Citation: Clinical and Translational Gastroenterology (2015) 6, e109; doi:10.1038/ctg.2015.33

www.nature.com/ctg

CLINICAL/NARRATIVE REVIEW

# Current Concepts in Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

Seth N. Sclair, MD[1], Ester Little, MD[2] and Cynthia Levy, MD[1]

**Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are chronic, cholestatic diseases of the liver with common clinical manifestations. Early diagnosis and treatment of PBC slows progression and decreases the need for transplant. However, one-third of patients will progress regardless of treatment. Bilirubin <1.0 and alkaline phosphatase <2.0 x the upper limit of normal at 1 year after treatment appear to predict 10-year survival. Ursodeoxycholic acid (UDCA) is the recommended treatment for PBC, and recent studies with obeticholic acid showed promising results for UDCA non-responders. Unlike PBC, no therapy has been shown to alter the natural history of PSC. The recommended initial diagnostic test for PSC is magnetic resonance cholangiopancreatography, typically showing bile duct wall thickening, focal bile duct dilatation, and saccular dilatation of the intra- and/or extrahepatic bile ducts. Immunoglobulin 4-associated cholangitis must be excluded when considering the diagnosis of PSC, to allow for proper treatment, and monitoring of disease progression. In addition to the lack of therapy, PSC is a pre-malignant condition and close surveillance is indicated.**

*Clinical and Translational Gastroenterology* (2015) **6,** e109; doi:10.1038/ctg.2015.33; published online 27 August 2015
**Subject Category:** Clinical Review

## INTRODUCTION

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are the two most common chronic cholestatic liver diseases. The prevalence of PBC ranges between 1.9 and 40.2 per 100,000 inhabitants, and may be rising, whereas the prevalence of PSC is as high as 16.2 per 100,000 inhabitants.

Other chronic cholestatic diseases including immunoglobulin 4-related disease, secondary sclerosing cholangitis of the critically ill, and idiopathic adulthood ductopenia are much rarer. Population-based studies are not available to determine their actual incidence or prevalence, and these entities are usually reported as case series. Idiopathic adulthood ductopenia, for instance, is usually described as a case report, with <100 cases in the literature.

This review will focus on the diagnosis and management of PBC and PSC. Notably, older "variant" syndromes of autoimmune cholangitis and pericholangitis have been re-classified as anti-mitochondrial antibody–negative PBC and small duct PSC, respectively, and will be discussed below.

## PRIMARY BILIARY CIRRHOSIS

**Diagnosis.** PBC is an autoimmune liver disease affecting mostly middle-aged women, manifesting clinically with symptoms of fatigue and pruritus in the context of chronically elevated alkaline phosphatase (ALP) levels. Liver histology is characterized by lymphocytic cholangiopathy of the small to medium-sized bile ducts (non-suppurative destructive cholangitis) and ductopenia.[1–3] In its classic presentation, such cholangitis becomes very exuberant, leading to formation of a granulomatous reaction named the "florid duct lesion" Figure 1. The hallmark serologic feature is the presence of anti-mitochondrial antibodies in >90% of cases.[4] Antinuclear antibodies are also commonly present in PBC with some of the antinuclear antibody subtypes being specific for PBC Table 1. These PBC-specific antinuclear antibodies can aid in the diagnosis of anti-mitochondrial antibody–negative PBC, and can provide prognostic information.

In the asymptomatic patient, PBC is suspected in the setting of chronic unexplained elevation of serum ALP, whereas symptomatic individuals may present with pruritus, fatigue, or complications of advanced liver disease. Disease progression results in the development of biliary cirrhosis and portal hypertension with some patients requiring liver transplantation.[2–4]

The incidence of PBC ranges between 0.33 and 5.8 per 100,000 per year, with prevalence rates of 1.91 to 40.2 per 100,000 in a systematic review.[5] However, three studies with rigorous methodology for diagnosis from the United States, United Kingdom and Iceland have reported higher prevalence rates ranging from 38.3 to 40.3 per 100,000, which are more representative of the true prevalence of the disease.[2]

**Natural history.** Disease progression occurs over many decades but varies from patient to patient. Before therapy with ursodeoxycholic acid (UDCA), patients with PBC had diminished survival compared with the general population. In

[1]Schiff Center for Liver Diseases, University of Miami Miller School of Medicine, Miami, Florida, USA and [2]Banner University Medical Center, Phoenix, Arizona, USA
Correspondence: Cynthia Levy, MD, Schiff Center for Liver Diseases, University of Miami Miller School of Medicine, 1500 NW 12th Avenue, Suite 1115, Miami, Florida 33136, USA. E-mail: clevy@med.miami.edu
Received 2 April 2015; accepted 23 July 2015

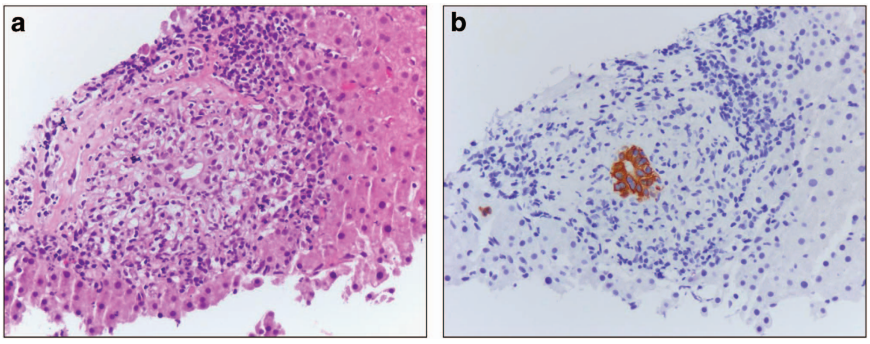


**Figure 1** Liver histology in primary biliary cirrhosis (PBC). (**a**) Photomicrograph of an hematoxylin and eosin (H & E) stain (x200 magnification) from a percutaneous liver biopsy demonstrating a classic florid duct lesion in a patient with PBC. (**b**) Immunostaining of the portal tract in **a** with anti-cytokeratin-7 highlighting the bile duct that is infiltrated with lymphocytes. Courtesy of Nilesh Kashikar MD, PhD (University of Miami).

**Table 1** Prevalence of ANA subtypes in PBC and clinical correlations

| ANA autoantibodies | Prevalence | Clinical correlation | References |
|---|---|---|---|
| Anti-gp210 | 22.2–26.2% | Associated with hepatic failure; increase sensitivity and specificity in diagnosis | 121–123 |
| Anti-centromere | 12.6–26.1% | Associated with portal hypertension, and hepatic failure | 121,124,125 |
| Anti-sp100 | 8.7–21.6% | Not associated with hepatic failure; increase sensitivity and specificity in diagnosis | 121 |
| Anti-chromatin | 5.4–25% | Not associated with hepatic failure | 121,125 |
| MIT3[a] | 82.2% | No correlation | 121 |
| Anti-kelch-like 12 | 16–40% | Increase sensitivity and specificity in diagnosis, particularly in AMA-negative PBC | 126 |
| Anti-hexokinase 1 | 16–45% | Increase sensitivity and specificity in diagnosis, particularly in AMA-negative PBC | 126 |

AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; PBC, primary biliary cirrhosis.
[a]MIT3: mitochondrial antigens (recombinant proteins containing PDC-E2, BCOADC-E2, OGDC-E2).

a study from England with 770 patients (all diagnosed with PBC before 1994), the risk of developing decompensated liver disease over 5 years was 15%.[6] As more patients are now diagnosed earlier and treated with UDCA, the progression of liver disease is slower. Consistent with this change in natural history is the decreasing number of liver transplants performed for PBC in North America and Europe.[7,8]

