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Developed under the direction and sponsorship of Ipsen Biopharmaceuticals.

Faculty Disclosure: Dr. Kowdley has been paid consulting fees by Ipsen.

2/2024 NON-US-003675

Primary Biliary Cholangitis: Managing a Progressive Liver Disease

Primary biliary cholangitis (PBC) is a progressive autoimmune liver disease that specifically targets biliary epithelial cells (BECs). Characteristic findings in PBC are bile duct injury, features of cholestasis, and hepatic fibrosis, usually accompanied by the presence of antimitochondrial antibody (AMA) in 90% to 95% of patients.[1,2] Disease course and progression rates are highly variable among individual patients.[3] PBC develops due to epigenetic or environmental triggers in genetically susceptible individuals **(Figure 1)**.[3,4]

In PBC, an aberrant immune response to PDC-E2–expressing BECs damages bile ducts. Further evidence supports a direct pathogenic effect of AMA on hepatobiliary tissues that may stimulate additional autoimmune responses.[3,5] Several genetic loci, particularly in genes associated with human leukocyte antigen, have been identified as associated with PBC.[5] Environmental triggers may include certain urinary tract infections, hormone replacement therapy, nail polish and hair dyes, cigarette smoking, and industrial toxins. Socioeconomic factors also may play a role in PBC development.[3,5]

PBC is a rare disease, with an estimated global prevalence of 14.6/100,000 people[6]; 9 in 10 patients are women.[2] Typical patients are women aged 40 to 60 years, and it is exceptionally rare under age 25. Diagnosis of asymptomatic PBC has increased with AMA testing, allowing early intervention and improving outcomes with medical therapy. Among patients asymptomatic at diagnosis, median time to symptom development is 2 to 4.2 years.[3] Without treatment, the long-term consequences of PBC can include shorter survival times compared with healthy people; symptomatic patients, in comparison to asymptomatic patients at diagnosis, can have shorter median survival.[3] Untreated PBC typically progresses to fibrosis, cirrhosis, and may lead to potential liver failure within 10 to 20 years.[6] The availability of successful treatments for PBC has the potential to prolong time to progression, reducing need for transplant, and underscoring the importance of early diagnosis.[3]

Symptoms

Many patients are asymptomatic when abnormal routine liver function tests (LFTs) trigger further evaluation. PBC should be considered in patients with chronic cholestasis, which may be suspected if there is an unexplained elevation in alkaline phosphatase (ALP) level.[3] Diagnosis may not be apparent due to the nature of symptoms such as fatigue and pruritus of varying severity. In my experience, symptomatic patients occasionally have been referred to other specialties, which delays accurate diagnosis because pruritus or sicca syndrome may not suggest liver disease. Other symptoms, although less common, include xanthomas, abdominal pain, sleep disturbance or mood disorders, and some autoimmune disorders **(Table 1)**.[3,5] Severe pruritus is typically the most bothersome symptom for patients, limiting daily activities, disrupting sleep, and undermining quality of life (QoL).

Comorbid extrahepatic autoimmune diseases (EAIDs) are another challenge; Sjögren syndrome prevalence of (47.4% in a US outpatient study), followed by autoimmune thyroid disease (9% to13%), and systemic sclerosis (2% to 4%).[3,7,8] Fortunately, comorbid EAIDs do not impact PBC outcomes.[8] Other extrahepatic complications include sicca complex (dry eye/dry mouth; 34%), hyperlipidemia (75%-96%), and osteoporosis (20% to 40%).[9]

Figure 1. Risk factors associated with PBC[4]

