Primary Biliary Cholangitis

Primary biliary cholangitis, previously known as primary biliary cirrhosis, is a chronic, cholestatic, inflammatory liver disease characterized by destruction of intrahepatic bile ducts resulting in progressive liver damage. The etiology of primary biliary cholangitis is still not fully understood but likely involves both environmental and genetic factors. If symptomatic, patients often present with fatigue and pruritus. About 95% of individuals with primary biliary cholangitis will have a positive anti-mitochondrial antibody. Current treatment options are limited primarily to ursodeoxycholic acid, while those with decompensated liver disease will require liver transplantation. We provide a review of the etiology, pathogenesis, natural history, diagnosis and management of primary biliary cholangitis.

EPIDEMIOLOGY, ETIOLOGY AND PATHOGENESIS

Primary biliary cholangitis (PBC) has an incidence rate of 0.9 to 5.8 per 100,000 people with an estimated female to male ratio of 10 to 1.\(^1,3\) PBC is more common in patients in Northern Europe, the United Kingdom and the northern United States. The prevalence seems to have increased over time, currently ranging from 1.91 to 40.2 per 100,000 people.\(^5\) The increase in prevalence is likely multifactorial with increased disease diagnosis and increased survival with improved treatment.

The etiology of PBC is not fully understood, but both genetic predisposition and environmental triggers likely play an important role. The prevalence of PBC is higher in families with an affected member, indicating a possible genetic component. Approximately 1.2% of children of PBC patients develop PBC, with the highest risk in daughters of women with PBC.\(^4\) Monozygotic twins have a high concordance rate of 0.63 for PBC.\(^5\) Additionally, several studies have shown a link between HLA alleles and PBC.\(^6-9\)

Several studies have shown increased incidence in areas of heavy pollution in both the US and UK, suggesting that environmental toxins may play a role in the development of PBC.\(^10,11\) Furthermore PBC has also been associated with infections, reproductive hormone replacement, hair dyes, nail polish, xenobiotics and tobacco use.\(^4,12,13\)
The hallmark of PBC is the destruction of small bile duct epithelial cells leading to ductopenia and persistent cholestasis. This is believed to be largely mediated by T-cell destruction. Hepatic damage and eventual liver failure results from ongoing retention of toxic substances. It is still unclear as to why biliary epithelial cells in particular are affected. Biliary epithelial cells express T-cell ligands that play a key role in induction of autolysis and may even act as antigen presenting cells, thereby amplifying the immune response. While it is unknown what initially triggers PBC, potential candidates include viral or bacterial infection, xenobiotics and human immunoregulatory defects.

Diagnosis

**Laboratory Markers**

PBC should be considered in patients with an elevated alkaline phosphatase level when other intrahepatic and extrahepatic causes of cholestasis have been excluded (Figure 1). Often abnormal laboratory markers are found incidentally prior to any symptom development. While serum aminotransferases are often elevated, this is not always the case. Total bilirubin may also be normal in early stages of the disease. Serum anti-mitochondrial antibody (AMA) is highly sensitive for PBC, with a positive result in 95% of patients with PBC and less than 1% in non-PBC patients. The targets of the anti-mitochondrial antibody all belong to the 2-oxo-acid dehydrogenase complex enzymes. They function to catalyze oxidative decarboxylation of keto acid substrates in the inner mitochondrial membrane. Approximately 5-10% of patients will have a negative or low titer AMA. In these patients, antibodies to the major M2 components, such as PDC-E2 or 2-oxo-glutaric acid dehydrogenase complex, may be present. Antinuclear antibodies have also been shown to be present in PBC, though the sensitivity is typically around 40-50%. Anti-Sp100 and anti-gp210 have high specificity to PBC and their presence is generally associated with more aggressive disease. Often these are specialized tests that are not readily available, thus AMA should be used as a primary method for screening for PBC.

**Histology**

While liver biopsy can be helpful, in patients with a cholestatic liver profile and positive AMA, a biopsy is not necessary in establishing the diagnosis. A liver biopsy should be obtained when AMA is absent or if there is a mixed biochemical or clinical picture. When pursuing a biopsy, it is important to obtain an adequate sample, as the distribution of bile duct destruction can be patchy. Generally, it is recommended that at least 10-15 portal tracts should be examined to rule out pathology. The characteristic histologic finding in PBC is an inflammatory infiltrate centered around the bile ducts. Infiltrating cells form granulomas consisting of lymphocytes, neutrophils, macrophages and plasma cells. This inflammatory process mainly affects the interlobular and septal bile ducts, sparing the large extrahepatic ducts. The degree of duct deformity can be staged using Ludwig’s staging criteria (Table 1). Stage 1 is described as portal inflammation, with stage 2 described as an extension of this inflammation to the periportal areas. Stage 3 consists of septal fibrosis or inflammatory bridging, and stage 4 is cirrhosis.

