Primary Sclerosing Cholangitis, Part 1: Epidemiology, Etiopathogenesis, Clinical Features, and Treatment

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Abstract: Primary sclerosing cholangitis (PSC) is a chronic, idiopathic cholangiopathy that can progress to cirrhosis, end-stage liver disease, hepatobiliary cancer, and/or colorectal cancer. The course of PSC is often complicated by portal hypertension, symptoms of cholestasis, and recurrent bacterial cholangitis, among other conditions, with a consequent decrease in survival (median, approximately 20 years) and quality of life. The etiopathogenesis of PSC remains poorly understood, and, as such, pharmacotherapy has yet to be definitively established. Despite its rarity, PSC is the fifth leading indication for liver transplantation (LT) in the United States. Although the only intervention known to extend survival of patients with PSC, LT is costly and invasive, and recurrent PSC affects approximately 30% of LT recipients. Over the past several years, owing in part to progress in the understanding of PSC, novel pharmacotherapeutics have been developed, some of which are currently in the PSC clinical trial pipeline. Here, in the first of a 2-part series, we provide a review and update of the epidemiology, etiopathogenesis, clinical features, and treatment of PSC. The second part of the series will focus on cancer risk, prevention, and surveillance of PSC.

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterized by stricturing of the intra- and/or extrahepatic ducts. PSC represents an important cause of morbidity and mortality in Western societies, with many patients ultimately requiring liver transplantation (LT) due to end-stage liver disease or other complications.[1-4] Patients with PSC are also at significantly increased risk of hepatobiliary cancer and colorectal cancer (CRC), particularly in the 70% of patients who also have inflammatory bowel disease (IBD).[5-7]

Currently, there is no known pharmacotherapy for PSC that halts disease progression. Numerous agents have been tested, although none have yielded convincingly promising results.[8-26] The rarity of PSC, its elusive etiopathogenesis, its long natural history, the challenges of retaining patients long enough in clinical trials to achieve sufficient endpoints, and the lack of validated surrogate biomarkers (eg, of treatment success) remain major barriers to developing effective and safe therapies for PSC.

Table 1. Phenotypic Variants of PSC

Variant[a]	Cholangiographic Features	Liver Histology Features
Classic PSC	Multifocal intrahepatic and extrahepatic strictures and resultant upstream (ie, proximal) ductal dilation	Typical changes (ie, nonsuppurative paucicellular cholangitis, periductal fibrosis, ductular reaction, and ductopenia)
Intrahepatic PSC	Multifocal intrahepatic strictures and resultant upstream (ie, proximal) segmental ductal dilation	Typical changes
Extrahepatic PSC	Extrahepatic-only strictures and resultant upstream (ie, proximal) ductal dilation	Nondiagnostic or nonspecific features of cholestasis, particularly in early-stage disease
Small-duct PSC	Normal findings	Typical changes

[a]All of these variants will generally have a cholestatic serum biochemical profile, although a small minority of patients can have normal serum liver test results.

PSC, primary sclerosing cholangitis.

Given the progressive nature of PSC and its associated morbidity and mortality, there is a large unmet need for effective medical therapies for this disease. Here, in the first of a 2-part series, we provide an overview and update of PSC, including its epidemiology, etiopathogenesis, clinical features, associated disorders, and potential therapies. The second part of the series will focus on cancer risk, prevention, and surveillance of PSC.

Clinical Epidemiology

PSC is most common in Northern European countries and North America, where the reported incidence and prevalence range from approximately 0.5 to 1.3 cases per 100,000 person-years and 3.85 to 16.2 cases per 100,000 person-years, respectively.[27-29] A recent British study reported an incidence of 0.68 per 100,000 person-years and a prevalence of 5.58 per 100,000 person-years[30]; these figures represent the highest incidence and prevalence reported to date in the United Kingdom. PSC appears to be much less common in Southern Europe[31] and Southeast Asia,[32] although in many regions (eg, much of the Eastern Hemisphere), its incidence and prevalence have not been well studied. The prevalence of PSC appears to be considerably higher in Australia than in New Zealand, although both areas have a higher prevalence than Southern Europe and Southeast Asia.[33,34] Epidemiologic studies of PSC in pediatric patients are scarce; however, the incidence and prevalence of PSC appear to be lower in children than in adults.[35]