One of every three patients with PBC treated with UDCA will fail treatment, and approximately 10% of these patients will progress to liver failure. Although several sets of criteria have been developed to evaluate response to treatment with UDCA, none is able to perfectly distinguish patients who are likely to progress from those with stable, non-progressive disease.[9–13] The Global PBC Study Group, a consortium of 15 North American and European centers, recently reported that serum levels of ALP and bilirubin followed annually correlated with important clinical outcomes. At 1-year of follow-up, ALP levels $<2.0$ x upper limit of normal (ULN) best predicted patient outcomes (c-statistic 0.71): those patients with $<2.0$ x ULN had an 84% 10-year survival compared with a 62% survival in those with serum ALP levels $\geq 2.0$ x ULN at 1 year. Further, bilirubin $\geq 1.0$ x ULN best predicted patient outcomes: those with bilirubin $<1.0$ x ULN had a 10-year survival of 86%, whereas those with bilirubin $\geq 1.0$ x ULN had a 41% survival ($P<0.001$). Combining ALP and bilirubin levels at these cutoffs predicted outcomes even better. These results remained significant in multiple sensitivity analyses even controlling for treatment with UDCA.[14] This landmark study importantly correlates hard clinical outcomes with surrogate markers of ALP and bilirubin levels, which is useful clinically in assessing prognosis and response to therapy and will allow future clinical trials to use bilirubin and ALP levels as end points.

## Management

*Ursodeoxycholic acid.* UDCA is the only drug approved by the United States Food and Drug Administration for the treatment of PBC. UDCA has multiple proposed mechanisms of action, including competitive inhibition of ileal absorption of hydrophobic bile acids and enrichment of the bile acid pool with less toxic, hydrophilic bile acids, and the stabilization of hepatocyte membranes. UDCA also has choleretic, anti-apoptotic, anti-inflammatory, and immunomodulatory actions.[15,16] Optimal dosing is 13–15 mg/kg, and a reduction in serum ALP is seen as early as 2–3 weeks after initiating therapy. Retrospective studies demonstrate that responders to UDCA will have a long-term survival approaching that of age- and gender-matched controls, whereas non-responders are at risk for progressive liver disease. However, long-term rigorous placebo-controlled studies have not been able to clearly demonstrate the benefit of UDCA on hard clinical outcomes.[1,17,18]

*Fibrates.* There is a growing literature regarding the use of fibric acid derivatives in the treatment of PBC. Fibrates are used primarily in the treatment of hypercholesterolemia and have incidentally showed decreases in liver biochemistry profiles.[4] The proposed mechanism is through activation of the peroxisome proliferator-activated receptor alpha pathway,

with modulation of bile acid synthesis and improved choleresis.[19] Several small studies from Japan, Israel, Europe, and the United States indicate that patients with PBC treated with fibrates improve serum ALP, along with other liver biochemistries and serum IgM levels. The only US study included 20 patients with incomplete response to UDCA, treated with fenofibrate 160 mg/day for 48 weeks; 55% patients had $\geq$40% reduction or normalization in ALP levels.[20] Similarly, a recent study from Spain included 30 patients with incomplete response and treated with bezafibrate 400 mg/day; 70% had biochemical response.[21]

Recently, an unblinded trial from Japan[22] randomized 27 patients to bezafibrate+UDCA ($n=13$) or UDCA alone ($n=14$). At the end of 8 years, mean ALP levels were 290 IU/l in the bezafibrate+UDCA group compared with 461 IU/l in the UDCA alone group ($P<0.05$). The Mayo PBC risk score, a validated model that predicts survival in PBC using the following clinical parameters are as follows: age, bilirubin, albumin, prothrombin time, and the presence of edema and usage of diuretics (http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/updated-natural-history-model-for-primary-biliary-cirrhosis); was evaluated as a secondary end point in the study and was lower in the bezafibrate+UDCA group (0.91 vs. 1.42, $P<0.05$). However, total bilirubin, albumin, aspartate aminotransferase, and alanine aminotransferase did not differ between the groups at the end of the study and there was an unexplained trend toward increased mortality in the bezafibrate combination group.

A systematic review summarizing fenofibrate as adjunct therapy in PBC reported a complete response rate of 69% (with an odds ratio of 82.8, 95% confidence interval 21.6–317.2 representing the odds of achieving a complete response after adding a fenofibrate).[23] The long-term effect of fibrates in PBC needs to be further evaluated before its recommendation in clinical practice.

*Budesonide.* Budesonide is a non-halogenated glucocorticoid absorbed in the small bowel with 90% hepatic first pass metabolism and potent glucocorticoid receptor-binding activity.[4] Two randomized controlled trials[24,25] and a third non-randomized, pilot study[26] have evaluated the combination of budesonide and UDCA on outcomes in PBC. Both randomized controlled studies showed a greater reduction in serum ALP and improved histology (grade and stage) in the budesonide+UDCA groups, whereas the UDCA alone group had histologic deterioration. In the non-randomized pilot study,[26] investigators noted a very modest effect on ALP level (21% reduction) and an increase in the Mayo PBC risk score, suggesting progression of disease. Side effects of budesonide in all three studies included mild glucocorticoid effects. Cirrhotics were not included in the randomized trials as pharmacokinetic studies suggested altered metabolism and a risk of portal vein thrombosis.[27] Thus, with few exceptions, use of budesonide is probably better reserved for patients with overlap syndrome with autoimmune hepatitis.

*Obeticholic acid.* Obeticholic acid is a derivative of chenodeoxycholic acid and a ligand and potent activator of farnesoid X receptor. Farnesoid X receptor regulates bile acid production and has both anti-inflammatory and anti-fibrotic properties.[1,4] A recent study reported on the efficacy of obeticholic acid in patients with inadequate response to UDCA.[28] This was a multicenter, randomized, placebo-controlled trial including 165 patients studying the efficacy of obeticholic acid at doses of 10, 25, 50 mg vs. placebo over a 3-month period. Primary end points of decrease in ALP levels were met, with reductions of 21–25% from baseline compared with 3% reduction in the placebo arm, $P<0.0001$. In an open-label extension of the study with 78 patients, the improvement in ALP was sustained. Pruritus was the most common adverse event, which was dose related and as high as 85% in the 25 mg arm. However, the prevalence of pruritus in the 10 mg arm was comparable to that of placebo (47% vs. 50%). Preliminary results from a recent follow-up study evaluating a lower starting dose of 5 mg/day, with titration up to 10 mg/day, seem to indicate similar efficacy and less itching.[29,30]

**Assessment of disease progression: cirrhosis, portal hypertension, and hepatocellular carcinoma (HCC)**

*Transient elastography.* Data on fibrosis quantification with transient elastography (i.e., Fibroscan) in PBC and other cholestatic liver diseases are scarce. In an initial study, Corpechot *et al.*[31] examined the performance of Fibroscan in patients with PBC and PSC; it included 69 patients with PBC who underwent paired Fibroscan measurements and liver biopsy. The area under the receiver operating characteristics were 0.92, 0.95, and 0.96 for $\geq$F2, $\geq$F3, and F4, respectively. Optimal liver stiffness values for F2, F3, and cirrhosis (F4) were 7.3, 9.8, and 17.3 kPa, respectively. In a second study by the same authors,[32] Fibroscan was performed serially on a cohort of 150 PBC patients treated with UDCA and liver stiffness measurement were correlated with survival. Area under the receiver operating characteristics for F1–F4 were 0.80, 91, 0.95, and 0.99, respectively, with the following cutoffs: 7.1, 8.8, 10.7, and 16.9 kPa, for F1–F4. The overall progression rate was $0.48 \pm 0.21$ kPa per year, but was more rapid in cirrhotics ($4.06 \pm 0.72$ kPa per year). Importantly, an increase of 2.1 kPa per year was associated with an 8.4-fold increase of liver decompensation and death. This latter study provides evidence for the use of non-invasive elastography technologies for the assessment of disease progression and response to therapy in patients with established PBC. A recent review on Fibroscan suggests a cutoff of 17.9 kPa to diagnosis cirrhosis in biliary liver diseases.[33]

