Title

Primary Biliary Cholangitis: A Brief Overview.

Journal

Clinical liver disease, 15(3)

ISSN

2046-2484

Authors

Louie, Justin S

Grandhe, Sirisha

Matsukuma, Karen

et al.

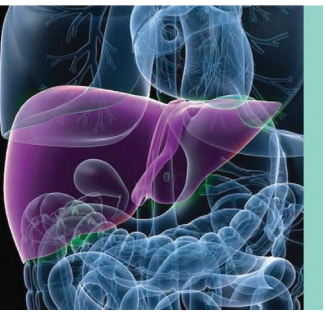
Publication Date

2020-03-01

DOI

10.1002/cld.867

Peer reviewed



Primary Biliary Cholangitis: A Brief Overview

Justin S. Louie, Sirisha Grandhe,* Karen Matsukuma,† and Christopher L. Bowlus**

Primary biliary cholangitis (PBC), previously referred to as primary biliary cirrhosis, is the most common chronic cholestatic autoimmune disease affecting adults in the United States.[1] It is characterized by a hallmark serologic signature, antimitochondrial antibody (AMA), and specific bile duct pathology with progressive intrahepatic duct destruction leading to cholestasis. PBC is potentially fatal and can have both intrahepatic and extrahepatic complications.

EPIDEMIOLOGY

PBC affects all races and ethnicities; however, it is best studied in the Caucasian population. The condition predominantly affects women older than 40 years, with a female/male ratio of 9:1.[2] Although the incidence of PBC appears to be stable, the overall prevalence of the disease is increasing.[3] An individual's genetic susceptibility, epigenetic factors, and certain environmental triggers seem to play important roles. Beyond simple increases in familial prevalence, a genetic cause for increased susceptibility is supported by the higher concordance of PBC in monozygotic compared with dizygotic twins.[4] In addition, certain human leukocyte antigen haplotypes have been associated with PBC, as well as variants at loci along the interleukin-12 (IL-12) immunoregulatory pathway (IL-12A and IL-12RB2 loci).[5]

PATHOGENESIS

The primary disease mechanism in PBC is thought to be T cell lymphocyte–mediated injury against intralobular biliary epithelial cells. This causes progressive destruction and eventual disappearance of the intralobular bile ducts. Molecular mimicry has been proposed as the initiating event in the loss of tolerance primarily to mitochondrial pyruvate dehydrogenase complex, E2, during which exogenous antigens evoke an immune response that recognizes an endogenous (self) antigen inciting an autoimmune reaction (Fig. 1). Suspected mimics include xenobiotics[6] and bacterial and viral antigens.[7] AMA, a

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine transaminase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate transaminase; gp210, glycoprotein 210; IL-12, interleukin-12; OCA, obeticholic acid; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

From the *Division of Gastroenterology & Hepatology, UC Davis School of Medicine, University of California Davis, Sacramento, CA; and †Department of Pathology, University of California Davis, Sacramento, CA.

Potential conflict of interest: Nothing to report.
Received June 11, 2019; accepted July 23, 2019.