As noted previously, approximately 70% of patients with PSC also have IBD, mainly ulcerative colitis,[36] whereas only 2% to 8.1% of patients with IBD have PSC,[37] although rates reach up to 14%.[38] The exact nature of the PSC-IBD relationship is not well understood. Notably, PSC and IBD can be diagnosed simultaneously, although in many patients, there is a dissociation in the time of diagnosis of PSC and IBD (with the diagnosis of IBD typically being made first). In addition, PSC can present after proctocolectomy for IBD, and IBD can present after LT for PSC.[39] The PSC-IBD phenotype is associated with milder colitis, rectal sparing, and backwash ileitis, and the extent and distribution of colitis are associated with the timing of the IBD diagnosis (ie, pre- vs post-PSC).[40] Pediatric PSC-IBD is generally more severe than adult-onset disease.[41,42]

It should be highlighted that PSC has phenotypic variants (Table 1) in addition to overlap syndromes and various disease mimics, whether biochemical, cholangiographic, or other types (Table 2). Recognizing and distinguishing these variants and mimics is critical for ensuring appropriate management, particularly for conditions with readily available therapies.

Etiopathogenesis

The etiopathogenesis of PSC remains uncertain, although PSC is increasingly thought to be a heterogeneous, complex disorder with environmental, immunobiologic, and genetic underpinnings (Figure). In addition, the epithelial cells lining the bile ducts (ie, cholangiocytes) are now thought to be not only a target of injury in PSC but also actively involved drivers in the course of disease.[3,43] Indeed, cholangiocytes are a morphologically, biochemically, and functionally dynamic population of cells. Various hypotheses regarding the etiopathogenesis of PSC have been proposed, and a prevailing theme is that predisposing genetic elements and (as of yet uncertain) environmental exposures intersect and together play a fundamental role (Figure).[1,2]

Perhaps the most contemporary and substantiated hypothesis regarding the etiopathogenesis of PSC, although still a work in progress, is the PSC-microbiome hypothesis.[44,45] This hypothesis, which represents an

expansion of the leaky gut hypothesis, is compatible with the aforementioned theme of environmental exposures and the notion that cholangiocytes play a central role in PSC, and is based on the association between PSC and IBD and the therapeutic benefits seen with specific antibiotics. The hypothesis posits that PSC may develop as a result of (1) increased enterohepatic circulation of microbial molecules (possibly facilitated by compromised intestinal barrier function), (2) alterations in microbial diversity and/or the repertoire of metabolites (eg, due to intestinal microbial dysbiosis), and/or (3) an aberrant or exaggerated cholangiocyte response (eg, induction of cholangiocyte senescence and senescence-associated secretory phenotype) to microbial molecules.[3,45,46] This is supported by various observations in vitro,[43,47,48] in animal models,[49-53] and in human PSC.[1,3,54-58]

Recently, several studies have explored the potential etiopathogenetic role of the microbiome in PSC. Compared to healthy controls and patients with IBD alone, patients with PSC have decreased microbial diversity and overrepresentation of *Escherichia, Fusobacterium, Enterococcus, Lactobacillus, Blautia, Veillonella,* Barnesiellaceae, Lachnospiraceae, *Megasphaera, Rothia, Ruminococcus,* and *Streptococcus*.[59-65] Conversely, patients with PSC have decreased populations of *Clostridium* cluster II, *Prevotella, Roseburia, Adlercreutzia,* and *Bacteroides* compared to healthy individuals and patients with IBD alone.[60,64,66] Additionally, patients with PSC-IBD have a distinct bile-acid profile compared to patients with IBD alone; the serum bile-acid pool is increased, but the stool bile-acid pool is decreased in patients with PSC-IBD compared to patients with IBD alone.[65] The unique microbial signature in patients with PSC-IBD is thought to lead to changes in the stool bile-acid pool (or vice versa), which could ostensibly explain the increased risk for CRC in PSC-IBD; however, further studies are needed.