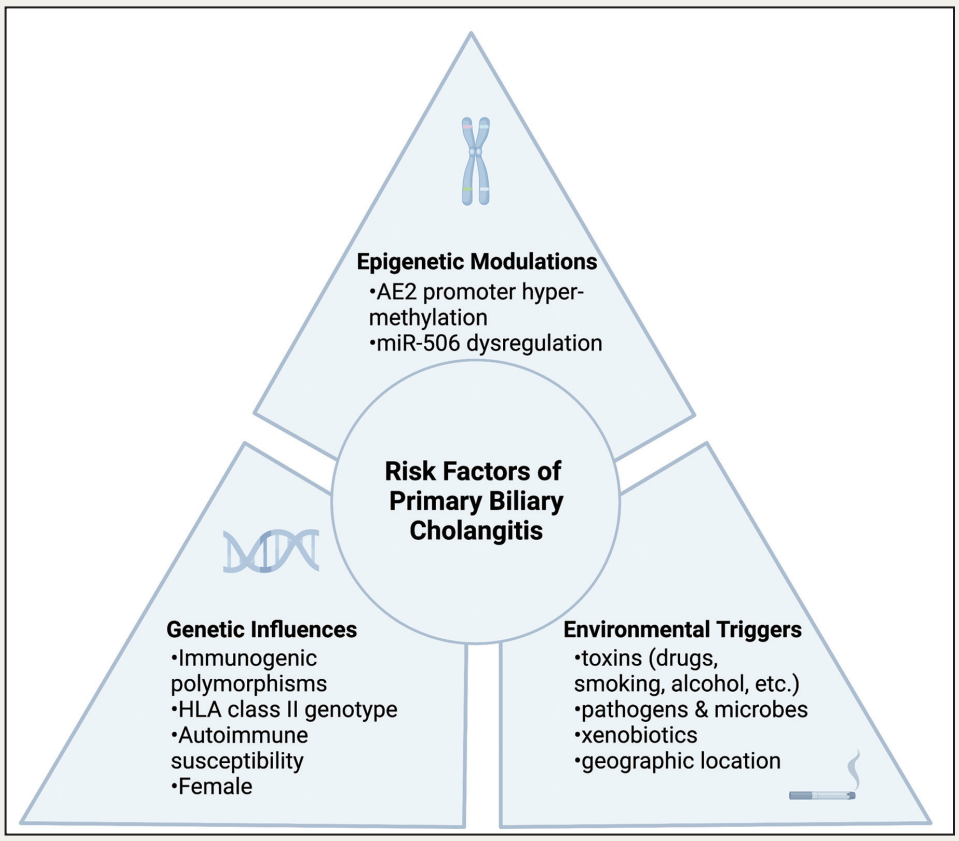

Fig. 1. Risk factors of primary biliary cholangitis. It is hypothesized that genetic factors and autoimmune susceptibility combined with certain environmental factors may trigger PBC. It is difficult to assess an individual's risk, but several factors have been correlated with an increased risk of developing PBC. Such factors include sex, age, geographic location, lifestyle choices, and inflammation. PBC, primary biliary cholangitis.

Modified from Medford 2023.

Diagnostic Pathway

Diagnosis of PBC can be confirmed if 2 of these 3 criteria are met: (1) elevated ALP level indicating a biliary source; (2) presence of AMA (or disease-specific antinuclear antibodies mentioned below) on validated assays; or (3) histopathologic evidence of nonsuppurative cholangitis.[3] The ALP level in noncirrhotic patients is a good indicator of inflammation and biliary damage severity.[3] A biopsy is rarely needed with a positive AMA test, but may be considered for AMA-negative patients or if autoimmune hepatitis (AIH) is suspected.[5] A small percentage of diagnoses are made using anti-gp210 and anti-sp100, which are PBC-specific antinuclear antibodies found in about 50% of AMA-negative patients.[1] Serum cholesterol is elevated in PBC—predominantly due to high-density vs low-density cholesterol— is not thought to increase cardiovascular risk.[3,5]

Differential diagnoses include biliary obstruction or stricture, primary sclerosis cholangitis, hepatitis, and drug- or toxin-induced hepatotoxicity.[10] AIH/PBC overlap typically refers to simultaneous AIH in people with a diagnosis of AMA-positive PBC.[3] Between 8% to 19% of patients with PBC may develop AIH/PBC overlap syndrome. AIH/PBC may be

Table 1. Clinical features of primary biliary cirrhosis[11]

Clinical features	Prevalence	Potential mechanism
Fatigue	20%-85%	Excessive manganese deposits in globus pallidum, elevated inflammatory cytokines
Pruritus	20%-75%	Cholestasis, increased opiodergic tone
Jaundice	10%-60%	Cholestasis
Xanthomas	15%-50%	Hypercholesterolemia and hyperlipidemia
Osteoporosis	35%	Disturbances in bone remodeling due to metabolic changes in PBC
Dyslipidemia	> 75%	Reduction in biliary secretion of cholesterol. Toxic effects of unconjugated bilirubin

Modified from Purohit 2015.

Table 2. Validated continuous scores using first-line therapy response at 12 months[14,15]

Score	Outcomes	Variables
UK-PBC[2]	Risk of liver transplant or liver-related death at 5, 10, or 15 years	**At baseline:** albumin, platelet count **At 12 months:** ALP, AST, ALT, bilirubin
GLOBE[15]	Liver transplant-free survival at 3, 5, and 10 years	Age at diagnosis **At 12 months:** ALP, bilirubin, albumin, platelet count

Modified from Martini 2023, Carbone 2016, and GLOBE.