*Esophageal varices in PBC.* Screening for esophageal varices is the current practice in patients with cirrhosis of any etiology.[34] However, liver biopsies are not done routinely in PBC, and complications of portal hypertension can precede the histologic development of cirrhosis because of portal venous compression, perisinusoidal fibrosis, and nodular regenerative hyperplasia.[17] In an original longitudinal study of 256 PBC patients, 31% developed esophageal varices over a median of 5.6 years and the corresponding 3-year survival rate was diminished in those who developed varices (59%).[35] In a more recent cohort study from two US centers, 37% of 91 patients with PBC who underwent screening endoscopy were found to have esophageal varices and an even higher percentage (47%) in the cross-validation group. Independent

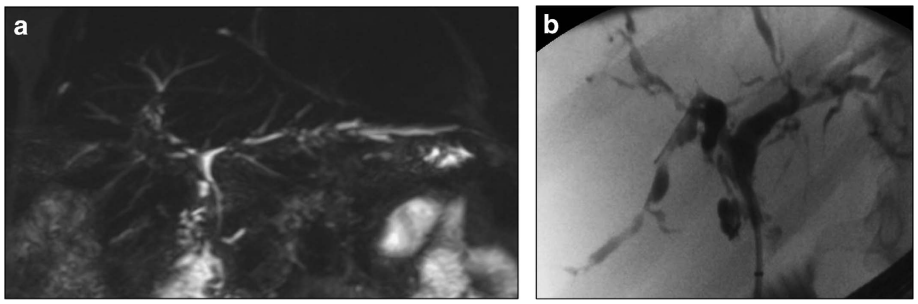


**Figure 2** Cholangiograms in PSC. (**a**) Cholangiogram from MRCP. (**b**) Cholangiogram from ERCP. Legend: 41-year-old female diagnosed with PSC 1 year prior, presenting with marked cholestasis and elevation of her liver chemistries who underwent MRCP showing beading and stricturing of the intrahepatic left ductal system and a dominant stricture in the right main hepatic duct. ERCP confirmed these findings, and the right hepatic duct was dilated. Brushings were negative for malignancy and FISH was negative for polysomy. Photos: courtesy of Enrico Souto, MD (University of Miami). ERCP, endoscopic retrograde cholangiopancreatography; FISH, fluorescence *in situ* hybridization; MRCP, magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis.

risk factors for the presence of esophageal varices were platelet count $<140{,}000$ and a Mayo PBC risk score $\geq 4.5$.[36] *Risk of HCC in PBC.* The Global PBC Study Group recently reported on the risk of HCC in PBC.[37] In this well-characterized cohort of 4,565 patients, there were 123 incident cases of HCC in 36,577 patient-years of follow-up (with an actuarial incidence rate of 3.4 cases per 1000 patient-years). Male gender, advanced biochemical disease, and thrombocytopenia at diagnosis represented factors associated with baseline future risk of HCC, consistent with prior studies.[38–41] UDCA therapy does not appear to affect or modulate the risk of HCC. However, those classified as biochemical non-responders (irrespective of therapy) were at increased risk to develop HCC and this was the most important independent risk factor in predicting HCC risk.

## PRIMARY SCLEROSING CHOLANGITIS

PSC is a rare chronic, cholestatic liver disease characterized by inflammation and fibrosis of the intra- and/or extrahepatic bile ducts. It leads to bile duct obstruction, biliary cirrhosis, and portal hypertension, ultimately causing liver failure.[40,42] PSC is closely associated with inflammatory bowel disease, present in 60-80% of patients. Conversely, the prevalence of PSC in patients with ulcerative colitis varies from 2.4 to 7.5%. Although ulcerative colitis affects both sexes equally, in PSC the male to female ratio is 2:1. The mean age at the time of the diagnosis is 40.[43–56]

The pathogenesis of PSC remains largely unknown. In addition to genetic predisposition, abnormalities of the gut–liver axis and bile toxicity are believed to have a role. This topic has been extensively reviewed elsewhere.[57–64] In this brief review, we will focus on diagnosis, treatment, and cancer surveillance in PSC.

**Diagnosis.** Fifteen to 40% of patients who have PSC are asymptomatic at diagnosis.[50,65] When present, the most common symptoms are fatigue, pruritus, and abdominal pain. As a result of the transient biliary obstruction seen in PSC, ascending cholangitis can be the first manifestation of the disease. Laboratory abnormalities in PSC are nonspecific. Elevated serum ALP at 3–10 x ULN is the most common finding. However, ALP can be normal or near normal. Biliary sludge and small stones may cause transient blockage and fluctuation in the levels of ALP and bilirubin. The aminotransferases are typically $<300$ IU/ml; albumin is normal in the early stages except in those with severe inflammatory bowel disease.[49,66,67]

Hypergamaglobulinemia, elevated immunoglobulin G and autoantibodies (perinuclear anti-neutrophil cytoplasmic antibodies, antinuclear antibodies, anti-smooth muscle antibodies, anti-cardiolipine, thyroperoxidase, and rheumatoid factor) are seen in 20 to 80% of patients with PSC.[68] These findings lack clinical correlation and do not have significant sensitivity or specificity. Anti-mitochondrial antibody is usually absent in PSC.[69]

Cross-sectional imaging may show bile duct wall thickening, focal bile duct dilatation, and saccular dilatation of the intrahepatic bile ducts.[67] Cholangiography is diagnostic and may be obtained using magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography. The images show short, annular strictures alternating with normal or mildly dilated segments of bile ducts conferring the classic beaded appearance Figure 2. As a result of its non-invasive characteristic and comparable accuracy, both American Association for the Study of Liver Diseases and European Association for the Study of the Liver recommend magnetic resonance cholangiopancreatography as first-line imaging.[67,70]

On histology, features of PSC include bile duct proliferation, periductular fibrosis, periductular inflammation, and bile duct obliteration. Mononuclear and polymorphonuclear cells infiltrate may be present. The most characteristic fibro-obliterative lesion (onion skinning) is seen in $<40\%$ of biopsy specimens.[71] Liver biopsy is not necessary for all patients with PSC, but it is invaluable to diagnose two special subsets of patients with PSC: small duct PSC and overlap with autoimmune hepatitis.

Patients with small duct PSC are characterized by having clinical, laboratory, and histological characteristics typical of PSC, but normal cholangiography. This subgroup comprises 6–16% of all PSC patients. Compared with those with classic PSC, patients with small duct PSC have slower rate of progression, better survival, and fewer require liver transplant or develop cholangiocarcinoma (CCA). However, about 20%

of these patients progress to large duct PSC over a median period of 7.4 years.[72–77]

Biopsy is also indicated to diagnose overlap of PSC and autoimmune hepatitis, seen mostly in children and young adults, with prevalence between 8 and 49%.[77,78] Importantly, this subgroup of patients may benefit from treatment with steroids.

**Differential diagnosis.** Secondary causes of sclerosing cholangitis must be excluded before establishing the diagnosis of PSC Box 1. One of the most important entities in the differential diagnosis of PSC is immunoglobulin 4-associated cholangitis or immunoglobulin 4-related sclerosing cholangitis. Both American Association for the Study of Liver Diseases and European Association for the Study of the Liver recommend checking immunoglobulin 4 levels in all patients with suspected PSC. Immunoglobulin 4-associated cholangitis is the biliary manifestation of a separate systemic disease: immunoglobulin 4-related disease. A cardinal feature of immunoglobulin 4-related disease is single or multiple organs' swelling raising suspicion for malignancy. The diagnosis is based on histological, imaging, and serological features, none of which is pathognomonic. Differentiation of PSC from immunoglobulin 4-associated cholangitis can be extremely challenging, but it is also crucial to allow for proper treatment and monitoring of disease progression. Importantly, approximately 10% of patients with PSC have elevated serum immunoglobulin 4 levels without meeting criteria for immunoglobulin 4-associated cholangitis. These patients appear to have a more aggressive disease course.[79,80] Table 2 summarizes the similarities and differences between the two diseases.[81–86]

**Treatment.** No medical therapy has been shown to prolong survival free of liver transplantation in patients with PSC. Although evidence is not as robust as it is for PBC, serum ALP is also resurfacing as a prognostic marker in PSC irrespective of treatment. Patients whose ALP remains persistently below 1.5 x ULN appear to have a better prognosis.[87–89] Whether serum ALP can be used as a reliable surrogate marker for long-term outcomes in PSC remains to be determined. Nevertheless, many of the studies below used serum ALP as a marker of response.