The role of genetics in the development and/or progression of PSC has long been suspected and is based on several lines of data. First, the risk of PSC is significantly increased in offspring and siblings of patients with PSC (hazard ratio, approximately 11).[67] Second, genome-wide association studies (GWASs) suggest that the human leukocyte antigen (HLA) gene family collectively represents the strongest risk locus associated with PSC[68]; associations have been described with both class 1 and 2 HLAs, including B8, DR3, DR2, and A1,[69] and with select haplotypes.[70] Moreover, variations in *MICA* (major histocompatibility complex class I–related *MIC* gene family) are associated with PSC predisposition; for example, independent of other HLA haplotypes, the *MICA* 002 allele appears to be associated with a significantly reduced risk of developing PSC, whereas the *MICA* 008 allele is associated with an increased risk.[71] Third, non-HLA PSC susceptibility and modifier genes have been identified, including (but not limited to) stromelysin-1 (ie, matrix metalloproteinase 3) and intracellular adhesion molecule 1.[72,73] In addition, recent GWASs have identified associations between PSC and (1) the fucosyltransferase 2 gene (found to influence the microbial community composition of the bile),[74] (2) the *IL2RA* gene (which regulates the number of FOXP3[+] regulatory T cells in peripheral blood),[75] (3) various other risk loci,[76,77] and (4) IBD at several new risk loci, including genetic variants associated with PSC progression.[78]

It is worth mentioning that numerous animal models have been developed to study PSC. Given the uncertainties regarding the etiopathogenesis of PSC, it is not surprising that no single model has fully recapitulated its

Table 2. Causes of Secondary Sclerosing Cholangitis and Mimics of PSC

Infectious Causes	AIDS cholangiopathy (eg, *Cryptosporidium parvum*, cytomegalovirus)
	Helminthic infection (eg, *Clonorchis*, *Opisthorchis*, *Ascaris*)
	Recurrent pyogenic cholangitis (also referred to as oriental cholangiohepatitis)
Intrinsic or Extrinsic Compressive Causes (Benign or Malignant)	Mirizzi syndrome
	Cholangiocarcinoma
	Diffuse intrahepatic malignancy
	Compressive lymphadenopathy
	Portal hypertensive biliopathy
	Postoperative strictures
	Chronic pancreatitis
Immunologic Causes	IgG4-associated cholangiopathy
	Eosinophilic cholangitis
	Mast cell cholangiopathy
	Histiocytosis X
	Systemic vasculitis
	Hepatic allograft rejection
	Primary biliary cholangitis
Ischemic Causes	Posttransplant nonanastomotic strictures
	Postintraarterial chemotherapy
	Postradiation therapy
Congenital and/or Idiopathic Causes	Choledochal cyst (eg, Caroli disease)
	Progressive familial intrahepatic cholestasis

IgG4, immunoglobulin G subclass 4; PSC, primary sclerosing cholangitis.

