cholestatic itch suggests some other factor as the pruritogen.

Abdominal Pain: Right upper quadrant pain is found in approximately 17% of patients with PBC. It is typically nonspecific in character, not progressive in nature, not well correlated with disease stage or hepatomegaly, and often disappears spontaneously. Its etiology is unknown.(108)

Other Autoimmune Conditions

There are three major autoimmune diseases that have been shown in a cohort study to occur significantly more often in PBC than the age-matched and sex-matched population: Sjögren's; Calcinosis, Raynaud's, Esophageal dysfunction, Sclerodactyly, and Telangectasias (CREST); scleroderma (systemic sclerosis); and Raynaud's disease.(109) Several reports suggest that patients with PBC have a greater risk of autoimmune thyroid disease; however, the latter is common in the general population. It is questionable whether celiac disease is or is not more common in PBC.(110)

Physical Examination

The physical examination in early-stage disease is usually normal, although hepatomegaly, excoriations, xanthelasma, and xanthoma may be seen. Jaundice is a late finding in patients with advanced liver disease. Increased melanin deposits causing hyperpigmentation are less common but may occur in later stages. Spider angiomata, edema, ascites, or splenomegaly may be found in the setting of portal hypertension. If limited scleroderma coexists, the examination may show sclerodoactyly or telangiectasias.

Special Cases

AMA-Negative PBC

The term AMA-negative PBC refers to those who lack serum AMA but whose clinical presentation, liver histology, and natural history are nearly identical to patients with typical AMA-positive PBC. The imprecise terms “autoimmune cholangiopathy” or “autoimmune cholangitis” should not be used interchangeably with AMA-negative PBC. Given the specificity of antibodies to sp100, gp210, anti-kelch-like 12, and anti-hexokinase 1 (when available), the diagnosis of AMA-negative PBC requires a liver biopsy only in the absence of these PBC-specific autoantibodies. Only true seronegative PBC requires a liver biopsy that should demonstrate the typical features of bile duct destruction seen in PBC—ideally a florid duct lesion and/or granulomas—in order to make a diagnosis of PBC.

Although AMA-negative PBC patients are nearly identical to AMA-positive PBC patients, minor differences have been noted, including a higher prevalence of antinuclear and anti-smooth muscle antibodies and lower serum IgM levels.(111-113) Compared with AMA-positive PBC patients, AMA-negative PBC patients have more nonhepatic autoimmune conditions(114, 115) and worse health-related quality of life in social and emotional domains.(116) Histologically, AMA-negative PBC has been shown to have greater bile duct damage and loss compared with AMA-positive PBC.(117, 118) However, treatment response to UDCA appears similar in AMA-negative and AMA-positive PBC patients, and whether there are differences in clinical outcomes has not been resolved.(113, 115)

Overlap of AIH with PBC

There is no formal definition of the overlap syndrome between PBC and AIH. PBC/AIH overlap usually refers to simultaneous AIH in patients who have a diagnosis of AMA-positive PBC and should not be used to refer to patients with AIH who have coincidental AMA. Conversely, "overlap" should not refer to PBC patients with serum antinuclear antibody and a mild degree of interface hepatitis because these are common features of PBC. Studies reported to date are of insufficient size to indicate with any degree of certainty how a diagnosis of PBC overlapping with AIH is different from uncomplicated PBC. Limited observational data suggest that biochemical response to therapy with UDCA for PBC/AIH overlap is no different from that observed in patients with PBC alone. A PBC/AIH overlap syndrome may also refer to patients with PBC followed sequentially by AIH or, less commonly, AIH followed by PBC.(119-121).

Diagnosis of PBC/AIH Overlap

There are two scoring systems that have been used to evaluate patients with PBC for simultaneous evidence of overlapping AIH. Both of these scoring systems are arbitrary and were developed as diagnostic criteria for AIH patients. The first is the International Autoimmune Hepatitis Group score, the original draft of which was validated in two independent patient populations diagnosed with AIH.

This score was subsequently revised(122) and, when applied to PBC cohorts, revealed that <1% of PBC patients met definite AIH diagnostic criteria, whereas 8% to 19% met probable AIH criteria.(123, 124) However, the International Autoimmune Hepatitis Group score was designed for the diagnosis of AIH with the exclusion of other liver diseases, including PBC, and therefore positive points are given for the absence of factors unrelated to a diagnosis of PBC—e.g., viral hepatitis and alcohol abuse—and negative scores are given for AMA and/or biochemical/histologic features of biliary disease. A simplified AIH scoring system has more recently been developed and, when applied to PBC patients, it identified

fewer patients meeting probable AIH criteria compared with the older scoring system (4% versus 12%).(125, 126) The most commonly applied system, the so-called Paris criteria, requires the presence of two of the following three diagnostic criteria:

A) Alanine aminotransferase activity >5 times the upper limit of normal;

B) IgG ≥2 times the upper limit of normal and/or positive anti-smooth muscle antibody;

C) Liver biopsy with moderate or severe interface hepatitis.(127)

These criteria have been met in 1% to 14.2% of PBC patients, with higher rates found in Hispanic PBC patients.(128-133) The wide variability among studies may be due to a variety of genetic and environmental factors as well as the nonuniform collection of biochemical, serological, immunological, and histological data.