*Ursodeoxycholic acid.* UDCA is the most extensively studied therapy for PSC. Multiple mechanisms of action have been proposed to justify its use in PSC, including its cytoprotective effect against apoptosis, anti-oxidant and choleretic properties, and immunomodulatory actions.[90]

Studies using 13 to 15 mg/kg/day of UDCA showed improvement in the biochemical liver abnormalities but no survival benefit or delay in the need for liver transplant.[91] A randomized study of placebo or UDCA 17–23 mg/kg/day with a 5-year follow-up showed improved serum liver biochemistries but no survival benefit, although the study was not properly powered for such analysis.[92] As a result of some benefit seen in pilot studies, a multicentric, randomized, double-blind controlled trial of 150 patients using UDCA dose of 28–30 mg/kg/day was designed and subsequently interrupted prematurely because patients assigned to the high-dose UDCA arm were two times more likely to reach one of the

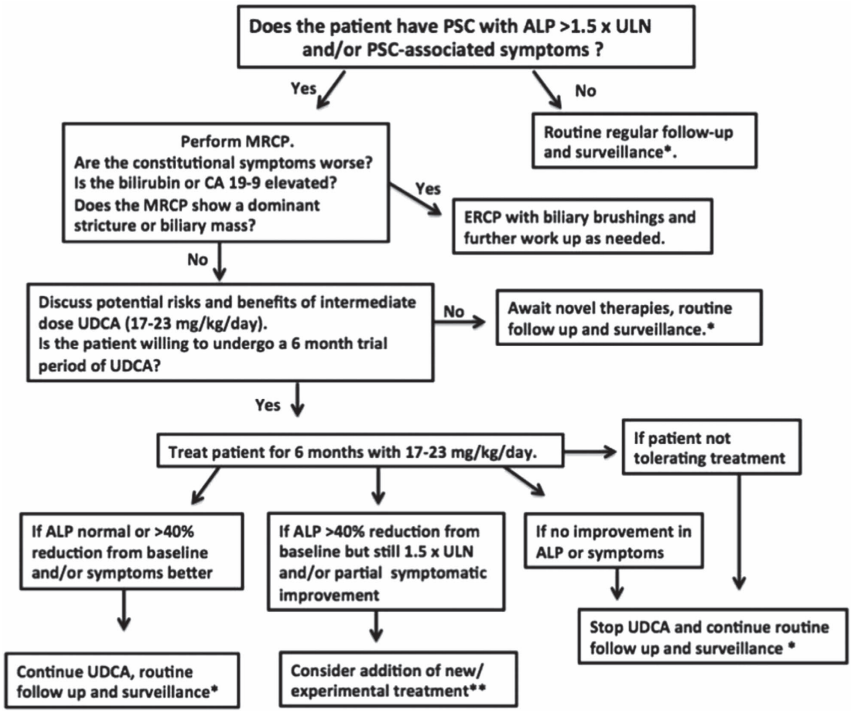


**Figure 3** Proposed algorithm for UDCA use in clinical practice. Modified from ref. 96. *Surveillance and management options reviewed on cancer surveillance section. **Referral to cholestatic liver disease specialist and/or tertiary care center for consultation may be advisable. CA 19-9, carbohydrate antigen 19-9; MRCP, magnetic resonance cholangiopancreatography.

**Box 1 Causes of secondary sclerosing cholangitis**

AIDS-associated cholangiopathy

Cholangiocarcinoma

Choledocholithiasis

Diffuse intrahepatic metastasis

Eosinophilic cholangitis

Hepatic inflammatory pseudo tumor

Histiocytosis X

IgG4-associated cholangitis

Intra-arterial chemotherapy

Ischemic cholangitis

Mast cell cholangiopathy

Portal hypertensive biliopathy

Recurrent pancreatitis

Recurrent pyogenic cholangitis

Surgical biliary trauma

study end points of death, need for liver transplant, or development of serious adverse events including CCA.[93] These results led the American Association for the Study of Liver Diseases to issue recommendations against using UDCA for patients with PSC, whereas European Association for the Study of the Liver suggests that there may be a selected group of patients who can benefit from UDCA.

Adding to the UDCA controversy, a recent study evaluating the effect of UDCA withdrawal showed that discontinuation of UDCA in patients with PSC caused significant deterioration in liver biochemistry.[94] The accompanying editorial by Tabibian and Lindor[95] suggested that perhaps until a safe and more effective treatment becomes available there may be a role for judicious use of UDCA in patients with well-compensated disease. The authors propose an individualized stepwise approach, exemplified in Figure 3.

*Immunosuppression.* Several immunosuppressive drugs have been studied in PSC, but none was found to prolong survival or time for transplantation and most had serious adverse effects.[67] To date, there is no indication for the use of immunosuppressant agents to treat PSC, except perhaps for patients with overlap PSC/autoimmune hepatitis and those with PSC and high immunoglobulin 4 serum levels.

*Antibiotics.* Several antibiotics have been used for the treatment of PSC, including minocycline, tetracycline, metronidazole, azithromycin, and vancomycin, with or without UDCA. Some of the studies showed improvement in the liver chemistries, but there is no long-term data and the number of patients was relatively small. A recent prospective clinical trial with rifaximin for patients with PSC failed to show biochemical improvement.[96]

**Table 2** Similarities and differences between PSC and IAC

| Disease process | PSC | IAC |
|---|---|---|
| Age at onset | 40 | 60 to 80 |
| Gender predominance | Male | Male |
| Cholestatic liver chemistry | Yes | Yes |
| Elevated serum IgG 4 | In 9 to 27% of patients | In all patients |
| IgG-4/IgG-1 ratio[a] | $< 0.24$ | $> 0.24$ |
| Cholangiographic features | Segmental strictures with proximal dilatation and sacculation of the bile ducts with beaded appearance | One or more strictures involving intrahepatic, proximal extrahepatic, or intrapancreatic bile ducts. Fleeting/migrating biliary strictures |
| Histopathologic features | Bile duct proliferation, periductal fibrosis with typical "onion skinning" lesions, periductular inflammation, and bile duct obliteration | Mixed lymphoplasmacytic infiltrate with $>10$ IgG-4-positive cells/h.p.f., storiform fibrosis, and obliterative phlebitis |
| Association with autoimmune pancreatitis | No | Yes |
| Association with IBD | Yes | No |
| Association with cholangiocarcinoma | Yes | No |
| Improvement in liver chemistry with UDCA | Yes | No |
| Improvement in liver chemistry corticosteroids | No | Yes |
| Progression to cirrhosis | Yes | No |

h.p.f., high-power field; IAC, immunoglobulin 4-associated cholangitis; IBD, inflammatory bowel disease; IgG 4, immunoglobulin 4; PSC, primary sclerosing cholangitis; UDCA, rsodeoxycholic acid.
[a]From reference Boonstra *et al.*,[86] this data needs to be externally validated.