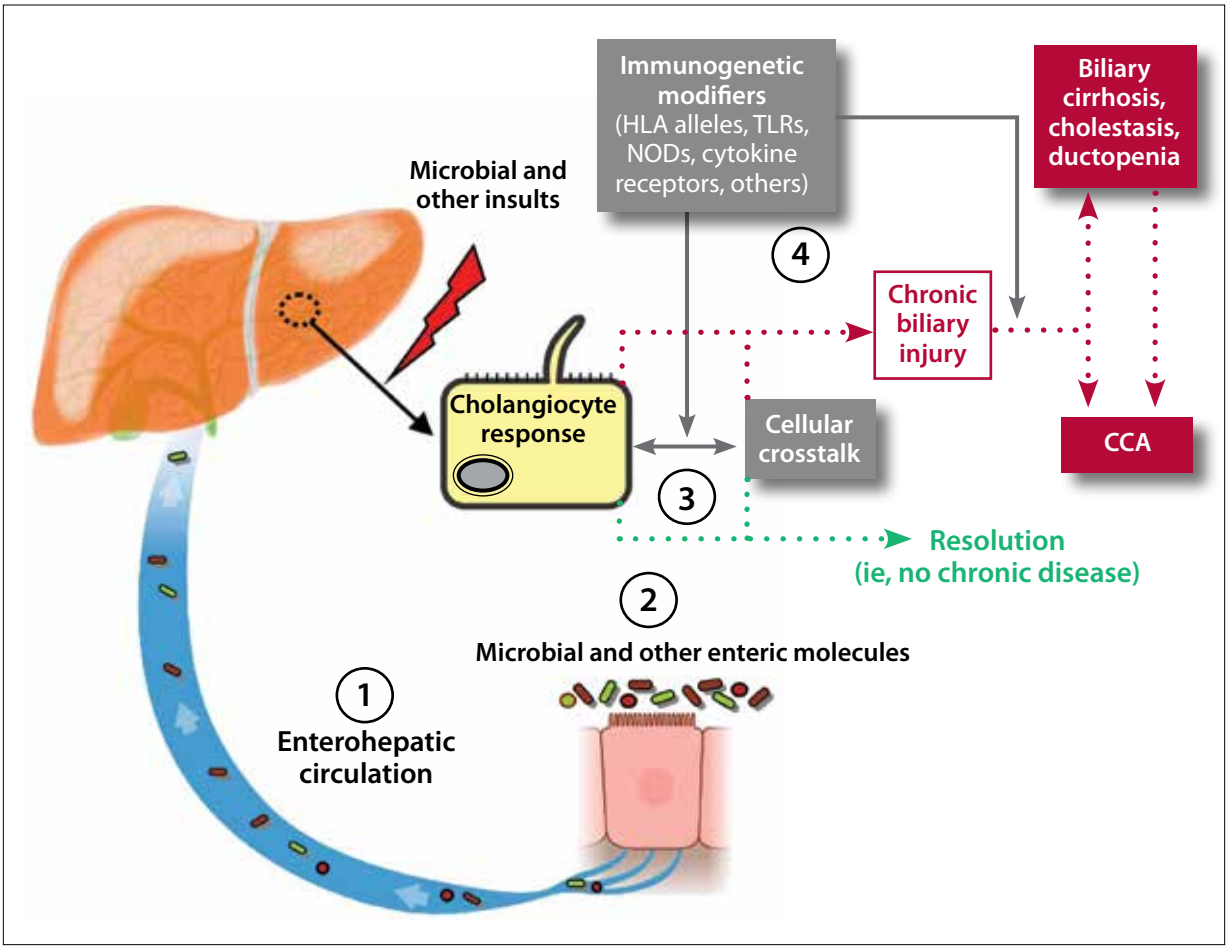

Figure. A conceptual model of the etiopathogenesis and natural history of PSC. Biliary epithelial cells (ie, cholangiocytes) exist in an environment with multiple potential etiologic mediators of hepatobiliary injury. Approximately 95% of bile acids are reabsorbed in the terminal ileum and, together with other intestinal molecules, are transported back to the liver via the enterohepatic circulation. Portal blood flows into hepatic sinusoids, wherein hepatocytes may take up and modify these molecules and secrete them into bile, which is synthesized by hepatocytes and delivered into canaliculi by means of specialized membrane transporters. Canalicular bile drains into the biliary tree and is modified by cholangiocytes as it percolates through the biliary tree. Cholangiocytes recognize (eg, through cell surface receptors) and react to various molecules and may release chemokines/cytokines, growth factors, and morphogens, initiating both autocrine and paracrine signaling cascades. With respect to the source of hepatobiliary injury, it remains uncertain whether there is (1) increased exposure to microbial molecules (eg, through the enterohepatic circulation, potentially facilitated by compromised intestinal barrier function), (2) alteration to the repertoire of microbial and other intestinal molecules (eg, due to microbial dysbiosis, xenobiotics), and/or (3) an aberrant or exaggerated cholangiocyte (or another hepatic cell) response to these molecules (eg, increased induction of cholangiocyte senescence and the senescence-associated secretory phenotype). In addition, host immunogenetics (4) likely modulate the development and/or impact of any of these variables and thus play a role in determining whether hepatobiliary injury resolves or if it persists and results in chronic disease (ie, PSC). These variables may also determine whether PSC progresses to its associated major clinical endpoints, including CCA and cirrhosis. Further investigation of the cellular, molecular, and microbial interactions and signaling represented in this figure is underway and expected to advance understanding of the etiopathogenesis of PSC.