Clinical Course of "Overlap" Syndrome

Small studies have reported outcomes in patients with simultaneous PBC/AIH overlap. Twenty-six patients with PBC/AIH overlap who were followed for a mean of 5 to 6 years were compared to 135 patients with classical PBC.(134) This study indicated a worse outcome in terms of complications of portal hypertension, death, or need for liver transplant in patients with PBC and a "probable" or "definite" International Autoimmune Hepatitis Group score. However, an estimated 50% of patients in either group had received treatment with UDCA, and some in both groups had received a variety of other therapies. UDCA with or without immunosuppressive therapy has been used, but no clear consensus in optimal therapy for these patients exists.(129, 130, 134, 135) There are no randomized, controlled data that indicate how best to treat patients thought to have simultaneous PBC/AIH overlap.

Consecutive PBC/AIH

Patients with AMA-positive PBC who respond biochemically to UDCA therapy may subsequently present with clinical features of AIH. These patients may no longer have AMA

seropositivity, and liver histology becomes more typical of AIH that responds to immunosuppressive therapy. Two studies found that approximately 2.5% of PBC patients develop a subsequent acute AIH,(119, 121), while the largest study found that only eight of 1476 patients with PBC later developed AIH.(120)

AMA-Positive AIH

There are few data on the prevalence of detectable serum AMA in patients who otherwise have typical features of AIH.(136) These data may be extracted from histologic review of patients with AIH, in whom small bile duct pathology was superimposed on a background of AIH.(137) In this case series, none of the five patients who tested positive for AMA (among 166 patients) had bile duct changes on examination of liver histology. There are case reports of patients with overt AIH who nevertheless tested AMA positive,(138, 139) but on long-term follow-up, these patients do not develop PBC.(136, 140)

Clearly, there is a need for better long-term analysis regarding the natural history of PBC with features of AIH in order to determine whether PBC/AIH overlap is a distinct clinical entity. In addition, the clinical benefit and harm of adding immunosuppressive medications to PBC patients with AIH features require further study.

Guidance Statements:

2. ***The diagnosis of AMA-negative PBC does not require a liver biopsy if other criteria are met, including cholestatic liver tests and PBC-specific autoantibodies such as sp100 or gp210.***
3. ***Liver biopsy to rule out concomitant AIH or other liver disease should be considered in PBC patients when the alanine aminotransferase activity is more than five times the upper limit of normal.***
4. ***In cases of suspected PBC/AIH overlap, treatment should be targeted at the predominant histological pattern of injury.***

Therapy for PBC

1. **UDCA**

UDCA at a dose of 13 to 15 mg/kg/day is the first-line therapy for PBC. The drug is initiated gradually and generally given in two divided doses, although it can be given once daily to improve compliance, particularly at bedtime. The proposed mechanisms of action of UDCA are multiple and include choleretic, cytoprotective, anti-inflammatory, and immunomodulatory properties.(141) A number of studies have shown the benefit of UDCA in this context.(58-63) Individual studies have demonstrated consistent evidence of improved liver biochemistries. Some studies with extended follow-up have also shown improved survival.(59, 62, 63) Other information comes from combining data sets to increase sample sizes, which has allowed assessment of the effects of therapy.(63) Some meta-analyses have questioned these results.(142) Often, these meta-analyses include studies of short duration and those that have used what is now known to be an inadequate dose of UDCA.(143)

UDCA is widely used and has demonstrated the ability to produce a reduction in need for liver transplantation for PBC.(144) In a large, international meta-analysis including 4845 patients, UDCA-treated individuals had significantly improved transplant-free survival at 5, 10, and 15 years compared with nontreated individuals (90%, 78%, and 66% versus 79%, 59%, and 32%, respectively).(77) The drug is used for patients with any stage of PBC as long as their liver biochemistries are abnormal. However, patients with earlier histologic stage usually respond more favorably to UDCA than patients with advanced disease, although patients with advanced disease may benefit in survival or avoid liver transplantation with this therapy.(63)

The dose of UDCA is important. A study comparing three different doses of UDCA showed that a dose of 13 to 15 mg/kg/day appeared superior to either a lower dose of 5 to 7 mg/kg/day or a higher dose of 23 to 25 mg/kg/day in biochemical responses and cost.(145) The studies that show an improvement in survival have all used this dose of 13 to 15 mg/kg/day. A direct comparison of different drug formulations has not been studied in patients with PBC. A short-term pharmacokinetic study of normal volunteers suggested substantial differences in bioavailability on the basis of preparation.(146)

Cholestyramine and other bile acid-binding sequestrants as well as some antacids may interfere with UDCA absorption. In cases of concomitant use, these should be administered at separate times, with the treatment administered at least 60 minutes prior to, or 4 hours after, bile acid treatment.(147) Dosage does not need to be adjusted for liver or renal disease.

Monitoring of treatment response is done using liver biochemical values. Specifically, serum ALP and total bilirubin predict outcomes in this context.(77) Improvement in liver tests are typically observed within a few weeks, and 90% of the improvement usually occurs within 6 to 9 months. About 20% of patients will have normalization of liver biochemistries after 2 years.(148)

Biochemical response should be assessed after 1 year of treatment with UDCA using one of many published criteria shown in Table 1.(60, 77-79, 149-152) When one of these binary definitions for response to UDCA is used, up to 40% of PBC patients will have an inadequate response to treatment.(150) In addition, scoring systems based on continuous variables have been specifically developed to assess prognosis after initiation of therapy with UDCA, as discussed previously. These scores identify patients who are at increased risk for progression to death or liver transplantation and who may benefit from adjuvant therapy. Transient elastography can also be used to risk-stratify patients with PBC: in one study, those with a liver stiffness >9.6 kPa were 5 times more likely to progress with clinical decompensation, death, or transplant.(80) Liver biopsy is not indicated as a means to monitor response to therapy.