View this article online at wileyonlinelibrary.com

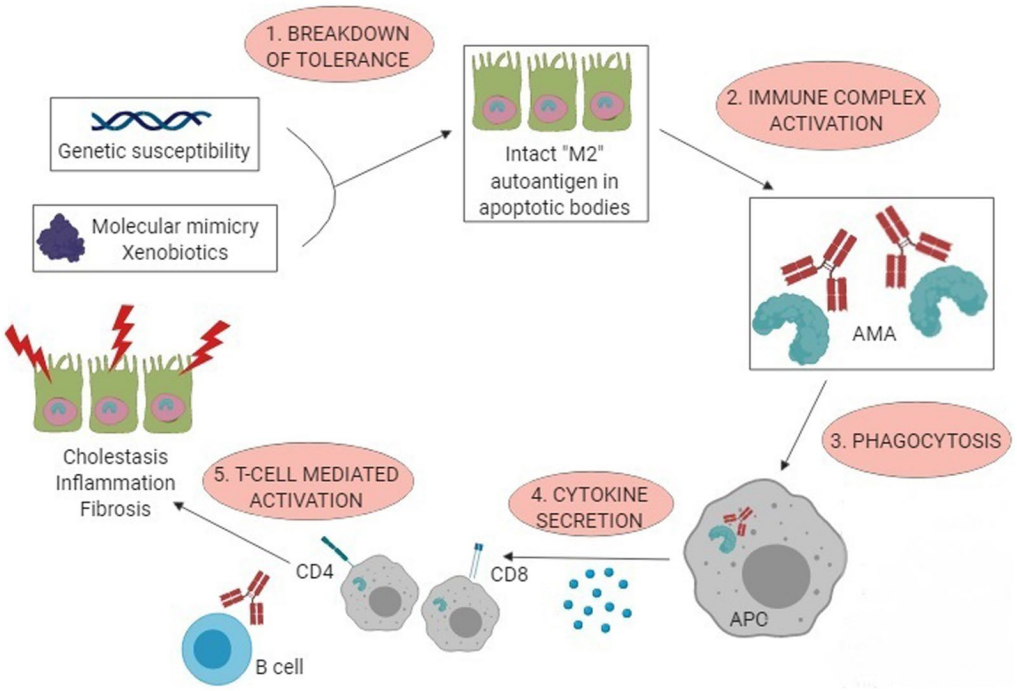


FIG 1 Model of the pathogenesis of PBC. In a genetically susceptible individual, environmental triggers lead to loss of tolerance to the mitochondrial antigen through molecular mimicry. Intact mitochondrial antigens in cholangiocytes undergoing apoptosis in the presence of AMAs and macrophages leads to an innate immune response and further enhancement of adaptive immune responses.

highly disease-specific autoantibody of PBC, targets four principal autoantigens, which are collectively referred to as the "M2" subtype of mitochondrial autoantigens. In addition to the humoral response, T cell responses including $CD4^+$ and $CD8^+$ T cells target the same antigen and are involved in the destruction of biliary epithelial cells. The resultant cholestasis with noxious bile acids causes "foamy" degeneration of hepatocytes and perpetuates the cycle of injury.

DIAGNOSIS

PBC should be suspected in the setting of chronic cholestasis, after exclusion of common causes of biliary obstruction, particularly in middle-aged females with unexplained elevations in serum alkaline phosphatase (ALP).[1] Aminotransferase levels may be mildly elevated as well. The diagnosis of PBC can be established when two of the following three criteria are met: biochemical evidence of cholestasis based on ALP elevation >1.5 times upper limit of normal (ULN); presence of AMA or other PBC-specific autoantibodies, including sp100 or glycoprotein 210 (gp210); and/or a liver biopsy demonstrating nonsuppurative cholangitis affecting septal and interlobular bile ducts (Fig. 2).[1]

Although most patients with PBC test positive for AMA, it can be absent in 10% to 20%. AMA-seronegative patients are often positive for antinuclear antibodies (ANAs), including the PBC-specific ANAs sp100 and gp210, as well as recently described anti-kelch-like 12 and anti-hexokinase 1 antibodies.[8] Liver biopsy may be considered in cases when a concomitant liver disease such as autoimmune hepatitis (AIH) or nonalcoholic fatty liver disease is suspected and is required to confirm the diagnosis of AMA-negative PBC when PBC-specific autoantibodies are also lacking. In this latter situation, histology should demonstrate identical histological findings to AMA-positive disease. However, consideration of differential diagnoses is important, particularly for AMA-negative PBC, including cholestatic drug-induced liver injury, biliary obstruction, sarcoidosis, nonalcoholic fatty liver disease, AIH, and primary sclerosing cholangitis. Treatment response is similar in AMA-positive and AMA-negative disease, although the latter may have a more severe course.