CCA, cholangiocarcinoma; HLA, human leukocyte antigen; NOD, nucleotide-binding oligomerization domain receptor; PSC, primary sclerosing cholangitis; TLR, toll-like receptor.

biochemical, cholangiographic, histologic, and premalignant features, as reviewed recently.[79] For example, the most widely studied model, the mdr2 (ABCB4) knockout mouse model, exhibits biochemical,[80] histologic,[81] and cholangiographic features of PSC[79,82]; however, there is no male predominance, disease severity appears to be greater in female mice (not corresponding to PSC), there is no association with IBD or cholangiocarcinoma (CCA), and the primary mechanism of injury is not representative of PSC. Thus, there is no consensus regarding the optimal

model, which has hindered development of new therapies. Of note, other murine models include the experimental biliary obstruction murine model (C57BL/6J), chemically induced cholangitis models using agents such as lithocholic acid and 3,5-diethoxycarbonyl-1,4-dihydrocollidine, and models involving biliary epithelial and endothelial cellular injury.[79,83,84] Also of note, an in-vitro model of persistent cholangiocyte injury has recently been developed[3] to facilitate the study of PSC and other cholangiopathies,[4] and demonstrates various features seen in isolated primary PSC cholangiocytes as well as cholangiocytes in PSC liver sections.[3,43] However, although this represents a useful culture-based system, a better animal model is still needed.

Management

Pharmacotherapy

As previously mentioned, there are no approved pharmacotherapies for PSC. Ursodeoxycholic acid (UDCA) is the most extensively investigated agent in PSC, but its current use in this disease is controversial.[85] Preliminary studies of UDCA in PSC showed improvement in liver biochemistries.[86-88] However, the results of the 2 largest clinical trials of UDCA in PSC were disappointing[16,18]; one trial used an intermediate dose of UDCA and showed only a trend toward statistically significant benefit, and the other trial used high-dose UDCA and was terminated early due to excess adverse events in the UDCA-treated group. Currently, some experts maintain that a trial of UDCA at intermediate doses (18-21 mg/kg body weight/day) should be considered.[1,2]

Recent advances in understanding the pathobiologic pathways implicated in cholestatic liver diseases have led to the development of several new experimental agents targeting these pathways.[89] Tables 3 and 4 summarize clinical trials that have been completed and those currently underway in patients with PSC. Some of the prominent clinical trial findings are noted in the following paragraphs.

24-Norursodeoxycholic Acid 24-Norursodeoxycholic acid (norUDCA), a C(23) homolog of UDCA, has been found to exert anticholestatic, anti-inflammatory, and antifibrotic effects in murine models.[80,82] In a phase 2 clinical trial, 161 patients with PSC were randomized to 1 of 3 doses of norUDCA (500, 1000, or 1500 mg per day) or placebo for 12 weeks.[90] Compared to placebo, norUDCA reduced serum alkaline phosphatase (ALP) levels by 12.3%, 17.3%, and 26.0% in the 500-, 1000-, and 1500-mg arms, respectively. No difference was reported in the incidence of pruritus between the treatment and placebo groups. A phase 3 trial of norUDCA in PSC is underway.

Obeticholic Acid Obeticholic acid (OCA) is an analog of chenodeoxycholic acid and an endogenous ligand of the farnesoid X receptor (FXR). FXR plays a key role in bile-acid homeostasis; its activation leads to transcriptional repression of the *CYP7A1* gene, which encodes cholesterol 7α hydroxylase (critical for bile-acid biosynthesis), through fibroblast growth factor 19 (FGF19) signaling and other pathways.[91] OCA has recently been approved by the US Food and Drug Administration (FDA) as therapy for primary biliary cholangitis (PBC).[92] Pruritus has been the most common and expected side effect in clinical trials, occurring in approximately 60% of patients treated with OCA in a dose-dependent manner, and 4% to 12% of patients discontinued OCA. Phase 3 clinical trial data are needed.

Simtuzumab Lysyl oxidase homolog 2 catalyzes the first step in the formation of cross-links in collagen and elastin and has been shown to contribute to hepatic fibrogenesis.[93] In a phase 2 clinical trial, 234 patients with PSC were randomized to weekly injections of simtuzumab (75 or 125 mg) or placebo for 96 weeks. Neither dose of simtuzumab led to significant reduction in ALP.[94] However, the role of simtuzumab in delaying the progression of fibrosis in PSC merits further study.