**Table 3** Current recommendations for cancer surveillance in patients with PSC

| Type of cancer | Recommendation |
|---|---|
| Cholangiocarcinoma | Ideally, MRI/MRCP with CA 19.9 yearly |
| Gallbladder carcinoma | No additional surveillance as patient are already undergoing cross-sectional imaging annually. Polyps larger than 0.8 cm constitute indication for cholecystectomy |
| Hepatocellular carcinoma | U/S every 6 months for those with cirrhosis (as in other causes of cirrhosis)—may alternate with the annual MRI done for CCA surveillance |
| Colorectal carcinoma in patients with concomitant IBD | Colonoscopy at diagnosis of PSC and every 1–2 years thereafter |

CA 19.9, carbohydrate antigen 19.9; CCA, cholangiocarcinoma; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis.

In another recent study, Tabibian *et al.*[97] randomized patients with PSC to vancomycin and metronidazole; each group was divided in low and high dose. Only patients in the vancomycin groups showed improvement in serum ALP at 12 weeks, the primary end point for the study. The Mayo PSC risk score, a validated model that predicts overall survival in patients with PSC using the following clinical data are as follows: age, bilirubin, aspartate aminotransferase, and history of variceal hemorrhage (www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/revised-natural-history-model-for-primary-sclerosing-chonalgitis); improved in the low-dose metronidazole and vancomycin groups, and pruritus improved in the high-dose metronidazole group. In a study with 14 children, treatment with oral vancomycin led to improvement in serum liver biochemistries and an increase in regulatory T cells. However, the immunological benefits were not always sustained after treatment was discontinued.[98,99]

### Other therapy

*Fibrates.* As discussed earlier, fibrates can reduce bile acid synthesis and promote choleresis through activation of peroxisome proliferator-activated receptors alpha. Two pilot studies evaluating the use of fibrates in patients with PSC showed a significant decrease in serum ALP. However, in both studies the number of patients was small.[100,101]

*Docosahexaenoic acid.* Cystic fibrosis transmembrane receptor dysfunction has been noted in patients with PSC, associated with changes in fatty acids and a decrease in docosahexaenoic acid levels. Correction of these abnormalities in animal studies led to reversal of bile duct injury. A small trial of 23 patients with PSC treated with docosahexaenoic acid showed correction of fatty acids levels, but only 22% of patients had a clinically significant reduction of serum ALP.[102] Further studies are warranted.

*All-trans retinoic acid.* All-trans retinoic acid is a potent inhibitor of bile acids in humans. In a recent study, 15 patients with PSC completed 12 weeks of combination treatment with all-trans retinoic acid and UDCA. Investigators observed a decrease in serum ALP, alanine aminotransferase and bile acids at the expense of frequent adverse events (headache and tinnitus); additional studies with a lower dose of all-trans retinoic acid are awaited.[103]

**Dominant strictures and cancer risk in PSC.** A dominant stricture, defined as an area of stenosis with diameter $<1.5$ mm in the common bile duct or $<1$ mm in the hepatic duct, is seen in up to 45% of patients with PSC at the time of diagnosis.[104] In addition, late dominant strictures can develop in 40–50% of patients with PSC followed over time.[89,105,106] Patients with PSC presenting with symptoms such as cholangitis, jaundice, pruritus, right upper quadrant abdominal pain, or worsening liver biochemistries, as well as those with a dominant stricture found incidentally on cross-sectional imaging, should be further evaluated with an endoscopic retrograde cholangiopancreatography. Endoscopic dilatation of a dominant stricture improves clinical symptoms and may improve prognosis.[107–109] Stent placement can lead to more complications of cholangitis than dilatation alone, but short-term use of stents may be helpful in patients with a severe stricture. Antibiotic prophylaxis post-procedure is recommended to prevent cholangitis.[107] The percutaneous approach carries increased morbidity and should be used only if the stricture is proximal, if there is altered anatomy, or if endoscopic retrograde cholangiopancreatography is not successful.[107] Surgical reconstruction with biliary-enteric drainage improves symptoms of obstruction but increases the risk of cholangitis and mortality. In addition, surgery promotes scaring that can interfere with a future liver transplant. Thus, surgical procedures are rarely used in clinical practice.[110]

An elevated carbohydrate antigen 19.9 is concerning for CCA,[111,112] however, an elevated carbohydrate antigen 19.9 is not a specific test to detect CCA and thus alone cannot be used to differentiate a malignant from a benign stricture.[113] All patients with a dominant stricture need to be evaluated for CCA with biopsy, if feasible, and brushings of the bile duct for cytology. Brushing cytology has a high specificity but low sensitivity and adding fluorescent *in situ* hybridization to routine cytology increases the sensitivity to 64%. The presence of polysomy on two sequential specimens has shown to increase the positive predictive value of fluorescent *in situ* hybridization to 69%.[114] Similarly, the finding of multifocal polysomy is associated with CCA: patients with multifocal polysomy compared with negative fluorescent *in situ* hybridization were found to have a hazard ratio of 82 of developing CCA, (95% confidence interval 24.5–277.3).[115]

In a Swedish cohort of 604 patients with PSC, the incidence of intra- and extrahepatic cancer was 13, and 37% of these cancers were diagnosed within a year of the diagnosis of PSC.[5,116] Specifically, the risk of hepatobiliary malignancies was 161 times that of the general population. In patients with concomitant inflammatory bowel disease, the risk of colorectal malignancy was 10 times that of the general

population. In spite of this, the currently available guidelines are not uniform in their recommendations for cancer surveillance in pts with PSC.[67,70,117] Table 3 depicts practical recommendations for cancer surveillance in patients with PSC.

The overall prognosis of CCA is poor, however, a multicenter study from 2012 showed a 72% 5-year survival free of cancer for patients with early-stage perihilar CCA who underwent neoadjuvant chemoradiation followed by liver transplant. Early detection of PSC is important in order to offer this subset of patients a chance of curative treatment.[118]

Liver transplantation is the definitive treatment for patients with PSC who develop decompensated cirrhosis, with a 5-year survival of 80 to 85%.[114,119] In special circumstances, a model for end-stage liver disease exception may apply, pending approval by the United Network of Organ Sharing regional review board: recurrent episodes of cholangitis, intractable pruritus, and perihilar CCA $<3$ cm without evidence of metastasis are the current criteria.[107] Recurrence of PSC after liver transplantation is seen in 20% of patients 5 years post-transplant,[120] however, it is usually well tolerated.

## CONCLUSION

PBC and PSC are both chronic, progressive, cholestatic liver diseases and as such share some of the clinical manifestations including pruritus, jaundice, complications of long standing cholestasis, and progression to cirrhosis and portal hypertension. The pathogenesis of PBC is better understood and an approved therapy is available, which slows progression of the disease. The greatest challenge for the clinician is the management of UDCA non-responders. PSC, on the other hand, is of unknown etiology and no therapy has been shown to change its outcomes. In addition to the lack of therapy, PSC is clearly a pre-malignant condition and close surveillance is indicated.

Much progress has been seen in the last 5 to 10 years; however, a substantial number of patients with both PBC and PSC will require liver transplantation. Although many gaps remain unfilled, we are likely to see, in the near future, the development of therapies that will further impact the quality of life and life expectancy of those affected by these diseases. Until then, prompt recognition and treatment, management and surveillance of the complications is essential in order to impact patients' outcomes.

## CONFLICT OF INTEREST

**Guarantor of the article:** Cynthia Levy, MD.
**Specific author contributions:** Seth N. Sclair—review of literature, writing of manuscript. He approves of the final draft. Ester Little—review of literature, writing of manuscript. She approves of the final draft. Cynthia Levy—review of literature, writing of manuscript. She approves of the final draft.
**Financial support:** None.
**Potential competing interests:** None.