**Imaging**

Abdominal imaging should be part of the workup for PBC and should be pursued at the onset of laboratory abnormalities or symptoms. Ultrasound is a cost-effective, non-invasive test for the initial evaluation of liver cirrhosis and has a sensitivity and specificity of about 80%. The use of Doppler can further enhance ultrasound leading to an increased sensitivity of 97% and specificity of 93%. Ultrasound is typically the modality of choice to screen for hepatocellular carcinoma in patients with cirrhosis, typically every 6-12 months. Computer tomography can aid in the exclusion of other etiologies such as mechanical biliary duct obstruction.
as well as help assess for advanced disease such as fibrosis or portal hypertension. Cholangiography may be pursued to exclude other biliary tract diseases such as sclerosing cholangitis. Recently, transient elastography has been utilized to evaluate liver fibrosis and has been found to have over 90% sensitivity and specificity for detecting advanced fibrosis in patients with PBC.\textsuperscript{27-29}

### Natural History

PBC is a progressive cholestatic liver disease that in its end stage can progress to cirrhosis. By clinical stage, PBC can be divided into pre-clinical, asymptomatic, symptomatic and advanced, which correspond to positive AMA only; positive AMA with liver function test abnormalities; the former along with symptoms of pruritus and fatigue; and cirrhosis, respectively (Table 2).\textsuperscript{1} Progression is determined by whether patients undergo treatment and by response to treatment.\textsuperscript{30} Recently a new scoring system has been developed to risk stratify patients with PBC using age and several laboratory markers.\textsuperscript{31} The GLOBE score is calculated as follows: 0.044378 x age at start of UDCS therapy + 0.93982 x bilirubin times the upper limit of normal at 1-year follow-up + 0.335648 x alkaline phosphatase time the upper limit of normal at 1-year follow-up – 0.002581 x platelet counts per 10\textsuperscript{9}/L at 1 year follow-up + 1.21685. The authors found the overall predictive value of the GLOBE score for transplantation or death, calculated via C-statistics, was 0.81 (CI 95%). Without treatment, the 10-year survival is 50-70% for asymptomatic patients and estimated at 5-8 years if symptomatic; liver failure develops in 15-25% of patients within 5 years.\textsuperscript{1} Interestingly, portal hypertension can develop prior to cirrhosis in PBC patients and most commonly manifests with esophageal varices that are present in up to a third of untreated advanced patients. The etiology is unclear but is thought to be due to nodular regeneration.\textsuperscript{1} Thus, screening with endoscopy for esophageal varices should begin prior to development of cirrhosis, with initiation of a non-selective beta-blocker if needed. Initiation of standardized treatment with ursodeoxycholic acid (UDCA) in the 1990s has been shown to delay progression: one trial in France showed 7% vs 34% progression from stage I or II to stage III or IV in the UDCA vs placebo groups.\textsuperscript{32} Nonetheless, improvement in survival has been inconsistently demonstrated.\textsuperscript{33-35} Poor prognostic factors include continued elevated alkaline phosphatase while on UDCA treatment, higher bilirubin levels, low albumin and high IgG levels.\textsuperscript{36} Lack of response to UDCA has also been linked to higher risk of hepatocellular carcinoma once cirrhosis develops.

Other common complications of PBC include...
Uncommon associated conditions include rheumatoid arthritis, which has been estimated to coexist with PBC in 1.8-5.6% of cases and is thought to result from common non-HLA risk loci identified in genome wide association studies.49-53 Notably, this should be distinguished from the more common occurrence of rheumatoid arthritis and liver fibrosis. Systemic lupus erythematosus (SLE) has been identified in 34 patients with PBC, 97% of which were female.54 Rarely, coexisting PBC and primary sclerosing cholangitis occur.55 Finally autoimmune thyroid disease, most frequently Hashimoto’s thyroiditis, has also been linked to PBC.56

**Management**

**Ursodeoxycholic Acid**

Currently UDCA is the only approved therapy for PBC. Several studies have shown that the use of UDCA is associated with improved liver biochemistries.57,58 Furthermore longitudinal studies have shown a survival benefit.33,34,36 While patients with histological evidence of early disease tend to respond better to UDCA, even patients with advanced disease benefit from UDCA.34 UDCA has even been shown to reduce the requirements of liver transplant in patients with PBC.59 Other studies, however, have found no benefit with UDCA.60,61 It is thought that these reviews included data from trials with shorter durations and lower doses of UDCA than what is believed therapeutic. It has become clear that the efficacy of UDCA is dose dependent.