Alteration of the Microbiome Oral vancomycin is a nonsystemic, selective antibacterial drug; it has been found to be well tolerated and associated with significant improvement in ALP and other markers in both adult and pediatric patients with PSC,[95-98] and pediatric patients have additionally experienced IBD-related symptom resolution.[95,96,99] A phase 3 clinical trial of vancomycin in PSC has been completed, and the data are awaiting analyses. Metronidazole has been shown to decrease ALP and bilirubin in PSC[98,100]; however, long-term safety is a concern, and longer-term clinical trials are lacking. Fecal microbiota transplantation has been investigated in 10 patients with PSC; 3 patients had at least a 50% reduction in ALP.[101] With interventions aiming to treat PSC through alteration of the microbiome, it would be of interest to examine intestinal microbial and metabolic changes (eg, bile acids), as such data may reveal further mechanistic and therapeutic insights.

Interruption of the Enterohepatic Circulation of Bile Acids Bile acids are secreted into the small intestine and are reabsorbed by the liver via the enterohepatic circulation. At the level of the intestine, absorption of bile acids occurs through the apical sodium-dependent bile-acid transporter (ASBT). LUM001 (an ASBT inhibitor) and NGM282 (a FGF19 analog) are currently in phase 2 clinical trials for the treatment of PSC.

Table 3. Completed Clinical Trials for the Treatment of PSC

Agent(s)	Sample Size, n	Study Design	Summary of Main Findings
Penicillamine[14]	39 vs 31 (drug vs placebo)	Double-blind, placebo-controlled	• No significant effect on survival • 21% stopped the drug due to side effects
Prednisone plus colchicine[17]	12	Open-label	• Improved serum liver biochemistries • No significant difference in histologic change
Methotrexate[143]	12 vs 12 (drug vs placebo)	Double-blind, placebo-controlled	• Decrease in ALP • No significant difference in histologic and cholangiographic progressions
Tacrolimus[25]	10	Open-label	• Decrease in ALP, bilirubin, AST, and ALT • 31% stopped the drug due to side effects
Colchicine[19]	44 vs 40 (drug vs placebo)	Double-blind, placebo-controlled	• No significant improvement in symptoms, histologic progression, and survival
UDCA plus methotrexate[15]	19	Open-label	• No effect on serum liver biochemistries • 26% stopped methotrexate due to side effects
UDCA[86,a]	51 vs 51 (drug vs placebo)	Double-blind, placebo-controlled	• Improved serum liver biochemistries • No significant clinical benefit in time to death, histologic progression, doubling of bilirubin, and need for liver transplantation
UDCA[16,18]	76 vs 74[16] (drug vs placebo) 91 vs 101[18] (drug vs placebo)	Double-blind, placebo-controlled	• No significant clinical benefit in primary endpoints (time to death or need for liver transplantation) in the Scandinavian trial • Early termination of the US trial due to futility and significant advantage of placebo over UDCA with regard to primary endpoints (time to development of cirrhosis, varices, cholangiocarcinoma, liver transplantation, or death)
Nicotine[9]	8	Open-label	• No significant improvement in serum liver biochemistries • 38% of patients reduced the dose due to adverse effects
Budesonide or prednisone plus UDCA[24]	6 vs 6 vs 6 (budesonide 9 mg vs prednisone 3 mg vs 10 mg)	Double-blind, randomized, pilot	• Improvement in ALP and pruritus in patients treated with prednisone
Budesonide[8]	21	Open-label, pilot	• Improvement in ALP, AST, and portal inflammation • Increase in bilirubin • Marked bone loss
Pentoxifylline[11]	20	Open-label, pilot	• No significant improvement in serum liver biochemistries
Cladribine[12]	4	Open-label, pilot	• No significant improvement in symptoms or serum liver biochemistries
Etanercept[144]	10	Open-label, pilot	• Resolution of pruritus in 40% • Increase in bilirubin • No change in ALP
Mycophenolate mofetil plus UDCA[145]	12 vs 13 (drug vs placebo)	Double-blind, randomized	• No significant improvement in serum liver biochemistries, liver histology, or cholangiographic findings
Metronidazole plus UDCA[100]	39 vs 41 (drug vs placebo)	Double-blind, randomized, placebo-controlled	• Improvement in ALP and histology compared to UDCA monotherapy group
Mycophenolate mofetil[22]	30	Open-label, pilot	• Improvement in ALP • 23% stopped the drug due to side effects
Infliximab[13]	6 vs 4 (drug vs placebo)	Double-blind, placebo-controlled	• No significant improvement in ALP or liver histology
Ecologic 641 (probiotic)[26]	7 vs 7 (drug vs placebo)	Double-blind, placebo-controlled	• No significant improvement in serum liver biochemistries or symptoms