The use of UDCA has been associated with a reduction of serum low-density lipoprotein cholesterol levels, a reduced risk of developing varices, and slower histologic progression. However, UDCA therapy does not improve fatigue, pruritus, associated bone disease, or autoimmune features found in association with PBC.(69, 89, 153, 154) Issues of patient adherence, the development of superimposed liver disease (including fatty liver), and coadministration with bile sequestrants (such as cholestyramine, colestipol, or colesevalam) should be considered for patients with suboptimal response. UDCA has minimal side effects and is generally well tolerated. A five-pound weight gain over the first year of

therapy has been reported and is not progressive.(155) Loose stools and/or thinning of the hair have also been reported infrequently.

2. OCA

OCA was approved by the Food and Drug Administration in May 2016 to be used in combination with UDCA in patients with PBC who have inadequate response to at least 1 year of treatment with UDCA, or as monotherapy for those patients who are intolerant to UDCA. OCA is a Farnesoid X Receptor (FXR) agonist that is 100 times more potent than the endogenous ligand, chenodeoxycholic acid.(156) Through FXR activation, OCA modulates bile acid synthesis, absorption, transport, secretion, and metabolism, with a net effect of choleresis.(157, 158) In animal models, FXR activation has demonstrated antifibrotic and anti-inflammatory properties as well.(157)

A phase 2 randomized controlled trial evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) against placebo for 3 months in a study including 165 patients.(159) A 21% to 25% reduction in ALP was achieved in the OCA groups compared with 3% reduction in the placebo group. Pruritus occurred more frequently in OCA-treated patients, in a dose-dependent fashion. Another phase 2 study launched simultaneously evaluated 2 OCA doses (10 mg and 50 mg) versus placebo as monotherapy in 59 patients with PBC. Serum ALP dropped by 53.9% in the 10-mg group, 37.2% in the 50-mg group, and by only 0.8% in the placebo group.(160) Again, pruritus was the most important adverse event, leading to discontinuation of 38% of study subjects in the 50-mg arm.

A larger phase 3 trial included 210 patients who were treated for 1 year in a randomized, placebo-controlled fashion, followed by an optional 6-year, long-term extension phase while continuing UDCA. The primary endpoint was a combination of reaching a serum level of ALP <1.67 times the upper limit of normal, with a reduction from baseline greater than 15%, and with normal bilirubin. Patients were randomized to placebo, 10 mg/day OCA, or a titration arm, in which subjects were started at 5 mg/day OCA and could increase to 10 mg/day after 6 months if they were tolerating the medication well and had not achieved the primary endpoint. After 1 year, this primary endpoint was met by 46% of patients in the

titration group, 47% in the 10 mg/day group, and 10% of patients in the placebo group.(161) Improvements in other liver chemistries and inflammatory markers were also noted in OCA-treated patients. The open-label phase is still ongoing, but the reduction in ALP was sustained through the second year of the study. As with the phase 2 studies, pruritus was the most common adverse event, but it was less common in patients undergoing dose titration, starting at 5 mg/day.

Although studies examining the efficacy of OCA on survival of patients with PBC are still ongoing, data obtained through microsimulation models suggest that the use of a combination of UDCA and OCA could decrease the 15-year cumulative incidences of decompensated cirrhosis, hepatocellular carcinoma, liver transplants, and liver-related deaths.(162) Based on the results, the recommended starting dose for patients with preserved synthetic function and well-compensated PBC is 5 mg daily. After 3 months, the dose can be increased to 10 mg daily if liver chemistries remain abnormal and the patient is tolerating the medication well.

The benefit of OCA in patients with decompensated liver disease is not established. Furthermore, in September 2017, the Food and Drug Administration issued a warning regarding inappropriate dosing of OCA in patients with moderate to severe liver impairment (Child-Pugh-Turcotte B and C), which was associated with worsening PBC and death. Therefore, the use of OCA in patients with decompensated PBC is not recommended.

3. Food and Herbals Used Therapeutically

Patients frequently ask about specific foods to use or avoid. There are no specific recommendations based on clinical evidence that any particular foods would be of benefit or should be avoided except uncooked seafood or unpasteurized milk. In patients who are obese and who may have superimposed steatohepatitis, a normal (ideal) body weight would be desirable. No information exists on risks of concurrent alcohol use or medications.

Complementary or alternative medicines have seldom been tested. Silymarin was tested in combination with UDCA but offered little additional benefit.(163) No other clinical evidence exists regarding clinical safety or efficacy of other herbal products.

4. Promising New Drugs

a. Fibrates

Fibrates are only approved by the Food and Drug Administration as lipid-lowering medications. These drugs activate the peroxisome proliferator activator receptor (PPAR), a nuclear receptor that is also involved in a variety of metabolic processes, including bile acid homeostasis; PPAR exists in 3 isoforms: α, δ, and γ. PPAR-α, in particular, regulates bile acid synthesis and detoxification, phospholipid secretion, and inflammatory pathways. Activation of PPAR-δ and -γ have more profound effects on lipid and glucose metabolism as well as anti-inflammatory and antifibrotic properties.(164)

Given the anticholestatic properties, fibrates have been evaluated in patients with PBC. An open-label study included 20 patients with an ALP value more than twice the upper limit of normal after UDCA treatment, who were treated with fenofibrate 160 mg/day for 48 weeks. Serum ALP decreased by approximately 50% at the end of the study period.(165) Another study included 48 patients with an incomplete response to UDCA who received additional treatment with the pan-PPAR isoform bezafibrate 400 mg/day for a median of 38 months. Of these, 54% normalized their ALP levels within the first 4 months of treatment.(166) Older patients and those with lower fibrosis scores were more likely to respond. Importantly, most patients who had pruritus at baseline noted significant improvement while on bezafibrate.