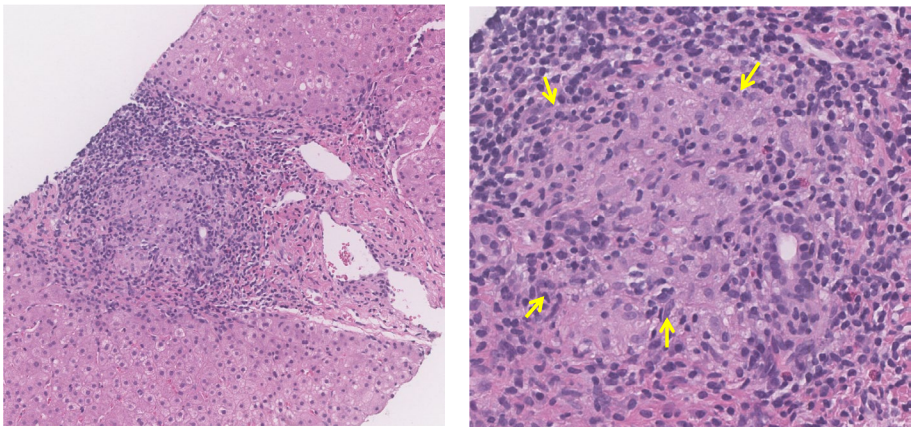


FIG 2 Typical liver histology of PBC demonstrating portal-based duct-centric inflammation, with prominent bile duct injury. Note the overlapping and disorganized appearance of the cholangiocyte nuclei, cytoplasmic eosinophilia, and intraepithelial lymphocyte (right upper and lower arrow). A loose aggregate of histiocytes (left upper and lower arrows) forms a vague granuloma adjacent to the bile duct. All images were digitally scanned at ×40 original magnification.

Much has been written about the overlap syndrome of PBC with AIH.[9] However, as noted earlier, many patients with PBC will have a positive ANA and mild-to-moderate elevation of serum aminotransferases. In addition, interface hepatitis is a common feature on liver biopsy, particularly in severe cases. Further, AMA can be found in a small proportion of patients with only AIH. The diagnosis of the small group of patients with PBC who truly have an overlap syndrome with AIH should be based on the Paris criteria,[10] which requires the presence of two of the following three criteria: (1) alanine aminotransferase activity >5 times ULN; (2) IgG ≥2 times ULN and/or positive anti-smooth muscle antibody; and (3) liver biopsy demonstrating moderate or severe interface hepatitis. Outcomes are thought to be worse in overlap disease, although optimal management has not been established.

MANAGEMENT

Ursodeoxycholic acid (UDCA) remains the foundation of treatment of PBC and has been associated with improvement in liver biochemical tests, a reduction in disease progression, and transplant-free survival (Table 1).[11] UDCA at a dosage of 13 to 15 mg/kg/day orally is recommended for patients with PBC regardless of histological stage. However, patients with advanced PBC and complications of portal hypertension may not benefit and should be considered for liver transplantation. Although the majority of patients with PBC treated with UDCA will have an adequate biochemical response that is associated with a normal transplant-free survival, up to 40% of patients will not and remain at risk for disease progression. A variety of prognostic models to assess UDCA biochemical response after initiation of

TABLE 1. TREATMENT OPTIONS FOR PATIENTS WITH PBC

Therapeutic Agent	Mechanism	Efficacy
UDCA	Secondary bile acid	• Improves liver biochemical tests • Delays progression of hepatic fibrosis • Improves time to liver transplantation • ~30%-45% have an inadequate response • Less effective in patients with PBC with late-stage disease
OCA	Farnesoid X receptor agonist	• Improves serum ALP and TB in patients with PBC who had an incomplete response or were intolerant to UDCA alone • May improve liver histology
Fibrates	Peroxisome proliferator-activated receptor agonists	• Decrease in ALP, ALT, and Gamma-glutamyl transferase • May arrest the progression of liver stiffness
Budesonide	Glucocorticoid	• Improves serum ALP in patients with PBC who have active interface hepatitis • Results in reduced bone mineral density