Note: Both scores were validated in European and North American populations.

AST = aspartate aminotransferase.

suspected when there is a high alanine transaminase (ALT):ALP ratio or very high ALT levels (>5 times upper limit of normal [ULN]).[3] Diagnosis requires confirmed PBC plus highly elevated ALT and serum immunoglobulin G; biopsy is required for histologic evidence of hepatitis.[5]

Treatment and Management of PBC

Over time, there has been a decrease in liver transplants needed for people living with PBC. To that end, a patient's response to medical therapy is the best predictor of transplant-free survival. ALP and bilirubin levels at diagnosis are reliable surrogate markers for prognosis and response to therapy.[3,5] Response to first-line therapy also has been validated as a predictor of risk for progression or transplant **(Table 2)**. AMA-positive patients with normal ALP levels are considered at low risk for PBC development and potentially can be followed up with periodic LFTs.[3] Symptomatic disease, elevated bilirubin, and ALP level ≥2 ULN are factors associated with worse prognosis.[2]

The goals of medical therapy are to slow progression of disease and address cholestatic symptoms. I always include patients in treatment decision-making and take into account their concerns and goals. It is imperative to empower patients to participate in their care and long-term health.

Monitoring for treatment response can begin as early as 6 months after initiation of first-line therapy and must be done at 12 months.[1] Recent research suggests that inadequate response (ALP 1.9 times ULN) at 6 months of treatment identifies patients who could benefit from second-line therapies.[13] Additional investigational therapies are being evaluated for patients with PBC

We are recognizing that routine monitoring of laboratory tests in PBC often is not done. Timely monitoring is crucial for identifying those who can benefit from second-line therapy. Follow-up blood tests are necessary at least every 6 months to identify changes in liver biochemical tests. We know that modest changes in serum ALP and bilirubin levels may make a difference in long-term outcomes.

Equally important from the patient's perspective is symptom management, as symptoms negatively impact daily life.[1,3] Chief among these is pruritus, which occurs in 20% to 70% of patients and may not respond to typically used first-line treatment options. Depending on severity, pruritus—which is worse at night—disrupts sleep, impairs QoL, and can lead to damaged skin surfaces due to scratching. A stepwise approach to pruritus management is recommended.[1] Although antihistamines are mentioned in guidelines, my preference is to avoid these drugs when treating cholestatic pruritus, since they may not be effective and exacerbate sicca syndrome and fatigue. Failing to recognize that pruritus may be related to liver disease sometimes delays diagnosis.

Fatigue impact is unrelated to the severity of underlying biliary disease and generally is unresponsive to medical therapies; however, it is important that patients be evaluated for secondary causes (eg, medications, anemia).[5] Patients with sicca symptoms may achieve some relief with artificial tears or medications that stimulate tear production and should review oral hygiene after Sjögren syndrome or other EAIDs have been ruled out.[5]

Patients with PBC have a lifelong disease, but it can be managed medically over the long term with preventive care and appropriate follow-up. Patients should be advised to abstain from alcohol and smoking and to avoid or manage obesity. Long-term follow-up is summarized in **Table 3**. Oral contraceptives, hormone replacement, and pregnancy may worsen pruritus due to the effects of estrogen on cholestasis.[3] About 20.7% of sisters and 7.8% of brothers of patients with PBC will be AMA positive, and ALP screening is recommended for first-degree female family members starting at age 30.[3]

Comprehensive care of patients with PBC often requires physicians to interact with other healthcare providers to ensure optimal pruritus management and accurate metabolic test result interpretation. In my practice, we tend to function as the medical home or coordinator for patients. We also know we can attempt to achieve normalization of ALP and bilirubin levels to maximize favorable long-term outcomes. This is particularly important now that we have several promising new investigational medications in clinical trials.

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Table 3. Recommended long-term follow-up for patients with PBC[3]

Action	Frequency
All Patients	
Liver function tests	Every 3 to 6 months
Bone mineral density	Every 2 years
Special Situations	
Assess vitamins A, D, E, and prothrombin time	Annually if bilirubin >2.0 mg/dL
Upper endoscopy	Every 1 to 3 years if: • Cirrhotic • Mayo risk >4.1 • Transient elastography ≥17 kPa
Ultrasound with or without alpha fetoprotein	Every 6 months if: • Suspected cirrhosis • Male patient

Modified from Lindor 2019.