In a larger, multicenter trial, 100 patients who were inadequate responders to UDCA were randomized to UDCA/placebo versus UDCA/bezafibrate and treated for 2 years. Patients on combination UDCA/bezafibrate had substantial improvement in liver chemistries, with 67% normalizing ALP and 30% normalizing all liver tests compared with 0% treated with placebo.(94) Furthermore, improvement in

pruritus and beneficial effects on markers of fibrosis were also observed. An ongoing study is further evaluating the effect of fibrates on pruritus (NCT02701166).

Notably, use of fibrates can be associated with myalgias and heartburn, and an elevation in serum creatinine is frequently observed. This is typically reversible and not associated with a decline in glomerular filtration rate, but it is attributed to an increase in creatinine production.(167) Similarly, an increase in bilirubin can occur and deserves further evaluation. This has been attributed to competitive inhibition of the transporter organic-anion-transporting polypeptide, which transports both bile acids and bilirubin, among other endogenous substances. Finally, fibrates can cause elevation of transaminases, which is also typically reversible. While hepatotoxicity is a concern, induction of transaminase genes has been demonstrated with fibrates that may not represent hepatotoxicity. The use of fibrates has not been studied in patients with decompensated liver disease and should be avoided. Therefore, long-term safety of fibrates in patients with PBC warrants additional studies.

b. Other Drugs

Other drugs have been tested, but none have been found as single agents to be of benefit. These include chlorambucil, penicillamine, cyclosporine, corticosteroids, azathioprine, mycophenolate mofetil, thalidomide, methotrexate, malotilate, and colchicine.(52, 168-177) Many of these have been used in combination with UDCA to see whether further improvement in liver disease could be effected. Doubling the dose of UDCA and the addition of colchicine, methotrexate, or silymarin have not been found to be of benefit over and beyond that achieved with UDCA alone.(163, 178, 179) Budesonide may be helpful, although this is controversial.(180)

Newer agents under consideration include the selective PPAR-δ agonist seladelpar(181) and other FXR agonists.

Guidance Statements:

5. ***UDCA in a dose of 13 to 15 mg/kg/day orally is recommended for patients with PBC who have abnormal liver enzyme values regardless of histologic stage.***

6. ***For patients requiring bile acid sequestrants, UDCA should be given at least 1 hour before or 4 hours after the bile acid sequestrant.***
7. ***Biochemical response to UDCA should be evaluated at 12 months after treatment initiation to determine whether patients should be considered for second-line therapy.***
8. ***Patients who are inadequate responders to UDCA (Table 1) should be considered for treatment with OCA, starting at 5 mg/day.***
9. ***Fibrates can be considered as off-label alternatives for patients with PBC and inadequate response to UDCA.***
10. ***Use of OCA and fibrates is discouraged in patients with decompensated liver disease (Child-Pugh-Turcotte B or C)***

Management of Symptoms

The symptoms of PBC significantly impair quality of life(182) and do not typically improve with UDCA or OCA treatment. Therefore, they warrant separate evaluation and treatment.

Management of Fatigue

Fatigue may be multifactorial, and causes other than PBC should be considered. These include hypothyroidism, depression, anemia, and sleep disorders such as sleep apnea. Altered serotonin neurotransmission may mediate fatigue in chronic liver disease(183); however, ondansetron—an antagonist to serotonin receptor 3—did not relieve fatigue in a clinical trial.(184) Fluoxetine, a selective serotonin reuptake inhibitor, also did not improve fatigue.(185) Patients with PBC-related fatigue have excessive daytime sleepiness. Modafinil, a stimulant used for narcolepsy, was originally reported to lessen fatigue in PBC in open-label studies.(186, 187) However, a subsequent placebo-controlled trial failed to show benefit.(188) At this time, there is no recommended therapy for the fatigue resulting from PBC. Education and counseling for patients in how to deal with these symptoms are important. Intractable

fatigue is not a valid indication for liver transplantation because fatigue usually persists post transplant.(189)

Management of Pruritus

Lifestyle interventions have not been tested in controlled clinical trials but have been reported by patients and experts to be helpful, including avoiding tight or itchy clothing, using moisturizers to treat dry skin, bathing with tepid (not hot) water, or even using ice packs to cool the skin.

Anion-Exchange Resins: Cholestyramine, colestipol, and colesevalam are nonabsorbable, highly positively charged resins that bind to negatively charged anions such as bile acids. It is not known which substance in the gut they may be binding to improve cholestatic itching, and clinical trials proving their efficacy are limited, but they have a long track record of clinical use.(190, 191) The recommended dose of cholestyramine is 4 g per dose to a maximum of 16 g/day given 1 hour after or 4 hours before other medications to avoid inhibiting their absorption and 20 minutes before meals. Some patients report bloating, constipation, and/or diarrhea with resins. Colestipol and colesevalam are available as pills and are preferred by some patients over the powder preparation of cholestyramine. Colesevalam was not effective in a single placebo-controlled trial of cholestatic pruritus.(192) However, only patients who had already failed other resins were enrolled.