1. Floreani A, Franceschet I, Perini L *et al.* New therapies for primary biliary cirrhosis. *Clin Rev Allergy Immunol* 2015; **48**: 263–272.
2. Flores A, Mayo MJ. Primary biliary cirrhosis in 2014. *Curr Opin Gastroenterol 2014* **30**: 245–252.
3. Selmi C, Bowlus CL, Gershwin ME *et al.* Primary biliary cirrhosis. *Lancet* 2011; **377**: 1600–1609.
4. Czul F, Peyton A, Levy C. Primary biliary cirrhosis: therapeutic advances. *Clin Liver Dis* 2013; **17**: 229–242.
5. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol* 2012; **56**: 1181–1188.
6. Prince M, Chetwynd A, Newman W *et al.* Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: follow-up for up to 28 years. *Gastroenterology* 2002; **123**: 1044–1051.
7. Lee J, Belanger A, Doucette JT *et al.* Transplantation trends in primary biliary cirrhosis. *Clin Gastroenterol Hepatol* 2007; **5**: 1313–1315.
8. Kuiper EM, Hansen BE, Metselaar HJ *et al.* Trends in liver transplantation for primary biliary cirrhosis in the netherlands 1988-2008. *BMC Gastroenterol* 2010; **10**: 144 230X-10-144.
9. Parés A, Caballería L, Rodés J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. *Gastroenterology* 2006; **130**: 715–720.
10. Corpechot C, Abenavoli L, Rabahi N *et al.* Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology* 2008; **48**: 871–877.
11. Corpechot C, Chazouillères O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. *J Hepatol* 2011; **55**: 1361–1367.
12. Kumagi T, Guindi M, Fischer SE *et al.* Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. *Am J Gastroenterol* 2010; **105**: 2186–2194.
13. Kuiper EM, Hansen BE, de Vries RA *et al.* Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. *Gastroenterology* 2009; **136**: 1281–1287.
14. 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.
15. Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. *Hepatology* 2002; **36**: 525–531.
16. Poupon R. Ursodeoxycholic acid and bile-acid mimetics as therapeutic agents for cholestatic liver diseases: an overview of their mechanisms of action. *Clin Res Hepatol Gastroenterol* 2012; **36**: S3–S12.
17. Lindor KD, Gershwin ME, Poupon R *et al.* Primary biliary cirrhosis. *Hepatology* 2009; **50**: 291–308.
18. Combes B, Luketic VA, Peters MG *et al.* Prolonged follow-up of patients in the US multicenter trial of ursodeoxycholic acid for primary biliary cirrhosis. *Am J Gastroenterol* 2004; **99**: 264–268.
19. Honda A, Ikegami T, Nakamuta M *et al.* Anticholestatic effects of bezafibrate in patients with primary biliary cirrhosis treated with ursodeoxycholic acid. *Hepatology* 2013; **57**: 1931–1941.
20. Levy C, Peter JA, Nelson DR *et al.* Pilot study: fenofibrate for patients with primary biliary cirrhosis and an incomplete response to to ursodeoxycholic acid. *Aliment Pharmacol Ther* 2011; **33**: 235–242.
21. Lens S, Leoz M, Nazal L *et al.* Bezafibrate normalizes alkaline phospatase in primary biliary cirrhosis patients with incomplete response to ursodeoxycholic acid. *Liver Int* 2014; **34**: 197–203.
22. Hosonuma K, Sato K, Yamazaki Y *et al.* A prospective randomized controlled study of long-term combination therapy using ursodeoxycholic acid and bezafibrate in patients with primary biliary cirrhosis and dyslipidemia. *Am J Gastroenterol* 2015; **110**: 423–431.
23. Grigorian AY, Mardini HE, Corpechot C *et al.* Fenofibrate is effective adjunctive therapy in the treatment of primary biliary cirrhosis: a meta-analysis. *Clin Res Hepatol Gastroenterol* 2015; **39**: 296–306.
24. Leuschner M, Maier K, Schlichting J *et al.* Oral budesonide and ursodeoxycholic acid for treatment of primary biliary cirrhosis: results of a prospective double-blind trial. *Gastroenterology* 1999; **117**: 918–925.
25. Rautiainen H, Kärkkäinen P, Karvonen A *et al.* Budesonide combined with UDCA to improve liver histology in primary biliary cirrhosis: a three-year randomized trial. *Hepatology* 2005; **41**: 747–752.
26. Angulo P, Jorgensen RA, Keach JC *et al.* Oral budesonide in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. *Hepatology* 2000; **31**: 318–323.
27. Hempfling W, Grunhage F, Dilger K *et al.* Pharmacokinetics and pharmacodynamic action of budesonide in early-and late-stage primary biliary cirrhosis. *Hepatology* 2003; **38**: 196–202.
28. Hirschfield GM, Mason A, Luketic V *et al.* Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. *Gastroenterology* 2014; **148**: 751–61e8.
29. Nevens F, Andreone P, Mazzella G *et al.* An International Phase 3 Study of the FXR agonist obeticholic acid in PBC patients: effects on markers of cholestasis associated with clinical outcomes and hepatocellular damageIn: *Hepatology* 2014 Wiley-Blackwell: Hoboken, NJ, USA, 2014 p 347A–348A.