treatment, including the GLOBE score,[12] can be used to help determine which patients may require second-line therapies (Table 2). The only approved treatment for patients with PBC who are inadequate responders to UDCA is obeticholic acid (OCA), starting at 5 mg/day and titrating to 10 mg/day based on response and tolerability.[13] Pruritus is a common adverse effect of OCA but rarely leads to discontinuation. Use of OCA in Child B and C cirrhosis requires dose adjustment and should be used with caution, if at all, in this setting. Fibrates, including bezafibrate and fenofibrate, have been advocated as off-label alternatives for these patients, although available data are limited to a single randomized controlled trial of bezafibrate.[14] Surprisingly, attempts to treat PBC with immunomodulators have not been successful to date.[15] Thus, the management of PBC is no longer as simple as starting UDCA and hoping for the best, but rather involves active monitoring of response and appropriate use of second-line therapies (Fig. 3).

Fatigue is a common symptom of PBC, does not correlate with disease stage, and does not improve with UDCA or OCA treatment. Other potential causes should be evaluated, in particular coexisting hypothyroidism and anemia. Pruritus is another frequent PBC manifestation and often requires adjunctive management with bile acid binding resins or rifampicin. Patients should be screened for osteopenia and osteoporosis at diagnosis, with ongoing subsequent

TABLE 2. PROGNOSTIC MODELS OF PBC AFTER TREATMENT WITH UDCA

Qualitative Model	Time of Evaluation	Definition
Barcelona criteria	1 year	Decrease in ALP >40% of baseline level or normalization of ALP
Global PBC	1 year	ALP < 2 ULN and TB ≤ 1 ULN
Paris I criteria	1 year	TB 1 mg/dL, ALP < 3 ULN, AST < 2 ULN
Paris II criteria	1 year	ALP and AST < 1.5 ULN, normalization of TB
Rotterdam criteria	1 year	Normalization of TB and/or albumin
Toronto criteria	>2 years	ALP ≤ 1.67 ULN
Quantitative Models	**Time of Evaluation**	**Variables**
GLOBE score	1 year	Baseline age, bilirubin, albumin, ALP, platelets
Mayo PBC score	Not applicable	Age, TB, albumin, prothrombin time, edema, diuretic use
UK-PBC	1 year	Baseline albumin and platelet count, TB, AST, ALT, and ALP

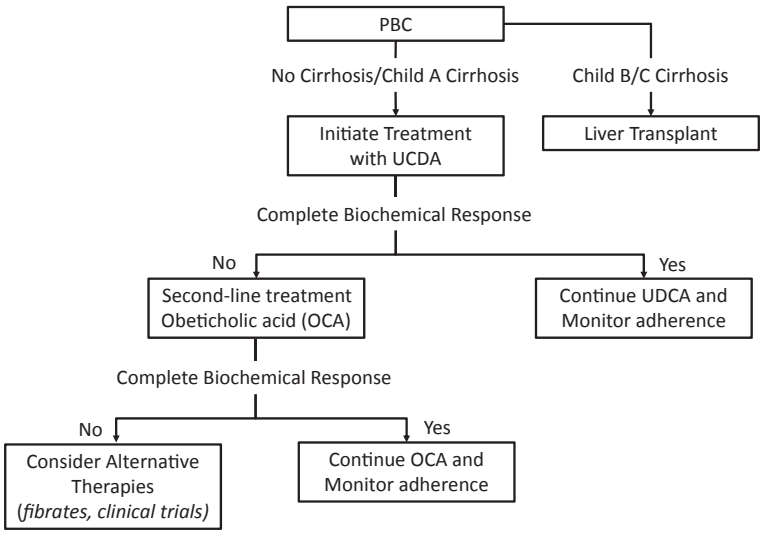


FIG 3 Treatment algorithm for patients with PBC. Initial treatment should begin with UDCA in all patients with PBC. Biochemical response should be assessed 6 to 12 months after starting UDCA. Patients with an inadequate biochemical response or who do not tolerate UDCA should be considered for treatment with UDCA or referred for clinical trials. Off-label use of alternative therapies can be considered, but the body of evidence supporting their use is limited. Patients with advanced cirrhosis should be considered for liver transplantation.