Rifampicin: Rifampicin, a pregnane X receptor agonist, has been used to successfully treat pruritus in patients with PBC in multiple small clinical trials at doses ranging from 150 mg daily to 300 mg twice daily.(193-196) Two meta-analyses have reported that rifampicin administration is associated with relief of pruritus in cholestasis.(197, 198) Although uncommon, drug-induced liver injuries—sometimes progressing to acute liver failure, hemolysis, renal impairment, and alteration in drug metabolism—have all been reported with rifampicin use such that use is

avoided in patients with bilirubin levels greater than 2.5 mg/dL, with close follow-up warranted.(195, 199) Rifampicin is also an enzyme inducer and has drug interactions with multiple medications, such as of serotonin reuptake inhibitors, so caution should be exercised with polypharmacy.(200)

Opiate Antagonists: Opiate antagonists interfere with the increased endogenous opioid levels of patients with cholestatic pruritus and are associated with improvement in itching symptoms. A meta-analysis included five trials, three that tested the effect of the oral opiate antagonists, naltrexone and nalmefene, and two that tested the effect of intravenous naloxone, with a reported total of 84 participants.(197) The meta-analysis concluded that opiate antagonists are significantly more likely to decrease pruritus compared with placebo. Patients with high opioidergic tone may experience an opiate withdrawal-like reaction to opioid antagonists, characterized by abdominal pain, high blood pressure, tachycardia, goose bumps, nightmares, and depersonalization.(201-204) To mitigate this effect, the dosage should be gradually introduced. For example, naltrexone can be started at a dose of 12.5 mg daily and increased by 12.5 mg every 3 to 7 days, until the pruritus is ameliorated. Alternatively, patients can be admitted to the hospital for intravenous infusions of naloxone as previously reported,(36) followed by the conversion to oral naltrexone. The withdrawal-like syndrome is usually self-limited, so motivated patients can be continued on therapy.(205) Long-term use of opiate antagonists has been associated with lowering of the pain threshold and unmasking of chronic pains.(206) Drug-induced liver injury from naltrexone is uncommon but possible, so follow-up of liver biochemistries is recommended.(207, 208)

Other Agents

Selective Serotonin Reuptake Inhibitors: Sertraline, given at a dose of 75 to 100 mg, helped relieve pruritus in a single, small placebo-controlled trial and in a retrospective case series. The effect was independent from an improvement in depression.(209) Other selective serotonin

reuptake inhibitor medicines have not been tested in cholestatic pruritus. Ondansetron, a serotonin antagonist, was initially reported to decrease cholestatic itch but was then later found to be no better than placebo in more rigorous trials.(210-212)

Phenobarbital: Phenobarbital can improve cholestatic pruritus but is a strong sedative that worsens or initiates fatigue, increases vitamin D deficiency, and has been associated with troublesome gingival hyperplasia.(213)

Antihistamines: Although the itch in cholestasis does not appear to be histamine-related, antihistamines may be beneficial in patients with cholestasis, probably due to their sedative properties.(214, 215) Patients with PBC and sicca symptoms may not tolerate the dry mouth side effect of antihistamines.(215)

Other treatments: Placebo itself is effective in ameliorating pruritus by about 20% to 40% in clinical trials, so results of uncontrolled trials should be interpreted with extreme caution. Nevertheless, case series have reported efficacy using plasmapheresis, albumin dialysis Molecular Adsorbent Recirculating System, nasobiliary or external biliary drainage, and light therapy.(216-218) Intractable pruritus can be a valid indication for liver transplantation.(219, 220) Newer agents under consideration for the treatment of cholestatic itch at the time of this publication include PPAR agonists, inhibitors of the ileal bile acid reabsorption transporter,(221) and autotaxin inhibitors.

Guidance Statements:

11. ***Anion-exchange resins should be used as initial therapy for patients with PBC who have pruritus.***
12. ***The following agents can be used for pruritus refractory to anion-exchange resins:***

a. Rifampicin 150 to 300 mg twice daily.

b. Oral opiate antagonists such as naltrexone titrated to a dose of 50 mg daily.

c. Sertraline 75 to 100 mg daily.

Management of Sicca Syndrome

Although not studied specifically in patients with PBC, accepted treatments for sicca syndrome appear to work equally well in this population.

Dry Eyes (Keratoconjunctivitis Sicca): Mildly dry eyes can be managed with hydroxypropyl methylcellulose or carboxymethylcellulose moisturizing eye drops as needed over the course of the day. Moderate to severe dry eyes should be referred to an eye specialist, who may use immunosuppressant agents, such as cyclosporine or lifitegrast.(222) Cholinergic agents, such as pilocarpine and cevimeline, can be very helpful, although other cholinergic side effects may include nausea, sweating, flushing, urinary frequency, dizziness, or diarrhea. There are also several ophthalmic procedures designed to improve dry eyes, including blocking the puncta with silicone plugs or cautery to prevent draining of tears, thermal or light therapy with eyelid massage to open blocked oil glands, and special contact lenses designed to trap moisture over the sclerae.

Dry Mouth (Xerostomia): Patients with dry mouth are at increased risk of dental caries and should receive regular professional dental cleanings and check-ups. Mild symptoms can be managed with frequent sips of water or sugar-free gum and candy to stimulate saliva production as well as the use of moisturizing mouthwashes, mouth spray, toothpastes, or saliva substitutes. For moderate to severe symptoms, cholinergic agents, such as pilocarpine and cevimeline, can be very helpful, although other cholinergic side effects (listed above) may occur.(223)

Guidance Statements:

13. ***Management of dry eyes can include the following:***
    a. ***Artificial tears should be used initially.***
    b. ***Pilocarpine or cevimeline can be used in patients for whom symptoms are refractory to artificial tears.***
    c. ***Cyclosporine* or *lifitegrast ophthalmic emulsion can be used in those refractory to other agents, preferably under the supervision of an ophthalmologist.***
14. ***The following therapies should be used for xerostomia and dysphagia:***
    a. ***Over-the-counter saliva substitutes can be tried.***
    b. ***Pilocarpine or cevimeline can be used if patients remain symptomatic despite saliva substitutes.***

Preventive Care and Other Considerations

The majority of individuals given a diagnosis of PBC currently have no symptoms referable to their liver disease. Not surprisingly, such individuals may believe that a lack of symptoms is synonymous with lack of significant disease. This lack of symptoms makes it particularly difficult for an individual to recognize the importance of preventive strategies in PBC. The strategies refer not only to the management and consequences of their liver disease but also associated diseases such as sicca syndrome, thyroid disease, and bone disease.