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hyperlipidemia, osteoporosis and vitamin deficiencies. Hyperlipidemia is characterized by a disproportionate increase in HDL, and overall levels can rise enough to cause xanthomas (Figure 2). Patients are not generally treated, as an increased risk of atherosclerotic events has not been demonstrated. Notably though, one meta-analysis did find a higher risk of coronary artery disease (CAD) in PBC patients (OR 1.27) while a similar study by the same author did not find any increased risk of stroke.37,38 Diarrhea and weight loss often occur in PBC patients due to malabsorption of dietary fat.39 Steatorrhea likely occurs due to a decrease in biliary secretion of bile acids. Osteoporosis is a frequent comorbidity, seen in 20-44% of patients with advanced disease; the proposed mechanism is inhibition of osteoblasts through retained bilirubin.40 Osteoporotic patients have normal vitamin D metabolism and are infrequently clinically symptomatic but may be monitored with DEXA scans and treated in the standard method with calcium/vitamin D and/or bisphosphonates. Fat-soluble vitamin deficiencies should be tested once cirrhosis or advanced disease develops and can be managed with supplementation. Late vitamin E deficiency may explain peripheral neuropathy associated with PBC.1

**Associated Disorders**

PBC is strongly associated Sjogren’s disease and autoimmune hepatitis (AIH) and less commonly with other autoimmune diseases. It has been estimated that up to half of PBC patients have a coexistent autoimmune disease.41-43 In particular, PBC-AIH overlap syndrome has been well documented although the exact criteria for diagnosing this disorder have been controversial. The most commonly used diagnostic criteria is the Paris criteria, which specifies that two conditions must be met to support each separate diagnosis (Table 3).44 In prior studies, PBC-AIH has been associated with worse prognosis compared to either individual entity however in the majority of cases patients who did poorly were not treated with dual therapy (i.e., UDCA and corticosteroids or other immunosuppression).45-47 The association with Sjogren’s and less commonly scleroderma and CREST have also been well documented and most commonly result in symptoms of xerostomia and keratoconjunctivitis sicca but also have been associated with esophageal dysmotility. Management is symptomatic with artificial tears, pilocarpine drops, saliva substitutes and adequate dental care.48

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Angulo et al. conducted a randomized trial to compare the efficacy of different doses of UDCA: low dose (5-7mg/kg/day), standard dose (12-15mg/kg/day) and high dose (23-25mg/kg/day). At 1 year follow-up, improvements in aspartate aminotransferase, ursodeoxycholic acid enrichment, alkaline phosphatase, and Mayo risk score were significantly greater in the standard and high-dose groups compared to the low-dose group. There was no significant difference between the standard and high-dose groups. The authors concluded that a dose of 12-15mg/kg/day is likely the preferred dose for the treatment of PBC. Yet another study found that high doses of UDCA did not provide a clinically significant benefit. There is no required dose adjustment for liver or renal disease. However bile acid binding sequesterants, such as cholestyramine and certain antacids, may interfere with UDCA absorption. It is recommended that these medications be administered at separate times to limit potential interactions. Response to UDCA is monitored using liver biochemistries. Normalization of liver biochemistries occur in about 20% of patients in a period of 2 years, with an additional 15% to 35% normalization in 5 years. An estimated 90% of improvement occurs within the first 6-9 months. In addition to improved liver biochemistries, the use of UDCA is associated with reduced histological progression, decreased development of varices, and lower serum low-density lipoprotein cholesterol levels. However it has been shown to be ineffective in treating fatigue, pruritus, bone disease and the autoimmune features of PBC. Currently there are no other agents that have been consistently shown to be effective in the management of PBC, either as monotherapy or in combination therapy with UDCA. Penicillamine, corticosteroids, chlorambucil, mycophenolate, methotrexate, azathioprine, colchicine, cyclosporine and malotilate have failed to show benefit as monotherapy. Combination therapy with UDCA in addition to colchicine, methotrexate or silymarin have not been shown to be better than monotherapy. Patients with decompensated disease will require liver transplant. Cholestatic disease accounted for 8.3% of all adult transplants in 2013, down from 11.1% in 2003. The use of UDCA has likely contributed to a decrease in the number of PBC patients with disease progression requiring transplant. Lee et al. conducted a retrospective study evaluating liver transplants in PBC patients from 1995 to 2006. The authors found that while the average number of total liver transplants increased at a rate of 249 transplants a year, transplants due to PBC decreased at an average rate of 5.4 cases per year, an overall decrease of 20%. The same study also looked at transplant rates of patients with primary sclerosing cholangitis and found no change over the same period. Overall transplantation yields excellent results with 90-95% 1-year patient survival, 1-year graft survival of 88% and 5-year graft survival of 78%. It is recommended that liver transplant referral be initiated at the onset of decompensated liver disease, when total bilirubin is greater than 6 mg/dl or if the Model for End-stage Liver Disease score is 12 or more. Rate of recurrence of PBC in liver transplant recipients is about 25%. As AMA sometimes persists after liver transplantation, liver biopsy is necessary for the definitive diagnosis of PBC recurrence post transplantation. There is some evidence that prophylactic UDCA after liver transplantation