30. Bowlus CL, Pockros PJ, Drenth J *et al.* Obeticholic acid in PBC patients: the utility of titration based on therapeutic response and tolerabilityIn: *Hepatology* 2014 Wiley-Blackwell: Hoboken, NJ, USA, 2014, p 353A.
31. Corpechot C, El Naggar A, Poujol-Robert A *et al.* Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. *Hepatology* 2006; **43**: 1118–1124.
32. Corpechot C, Carrat F, Poujol-Robert A *et al.* Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. *Hepatology* 2012; **56**: 198–208.
33. Tapper EB, Castera L, Afdhal NH. FibroScan (vibration-controlled transient elastography): where does it stand in the united states practice. *Clin Gastroenterol Hepatol* 2015; **13**: 27–36.
34. Garcia-Tsao G, Sanyal AJ, Grace ND *et al.* Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; **46**: 922–938.
35. Gores GJ, Wiesner RH, Dickson ER *et al.* Prospective evaluation of esophageal varices in primary biliary cirrhosis: development, natural history, and influence on survival. *Gastroenterology* 1989; **96**: 1552–1559.
36. Levy C, Zein CO, Gomez J *et al.* Prevalence and predictors of esophageal varices in patients with primary biliary cirrhosis. *Clin Gastroenterol Hepatol* 2007; **5**: 803–808.
37. Trivedi PJ, Lammers WJ, van Buuren HR *et al.* On behalf of the Global PBC Study GroupStratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. *Gut*; advance online publication, 7 January 2015; doi: 10.1136/gutjnl-2014-308351 (e-pub ahead of print).
38. Suzuki A, Lymp J, Donlinger J *et al.* Clinical predictors for hepatocellular carcinoma in patients with primary biliary cirrhosis. *Clin Gastroenterol Hepatol* 2007; **5**: 259–264.
39. Cavazza A, Caballería L, Floreani A *et al.* Incidence, risk factors, and survival of hepatocellular carcinoma in primary biliary cirrhosis: comparative analysis from two centers. *Hepatology* 2009; **50**: 1162–1168.
40. Harada K, Hirohara J, Ueno Y *et al.* Incidence of and risk factors for hepatocellular carcinoma in primary biliary cirrhosis: national data from Japan. *Hepatology* 2013; **57**: 1942–1949.
41. Kuiper EM, Hansen BE, Adang RP *et al.* Study GroupRelatively high risk for hepatocellular carcinoma in patients with primary biliary cirrhosis not responding to ursodeoxycholic acid. *Eur J Gastroenterol Hepatol* 2010; **22**: 1495–1502.
42. Wiesner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. *Gastroenterology* 1980; **79**: 200–206.
43. Schrumpf E, Elgjo K, Fausa O *et al.* Sclerosing cholangitis in ulcerative colitis. *Scand J Gastroenterol* 1980; **15**: 689–697.
44. Shepherd HA, Selby WS, Chapman RW *et al.* Ulcerative colitis and persistent liver dysfunction. *Q J Med* 1983; **52**: 503–513.
45. Tobias R, Wright JP, Kottler RE *et al.* Primary sclerosing cholangitis associated with inflammatory bowel disease in cape town, 1975 - 1981. *S Afr Med J* 1983; **63**: 229–235.
46. Wiesner RH, Grambsch PM, Dickson ER *et al.* Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. *Hepatology* 1989; **10**: 430–436.
47. Olsson R, Danielsson A, Jarnerot G *et al.* Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. *Gastroenterology* 1991; **100**: 1319–1323.
48. Escorsell A, Parés A, Rodés J *et al.* Epidemiology of primary sclerosing cholangitis in Spain. *J Hepatol* 1994; **21**: 787–791.
49. Lee Y, Kaplan MM. Primary sclerosing cholangitis. *N Engl J Med* 1995; **332**: 924–933.
50. Broome U, Olsson R, Loof L *et al.* Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut* 1996; **38**: 610–615.
51. Bernstein CN, Blanchard JF, Rawsthorne P *et al.* The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2001; **96**: 1116–1122.
52. Bambha K, Kim WR, Talwalkar J *et al.* Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a united states community. *Gastroenterology* 2003; **125**: 1364–1369.
53. Kingham JG, Kochar N, Gravenor MB. Incidence, clinical patterns, and outcomes of primary sclerosing cholangitis in South Wales, United Kingdom. *Gastroenterology* 2004; **126**: 1929–1930.
54. Levy C, Lindor KD. Primary sclerosing cholangitis: epidemiology, natural history, and prognosis. *Semin Liver Dis* 2006; **26**: 22–30.
55. Molodecky NA, Kareemi H, Parab R *et al.* Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. *Hepatology* 2011; **53**: 1590–1599.
56. Hirschfield GM, Karlsen TH, Lindor KD *et al.* Primary sclerosing cholangitis. *Lancet* 2013; **382**: 1587–1599.
57. Yang X, Cullen SN, Li JH *et al.* Susceptibility to primary sclerosing cholangitis is associated with polymorphisms of intercellular adhesion molecule-1. *J Hepatol* 2004; **40**: 375–379.
58. Bergquist A, Montgomery SM, Bahmanyar S *et al.* Increased risk of primary sclerosing cholangitis and ulcerative colitis in first-degree relatives of patients with primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2008; **6**: 939–943.
59. Karlsen TH, Franke A, Melum E *et al.* Genome-wide association analysis in primary sclerosing cholangitis. *Gastroenterology* 2010; **138**: 1102–1111.
60. Liu JZ, Hov JR, Folseraas T *et al.* Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis. *Nat Genet* 2013; **45**: 670–675.
61. Hirschfield GM, Chapman RW, Karlsen TH *et al.* The genetics of complex cholestatic disorders. *Gastroenterology* 2013; **144**: 1357–1374.
62. Eksteen B. Advances and controversies in the pathogenesis and management of primary sclerosing cholangitis. *Br Med Bull* 2014; **110**: 89–98.
63. Tabibian JH, O'Hara SP, Lindor KD. Primary sclerosing cholangitis and the microbiota: current knowledge and perspectives on etiopathogenesis and emerging therapies. *Scand J Gastroenterol* 2014; **49**: 901–908.
64. Ali AH, Carey EJ, Lindor KD. Current research on the treatment of primary sclerosing cholangitis. *Intractable Rare Dis Res* 2014; **4**: 1–6.
65. Tischendorf JJ, Hecker H, Krüger M *et al.* Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: a single center study. *Am J Gastroenterol* 2007; **102**: 107–114.
66. Silveira MG, Lindor KD. Clinical features and management of primary sclerosing cholangitis. *World J Gastroenterol* 2008; **14**: 3338–3349.
67. Chapman R, Fevery J, Kalloo A *et al.* Diagnosis and management of primary sclerosing cholangitis. *Hepatology* 2010; **51**: 660–678.
68. Yimam KK, Bowlus CL. Diagnosis and classification of primary sclerosing cholangitis. *Autoimmun Rev* 2014; **13**: 445–450.
69. Angulo P, Peter JB, Gershwin ME *et al.* Serum autoantibodies in patients with primary sclerosing cholangitis. *J Hepatol* 2000; **32**: 182–187.
70. European Association For The Study Of The LiverEASL clinical practice guidelines: management of cholestatic liver diseases. *J Hepatol* 2009; **51**: 237–267.
71. Portmann B, Zen Y. Inflammatory disease of the bile ducts–cholangiopathies: liver biopsy challenge and clinicopathological correlation. *Histopathology* 2012; **60**: 236–248.
72. Angulo P, Maor-Kendler Y, Lindor KD. Small-duct primary sclerosing cholangitis: a long-term follow-up study. *Hepatology* 2002; **35**: 1494–1500.
73. Bjornsson E, Boberg KM, Cullen S *et al.* Patients with small duct primary sclerosing cholangitis have a favourable long term prognosis. *Gut* 2002; **51**: 731–735.
74. Broomé U, Glaumann H, Lindström E *et al.* Natural history and outcome in 32 Swedish patients with small duct primary sclerosing cholangitis (PSC). *J Hepatol* 2002; **36**: 586–589.
75. Kaplan GG, Laupland KB, Butzner D *et al.* The burden of large and small duct primary sclerosing cholangitis in adults and children: a population-based analysis. *Am J Gastroenterol* 2007; **102**: 1042–1049.
76. Björnsson E, Olsson R, Bergquist A *et al.* The natural history of small-duct primary sclerosing cholangitis. *Gastroenterology* 2008; **134**: 975–980.
77. Singal A, Stanca C, Clark V *et al.* Natural history of small duct primary sclerosing cholangitis: a case series with review of the literature. *Hepatol Int* 2011; **5**: 808–813.
78. Luth S, Kanzler S, Frenzel C *et al.* Characteristics and long-term prognosis of the autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome. *J Clin Gastroenterol* 2009; **43**: 75–80.
79. Bjornsson E, Chari S, Silveira M *et al.* Primary sclerosing cholangitis associated with elevated immunoglobulin G4: clinical characteristics and response to therapy. *Am J Ther* 2011; **18**: 198–205.
80. Mendes FD, Jorgensen R, Keach J *et al.* Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. *Am J Gastroenterol* 2006; **101**: 2070–2075.
81. Ghazale A, Chari ST, Zhang L *et al.* Immunoglobulin G4–associated cholangitis: clinical profile and response to therapy. *Gastroenterology* 2008; **134**: 706–715.
82. Silveira MG. IgG4-associated cholangitis. *Clin Liver Dis* 2013; **17**: 255–268.
83. Brito-Zerón P, Ramos-Casals M, Bosch X *et al.* The clinical spectrum of IgG4-related disease. *Autoimmun Rev* 2014; **13**: 1203–1210.
84. Imam MH, Talwalkar JA, Lindor KD. An update on primary sclerosing cholangitis: from pathogenesis to treatment. *Minerva Gastroenterol Dietol* 2013; **59**: 49–58.
85. Alamino RP, Espinoza LR, Zea AH. The great mimicker: IgG4-related disease. *Clin Rheumatol* 2013; **32**: 1267–1273.
86. Boonstra K, Culver EL, de Buy Wenniger LM *et al.* Serum immunoglobulin G4 and immunoglobulin G1 for distinguishing immunoglobulin G4-associated cholangitis from primary sclerosing cholangitis. *Hepatology* 2014; **59**: 1954–1963.
87. Al Mamari S, Djordjevic J, Halliday JS *et al.* Improvement of serum alkaline phosphatase to< 1.5 upper limit of normal predicts better outcome and reduced risk of cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol* 2013; **58**: 329–334.
88. Lindström L, Hultcrantz R, Boberg KM *et al.* Association between reduced levels of alkaline phosphatase and survival times of patients with primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2013; **11**: 841–846.
89. Rupp C, Rössler A, Halibasic E *et al.* Reduction in alkaline phosphatase is associated with longer survival in primary sclerosing cholangitis, independent of dominant stenosis. *Aliment Pharmacol Ther* 2014; **40**: 1292–1301.
90. Hofmann AF. Bile acids: trying to understand their chemistry and biology with the hope of helping patients. *Hepatology* 2009; **49**: 1403–1418.
91. Lindor KD. Ursodiol for primary sclerosing cholangitis. *N Engl J Med* 1997; **336**: 691–695.
92. Olsson R, Boberg KM, de Muckadell OS *et al.* High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. *Gastroenterology* 2005; **129**: 1464–1472.