In terms of liver disease progression, the same advice applies to patients with PBC as for any other form of liver disease—avoid alcohol consumption in excess, obesity, and cigarette smoking. These comorbidities both promote disease progression and may put the individual at risk of not being accepted for a liver transplant should the latter become necessary.

PBC patients with cirrhosis should be informed about the risk of using nonsteroidal anti-inflammatory drugs, benzodiazepines, and aminoglycoside antibiotics. Additionally, they should be

advised to inform other physicians—particularly surgeons and anesthesiologists—before they have surgery that they have cirrhosis.

General Advice

Hormone Replacement and Pregnancy

Estrogens promote cholestasis, so oral contraceptive pills and estrogen supplements may induce or worsen pruritus. Similarly, during pregnancy, itching may become severe even early on in the pregnancy, and it may fail to resolve completely after delivery in patients with PBC. There are limited data about fertility or infant outcome in PBC patients.

As with all other women with cirrhosis who become pregnant, it is advisable to check for varices in the second trimester after the mother's blood volume increases markedly. Treatment with beta blockers is safe in pregnancy. A short second stage of labor is optimal because the Valsalva maneuver may precipitate variceal hemorrhage.

Screening Family Members

Family members of patients with PBC are at increased risk of developing the disease, particularly among female FDRs, including sisters and daughters.(43) The value of screening family members has not been firmly established; however, screening is usually recommended for female FDRs beginning at age 30. Screening is usually done by measuring the serum ALP level, and if it is elevated, by assessing for AMA; this could be repeated at 5-year intervals if AMA-negative initially.

Long-Term Follow-Up

UDCA should be continued indefinitely; data regarding long-term OCA are lacking. Periodic monitoring of liver tests should be performed at 3-month to 6-month intervals. This helps detect patients who are inadequate responders to UDCA after 12 months of therapy, lack of adherence, and the rare patients who go on to develop AIH.(121, 135, 224, 225) Thyroid status should be monitored annually. For

patients with known cirrhosis with a Mayo risk score >4.1 or transient elastography values ≥17 kPa, upper endoscopy to assess for varices should be done every 2 to 3 years. Bone mineral density should be assessed every 2 years, depending on baseline density and severity of cholestasis. Similarly, fat-soluble vitamin levels should be monitored annually in patients with jaundice. Ultrasound screening for hepatocellular cancer should be performed every 6 months in patients with cirrhosis and men with PBC (Table 2).

Complications Related to Cirrhosis

Hepatocellular Carcinoma

Although less frequently than for viral hepatitis or hemochromatosis patients, patients with PBC have a slightly increased risk of hepatocellular carcinoma. Men and patients with advanced disease are most apt to develop hepatocellular cancer, which was found at a rate of 3.9 cases in 1000 per year of follow-up. Suboptimal response to UDCA was an important risk factor(226) although treatment with UDCA did not change the risk overall. Surveillance with regular imaging was associated with better clinical outcome of PBC patients who develop HCC.(227-230) Regular screening for hepatocellular carcinoma with cross-sectional imaging at 6-month intervals is currently advised for men and patients with cirrhosis.(231) In patients without liver biopsy, screening should be considered for patients with a low platelet count, a Mayo risk score >4.1, or a transient elastography value ≥17 kPa.

Management of Portal Hypertension

Patients with PBC may develop portal hypertension as a result of biliary cirrhosis or—in the precirrhotic stage of the disease—in association with nodular regenerative hyperplasia.(232, 233) The approach to gastroesophageal varices and variceal hemorrhage in patients with PBC follows the guidance published by the American Association for the Study of Liver Diseases (AASLD) in 2016,(234)which includes a screening upper endoscopy at the time the diagnosis of cirrhosis is suspected.

Platelet counts can be used to determine the need for endoscopic surveillance: one study used a platelet count of <200,000/mm^3(235) as a cutoff point, and another used 140,000/mm^3.(236) Patients with transient elastography values ≥17 kPa could also be considered for surveillance, although this has yet to be studied. One study showed that 6% of patients with PBC without cirrhosis had varices.(91) Another study suggests that varices are virtually never found unless the Mayo risk score is at least 4.1.(78) Nonselective beta blockers or endoscopic varices ligation is indicated in patients with large esophageal varices, consistent with the newly published AASLD guidance.(234) The guidelines suggest that the decision regarding what intervention to use be considered in the context of local expertise, resources, and patient preference.

Variceal bleeding that does not respond to pharmacological and endoscopic therapy in patients with PBC in the precirrhotic stage of the disease poses a specific challenge because orthotopic liver transplantation is not desirable in patients with good synthetic liver function. In this context, transjugular intrahepatic portosystemic shunts are therapeutic alternatives. Distal splenorenal shunts are rarely used but have not been associated with accelerated liver failure in patients with PBC.(237)

Guidance Statements:

15. ***Patients with suspected cirrhosis should undergo endoscopic screening for varices at the time of diagnosis.***
16. ***Regular screening for hepatocellular carcinoma with cross-sectional imaging at 6-month intervals is currently advised for men and patients with cirrhosis.***