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<tr>
<th>Primary Biliary Cholangitis</th>
<th>Autoimmune Hepatitis</th>
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<tr>
<td>Serum alkaline phosphatase (ALP) level 2 fold greater than upper limit of normal or serum gamma-glutamyltransferase level 5-fold greater than upper limit of normal</td>
<td>Serum alanine aminotransferase level 5-fold greater than upper limit of normal</td>
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<tr>
<td>Positive test for anti-mitochondrial antibody</td>
<td>IgG level 2-fold greater than upper limit of normal or a positive test for anti-smooth muscle antibody</td>
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<tr>
<td>Liver biopsy specimen showing floribdile duct lesions</td>
<td>Liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis</td>
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might reduce the risk of recurrence.35

**Symptom Management**

Fatigue is a common symptom experienced by PBC patients. Unfortunately, there is no current recommendation in regards to managing fatigue. UDCA has not been shown to be effective. Other medications used to manage fatigue of chronic liver disease such as ondansetron and fluoxetine have also not been shown to be effective.36,37 Many PBC patients complain of excessive daytime sleepiness and there is a strong association with fatigue and altered sleep.38 Modafinil, a medication used to mitigate daytime somnolence associated with shift work, has been shown to have some beneficial impact in treating fatigue in PBC patients.89

Pruritus is another common symptom experienced by PBC patients. UDCA is not effective in managing pruritus. Cholestyramine is effective in alleviating pruritus at doses of 4g/day with a max dose of 16g/day.90,91 As mentioned earlier, it is important to separate the administration of bile acid binding sequestrants and UDCA as the interaction can decrease the absorption of UDCA. A separation of at least 2-4 hours is recommended.1 Rifampicin has also been shown to be effective in the management of pruritus.92-95 Current guidelines recommend a dose of 150mg daily for bilirubin less than 3mg/dL and 150mg twice daily if the bilirubin is greater.1 Chronic use of rifampicin has been associated with serious side effects such as hepatic or renal injury and hemolysis. Furthermore rifampicin has been shown to decrease the effectiveness of serotonin reuptake inhibition leading to serotonin withdrawal syndrome.96 Close monitoring of liver function and blood counts is recommended for any patient on rifampicin.1 Opiate antagonists, such as naltrexone, have also been shown to ameliorate pruritus.97

**CONCLUSION**

Primary biliary cholangitis is a chronic progressive cholestatic disease that results in autoimmune mediated hepatic damage. Patients present with non-specific symptoms of fatigue and pruritus. Positive AMA is a hallmark of PBC. PBC is often associated with other autoimmune mediated disease such as Sjogren’s disease and autoimmune hepatitis. Common complications of PBC include hyperlipidemia, osteoporosis, and vitamin deficiencies. Treatment is primarily UDCA with strong data supporting benefits in mortality and progression of disease, especially when initiated early. Patients with advanced disease can develop cirrhosis and its complications such as ascites and varices. These patients often require liver transplantation. Further research is needed to better understand the etiology and pathogenesis in order to develop additional management strategies.

**References**

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