93. Lindor KD, Kowdley KV, Luketic VA *et al.* High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology* 2009; **50**: 808–814.
94. Wunsch E, Trottier J, Milkiewicz M *et al.* Prospective evaluation of ursodeoxycholic acid withdrawal in patients with primary sclerosing cholangitis. *Hepatology* 2014; **60**: 931–940.
95. Tabibian JH, Lindor KD. Ursodeoxycholic acid in primary sclerosing cholangitis: if withdrawal is bad, then administration is good (right?). *Hepatology* 2014; **60**: 785–788.
96. Tabibian JH, Gossard A, El-Youssef M *et al.* Prospective clinical trial of rifaximin therapy for patients with primary sclerosing cholangitis. *Am J Ther* 2014.
97. Tabibian J, Weeding E, Jorgensen R *et al.* Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis-a pilot study. *Aliment Pharmacol Ther* 2013; **37**: 604–612.
98. Davies YK, Cox KM, Abdullah BA *et al.* Long-term treatment of primary sclerosing cholangitis in children with oral vancomycin: an immunomodulating antibiotic. *J Pediatr Gastroenterol Nutr* 2008; **47**: 61–67.
99. Abarbanel DN, Seki SM, Davies Y *et al.* Immunomodulatory effect of vancomycin on treg in pediatric inflammatory bowel disease and primary sclerosing cholangitis. *J Clin Immunol* 2013; **33**: 397–406.
100. Chazouilleres O, Corpechot C, Gaouar F *et al.* Fenofibrate improves liver tests in primary sclerosing cholangitis with incomplete biochemical response to ursodeoxycholic acidIn: *Hepatology* 2010Wiley-Blackwell Commerce: Malden, MA, USA, 2010 p 488A.
101. Dejman A, Clark V, Martin P *et al.* Tu1002 fenofibrate improves alkaline phosphatase in primary sclerosing cholangitis. *Gastroenterology* 2013; **144** S 1028-S–1029.
102. Martin C, Blanco P, Keach J *et al.* The safety and efficacy of oral docosahexaenoic acid supplementation for the treatment of primary sclerosing cholangitis–a pilot study. *Aliment Pharmacol Ther* 2012; **35**: 255–265.
103. Assis DN, Abdelghany O, Cai S *et al.*Efficacy trial of all-trans retinoic acid (ATRA) in combination with ursodeoxycholic acid (UDCA) in primary sclerosing cholangitis (PSC)In: *Hepatology* 2014Wiley-Blackwell: Hoboken, NJ, USA, 2014 p 346A–347A.
104. Björnsson E, Lindqvist-Ottosson J, Asztely M *et al.* Dominant strictures in patients with primary sclerosing cholangitis. *Am J Gastroenterol* 2004; **99**: 502–508.
105. Rudolph G, Gotthardt D, Klöters-Plachky P *et al.* Influence of dominant bile duct stenoses and biliary infections on outcome in primary sclerosing cholangitis. *J Hepatol* 2009; **51**: 149–155.
106. Stiehl A, Rudolph G, Klöters-Plachky P *et al.* Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. *J Hepatol* 2002; **36**: 151–156.
107. Lindor KD, Kowdley KV, Harrison ME. ACG clinical guideline: primary sclerosing cholangitis. *Am J Gastroenterol* 2015; **110**: 646–659.
108. Gluck M, Cantone NR, Brandabur JJ *et al.* A twenty-year experience with endoscopic therapy for symptomatic primary sclerosing cholangitis. *J Clin Gastroenterol* 2008; **42**: 1032–1039.
109. Baluyut AR, Sherman S, Lehman GA *et al.* Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. *Gastrointest Endosc* 2001; **53**: 308–312.
110. Farges O, Malassagne B, Sebagh M *et al.* Primary sclerosing cholangitis: liver transplantation or biliary surgery. *Surgery* 1995;**117**:146–155.
111. Barr Fritcher EG, Voss JS, Jenkins SM *et al.* Primary sclerosing cholangitis with equivocal cytology: fluorescence in situ hybridization and serum CA 19-9 predict risk of malignancy. *Cancer Cytopathol* 2013; **121**: 708–717.
112. Levy C, Lymp J, Angulo P *et al.* The value of serum CA 19-9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. *Dig Dis Sci* 2005; **50**: 1734–1740.
113. Venkatesh PG, Navaneethan U, Shen B *et al.* Increased serum levels of carbohydrate antigen 19-9 and outcomes in primary sclerosing cholangitis patients without cholangiocarcinoma. *Dig Dis Sci* 2013; **58**: 850–857.
114. Fritcher EGB, Kipp BR, Voss JS *et al.* Primary sclerosing cholangitis patients with serial polysomy fluorescence in situ hybridization results are at increased risk of cholangiocarcinoma. *Am J Gastroenterol* 2011; **106**: 2023–2028.
115. Eaton JE, Fritcher EGB, Gores GJ *et al.* Biliary multifocal chromosomal polysomy and cholangiocarcinoma in primary sclerosing cholangitis. *Am J Gastroenterol* 2015; **110**: 299–309.
116. Boonstra K, Weersma RK, Erpecum KJ *et al.* Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology* 2013; **58**: 2045–2055.
117. Razumilava N, Gores GJ, Lindor KD. Cancer surveillance in patients with primary sclerosing cholangitis. *Hepatology* 2011; **54**: 1842–1852.
118. Murad SD, Kim WR, Harnois DM *et al.* Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 2012;**143**:e3.
119. Graziadei IW, Wiesner RH, Marotta PJ *et al.* Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. *Hepatology* 1999; **30**: 1121–1127.
120. Campsen J, Zimmerman MA, Trotter JF *et al.* Clinically recurrent primary sclerosing cholangitis following liver transplantation: a time course. *Liver Transplant* 2008; **14**: 181–185.
121. Nakamura M, Kondo H, Mori T *et al.* Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. *Hepatology* 2007; **45**: 118–127.
122. Miyachi K, Hankins RW, Matsushima H *et al.* Profile and clinical significance of anti-nuclear envelope antibodies found in patients with primary biliary cirrhosis: a multicenter study. *J Autoimmun* 2003; **20**: 247–254.
123. ITOH S, ICHIDA T, YOSHIDA T *et al.* Autoantibodies against a 210kDa glycoprotein of the nuclear pore complex as a prognostic marker in patients with primary biliary cirrhosis. *J Gastroenterol Hepatol* 1998; **13**: 257–265.
124. Yang W, Yu JH, Nakajima A *et al.* Do antinuclear antibodies in primary biliary cirrhosis patients identify increased risk for liver failure? *Clin Gastroenterol Hepatol* 2004; **2**: 1116–1122.
125. Agmon-Levin N, Shapira Y, Selmi C *et al.* A comprehensive evaluation of serum autoantibodies in primary biliary cirrhosis. *J Autoimmun* 2010; **34**: 55–58.
126. Norman GL, Yang C, Ostendorff HP *et al.* Anti-kelch-like 12 and anti-hexokinase 1: novel autoantibodies in primary biliary cirrhosis. *Liver Int* 2015; **35**: 642–651.