Complications Related to Chronic Cholestasis

Osteopenia/Osteoporosis

Patients with fibrotic PBC have a significantly greater risk of osteopenia and osteoporosis than do age-matched and sex-matched controls.(238) Baseline and regular screening every 2 years using bone mineral density testing is appropriate. As for all perimenopausal and postmenopausal women, daily

calcium (1500 mg/day) and vitamin D supplements (1000 International Units/day) may be advisable if there is no history of renal stones. Vitamin D levels should be measured annually in patients with advanced disease. In patients identified as having osteoporosis, alendronate was shown in a randomized controlled trial to significantly improve bone density compared with placebo. Etidronate was ineffective compared with placebo, but monthly ibandronate was found comparable to weekly alendronate in safety and efficiency.(239) Parenteral bisphosphonates also have been used in a smaller number of PBC patients.(239-242) Hormone replacement therapy led to some improvement in bone mineral density, but these agents are seldom used because of safety concerns.(243)

Guidance Statements:

17. Patients with PBC should be provided 1000 to 1500 mg of calcium and 1000 International Units of vitamin D daily in the diet and as supplements if needed.

18. Oral alendronate (70 mg weekly) or other effective bisphosphonates should be considered if patients are osteoporotic. Oral bisphosphonates should be avoided if patients have acid reflux or known varices.

Hyperlipidemia

All chronic cholestatic liver diseases may be complicated by hyperlipidemia. For the most part, this is of little consequence in PBC, and retrospective studies suggest that there is no increased risk of cardiovascular disease in patients with PBC and hypercholesterolemia.(84, 244-246) This has been challenged by a meta-analysis which identified a pooled risk of 1.57 (95% CI, 1.21-2.06)(247), and another series suggests that special attention be given to those PBC patients with concomitant hypertension.(248) UDCA will lower low-density lipoprotein cholesterol levels and is the initial step. However, when there is also a family history of lipid abnormalities or cardiovascular disease risk factors, treatment with cholesterol-lowering drugs may be appropriate. Statins (3-hydroxy-3-methylglutaryl

coenzyme A reductase inhibitors) appear to be safe even if serum liver tests are abnormal,(249) and fibrates have been used safely.(250, 251)

Guidance Statements:

19. Patients with elevated lipid levels and at risk for cardiovascular disease can be considered for lipid-lowering therapy.

Fat-Soluble Vitamins

Most PBC patients do not develop fat-soluble vitamin (vitamins A, D, E, and K) deficiency. If patients become jaundiced, then routine measurement of vitamin levels is recommended, and if deficiencies are found, then patients should be given oral supplementation of vitamins A, D, E, and K, using standard water-soluble preparations. If the international normalized ratio is prolonged and does respond to a vitamin K trial, then subcutaneous vitamin K should be given therapeutically.

Guidance Statements:

20. Fat-soluble vitamin deficiencies should be treated with parenteral or water-soluble supplements.

Liver Transplantation

Indications for liver transplantation for patients with PBC are similar to those with other forms of chronic liver disease. Patients should be referred for liver transplant evaluation in the setting of decompensated cirrhosis, a Model for End-Stage Liver Disease score ≥15, a total bilirubin greater than 6 mg/dL, or a Mayo risk score greater than 7.8.(71, 252) Severe intractable pruritus is an exceptional indication for liver transplantation. Chronic fatigue is not an indication for transplant because this symptom is not universally reversible after liver transplantation.

In the mid-1980s, PBC was the leading indication for liver transplantation in the United States. Two decades later, a study showed that, despite an increase in the number of transplants performed in the United States in the previous 10 years, the number of patients with PBC requiring transplant had declined by about 20%. In a more recent study querying the United Network for Organ Sharing database, the frequency of liver transplantation for PBC was again noted to be decreasing.(253) The outcome of liver transplantation for patients with PBC is more favorable than for nearly all other disease categories. In the same study, the 1-, 3-, 5-, and 10-year graft survival rates were 85%, 80%, 78.1%, and 71.9%, and the 1-, 3-, 5-, and 10-year patient survival rates were 90.2%, 86.7%, 84.4%, and 79%, respectively.(253)

Osteopenia may worsen for the first 6 months after transplantation, yet bone mineral density returns to baseline after 12 months and improves thereafter.(254) Alendronate is a more effective treatment than etidronate,(255) but there are no studies to confirm the long-term efficacy of any treatment. As could be expected, a monthly regimen with ibandronate is associated with higher adherence compared with a weekly alendronate regimen, and both drugs have a comparable efficacy and safety profile.(239)

Some 20% to 30% of patients with PBC who undergo transplantation develop recurrent disease over 10 years and up to 50% do so by 20 years of follow-up. The median time to recurrence is 3 to 6 years.(256, 257) Fortunately, recurrent PBC infrequently affects long-term patient or graft survival.(258) Long-term immunosuppression with a cyclosporine-based regimen seems to be associated with reduced incidence of recurrent PBC, but this is not proven.(259) Risk factors for accelerated recurrent PBC may include tacrolimus therapy and advanced donor age. In a recent study, a higher Model for End-Stage Liver Disease score at the time of wait list registration was also associated with increased recurrence rates.(257)

UDCA improves liver biochemistries and may delay histologic progression of recurrent PBC. Although the influence of UDCA on the natural history of recurrent disease requires further study in the context of randomized controlled trials,(260) patients on UDCA post liver transplantation appear to have lower recurrence rates compared with patients who did not receive UDCA post transplant (21% versus

62%; $P = 0.004$).(257)

After liver transplantation, pruritus improves, sicca syndrome is unchanged, bone disease worsens initially and then improves, and AMA may persist or reappear but does not signal the recurrence of PBC. Fatigue improves in a subset of patients with PBC, but moderate to severe fatigue continues to affect nearly half of patients 2 years after liver transplantation.(189)

Guidance Statements:

21. Patients with manifestations of end-stage PBC should be referred for liver transplantation when their Model for End-Stage Liver Disease score exceeds 14.