monitoring. In addition, patients with jaundice should be screened for fat-soluble vitamin deficiencies. Notably, elevated serum lipids are common in PBC; there is no apparent increased risk for acute coronary events or stroke. Patients with PBC have a slightly increased risk for HCC, and regular screening for HCC with cross-sectional imaging every 6 months is currently advised for patients with cirrhosis.

The number of liver transplants performed for PBC has been decreasing, but transplant remains an important option for patients with advanced disease. Although recurrent PBC has been reported to occur in as high as 35%, outcomes from liver transplantation in PBC are excellent. Recent reports suggest that prophylactic treatment with UDCA after liver transplant may prevent recurrent PBC and prolong survival.

SUMMARY

PBC is a rare autoimmune, cholestatic liver disease that in most cases can be adequately treated with UDCA. However, even asymptomatic patients with persistently elevated liver tests remain at risk for disease progression and should be considered for second-line therapies.

CORRESPONDENCE

Christopher L. Bowlus, Division of Gastroenterology and Hepatology, UC Davis School of Medicine, 4150 V Street, PSSB 3500, Sacramento, CA 95817. E-mail: clbowlus@ucdavis.edu

REFERENCES

1) Lindor KD, Bowlus CL, Boyer J, et al. Primary biliary cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology 2019;69:394-419.

2) Selmi C, Bowlus CL, Gershwin ME, et al. Primary biliary cirrhosis. Lancet 2011;377:1600-1609.

3) Lu M, Zhou Y, Haller IV, et al. Increasing prevalence of primary biliary cholangitis and reduced mortality with treatment. Clin Gastroenterol Hepatol 2018;16:1342-1350.e1.

4) Selmi C, Mayo MJ, Bach N, et al. Primary biliary cirrhosis in monozygotic and dizygotic twins: genetics, epigenetics, and environment. Gastroenterology 2004;127:485-492.

5) Hirschfield GM, Liu X, Xu C, et al. Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. N Engl J Med 2009;360:2544-2555.

6) Tanaka T, Zhang W, Sun Y, et al. Autoreactive monoclonal antibodies from patients with primary biliary cholangitis recognize environmental xenobiotics. Hepatology 2017;66:885-895.

7) Wang JJ, Yang GX, Zhang WC, et al. Escherichia coli infection induces autoimmune cholangitis and anti-mitochondrial antibodies in non-obese diabetic (NOD).B6 (Idd10/Idd18) mice. Clin Exp Immunol 2014;175:192-201.

8) Norman GL, Yang CY, Ostendorff HP, et al. Anti-kelch-like 12 and anti-hexokinase 1: novel autoantibodies in primary biliary cirrhosis. Liver Int 2015;35:642-651.

9) To U, Silveira M. Overlap syndrome of autoimmune hepatitis and primary biliary cholangitis. Clin Liver Dis 2018;22:603-611.

10) Chazouilleres O, Wendum D, Serfaty L, et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology 1998;28:296-301.

11) Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology 2014;147:1338-1349.e5, quiz e15.

12) Lammers WJ, Hirschfield GM, Corpechot C, et al. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. Gastroenterology 2015;149:1804-1812.e4.

13) Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med 2016;375:631-643.

14) Corpechot C, Chazouilleres O, Rousseau A, et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. N Engl J Med 2018;378:2171-2181.

15) Bowlus CL, Yang GX, Liu CH, et al. Therapeutic trials of biologics in primary biliary cholangitis: an open label study of abatacept and review of the literature. J Autoimmun 2019;101:26-34.