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AASLD APPROVAL

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Table 1. Assessing Biochemical Response

Arranged by year	Response criteria
Rochester I (78)	ALP ≤2× ULN
Barcelona (60)	Reduction in ALP ≥40% from baseline or normalization of ALP
Paris I (149)	ALP ≤3× ULN; AST ≤2× ULN; and TB ≤1 mg/dL
Rotterdam (150)	TB <1× ULN and albumin >1× LLN
Toronto (151)	ALP ≤1.67× ULN
Paris II (152)	ALP ≤1.5× ULN; AST ≤1.5× ULN; and TB ≤1 mg/dL
Rochester II (79)	ALP ≤2× ULN
Global (77)	ALP ≤2× ULN

ALP, alkaline phosphatase; AST, aspartate aminotransferase; TB, total bilirubin, ULN, upper limit of normal.

Table 2. Follow-Up of PBC

Liver tests every 3-6 months
TSH annually
Bone mineral densitometry every 2 years
Vitamins A, D, E and prothrombin time annually if bilirubin >2.0
Upper endoscopy every 1-3 years if cirrhotic, Mayo risk score >4.1, or transient elastography shows a score ≥17 kPa*
Ultrasound with or without alpha fetoprotein in patients with known or suspected cirrhosis† and men every 6 months

*Interval determined by findings on previous EGD.
†Platelets <140,000/mm^3 or Mayo risk score ≥4.1.
Upper endoscopy PBC, primary biliary cholangitis; TSH, thyroid stimulating hormone.

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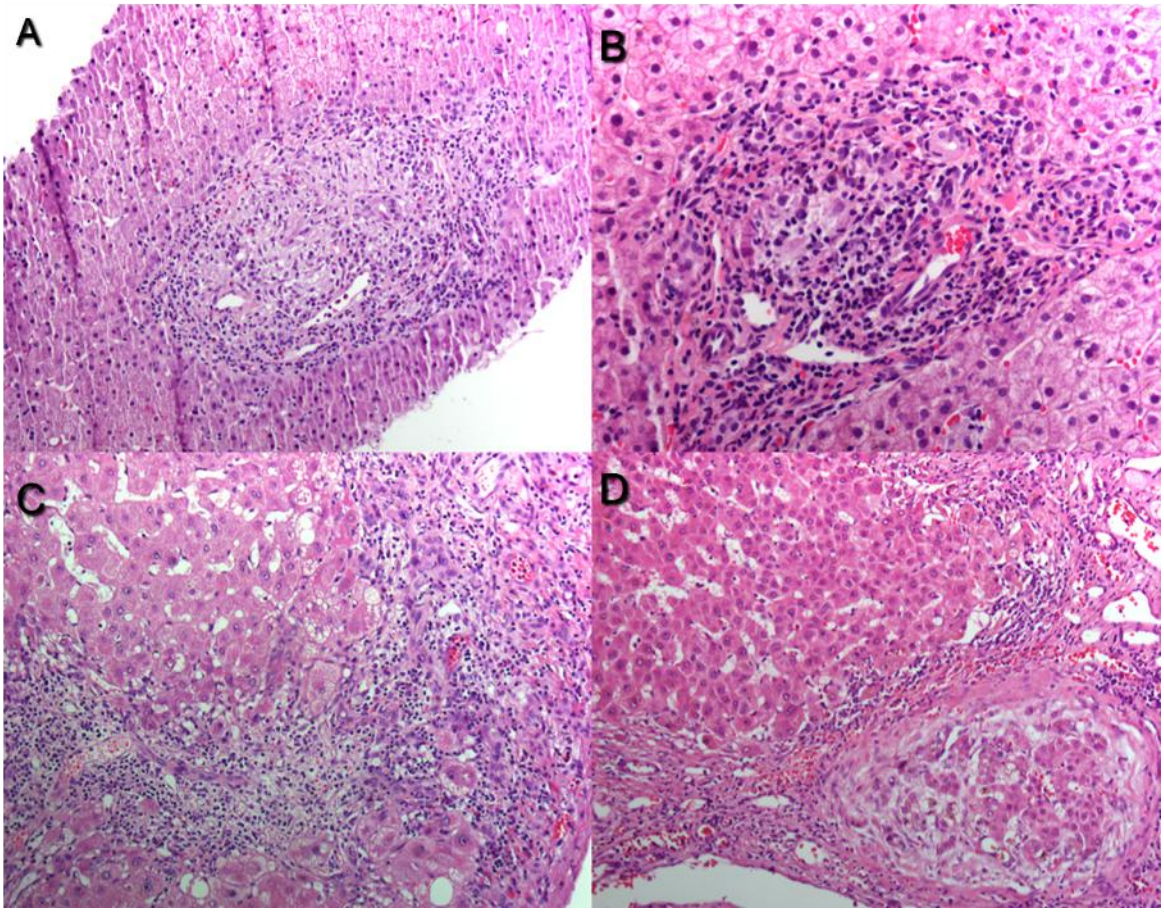

A. Stage 1 PBC, with portal inflammation and a florid ductal lesion, hematoxylin-eosin, magnification 20x
B. Stage 2 PBC, with portal inflammation, focal interface hepatitis and bile ductular proliferation, hematoxylin-eosin, magnification 40x
C. Stage 3 PBC, with bridging inflammation, hematoxylin-eosin, magnification 20x
D. Stage 4 PBC, showing cirrhosis with ductopenia, hematoxylin-eosin, magnification 20x.