(Table continues on the following page.)

Table 3. *(Continued)* Completed Clinical Trials for the Treatment of PSC

Agent(s)	Sample Size, n	Study Design	Summary of Main Findings
Vancomycin in pediatric patients[95,96,99,146,147]	19 (total of the 5 studies)	Open-label, pilot, and case series	• Improvement in GGT, ALT, C-reactive protein, symptoms, and cholangiographic findings
Vancomycin or metronidazole in adults[98]	8 vs 9 vs 9 vs 9 (low-dose vs high-dose vancomycin vs low-dose vs high-dose metronidazole)	Randomized, double-blind	• Improvement in ALP (primary endpoint) in the vancomycin groups • Decrease in bilirubin in the low-dose metronidazole group and trend toward significant decrease in the low-dose vancomycin group (*P*=.06) • Decrease in Mayo PSC risk score in the low-dose vancomycin group and low-dose metronidazole group
Vancomycin[97]	18 vs 11 (drug vs placebo)	Triple-blind, randomized, placebo-controlled	• Improvement in ALP, GGT, and symptoms
Rifaximin[21]	16	Open-label, pilot	• No significant improvement in serum liver biochemistries or symptoms
Minocycline[20]	16	Open-label, pilot	• Improvement in ALP
Bezafibrate[148]	15	Open-label, pilot	• Improvement in ALP, GGT, ALT, and AST
All-trans retinoic acid plus UDCA[149]	15	Open-label, pilot	• Improvement in ALP and ALT
Obeticholic acid[150]	76 (total)[b]	Randomized, double-blind, placebo-controlled	• Preliminary data presented at the 2017 AASLD meeting • Improvement in ALP
Simtuzumab[151]	79 vs 77 vs 78 (drug 75 mg/day vs 125 mg/day vs placebo)	Randomized, double-blind, placebo-controlled	• Preliminary data presented at the 2017 EASL meeting • No significant change in ALP, hepatic collagen, and fibrosis stage
NorUDCA[90]	39 vs 41 vs 39 vs 40 (drug 500 mg/day vs 1000 mg/day vs 1500 mg/day vs placebo)	Double-blind, randomized, placebo-controlled	• Improvement in ALP in all 3 arms • Pruritus was the main side effect

[a]Numerous other studies of UDCA alone have also been reported.[1,2] [b]76 patients were randomized to placebo (n=25), drug 1.5 mg (n=25), and drug 5 mg (n=26) once daily for 12 weeks. Patients tolerating the drug were titrated from 1.5 mg to 3 mg (n=22) or from 5 mg to 10 mg (n=16).

AASLD, American Association for the Study of Liver Diseases; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EASL, European Association for the Study of the Liver; GGT, gamma-glutamyl transpeptidase; norUDCA, 24-norursodeoxycholic acid; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

Other Agents BTT1023 (a human monoclonal antibody that binds vascular adhesion protein-1), mitomycin-C (an antineoplastic agent), curcumin (an anti-inflammatory, antifibrotic, and antisenescent agent), and cenicriviroc (a dual C-C chemokine receptor [CCR] 2 and CCR5 antagonist) are all undergoing evaluation for use in PSC.

Endoscopic Management

With the advent of magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiography (ERC) has largely become a therapeutic modality in PSC.[102] Of the various potential applications of ERC in patients with PSC (eg, choledocholithiasis, acute cholangitis, palliative stenting of CCA), one of the most common and important indications is management of dominant strictures (DSs), which are loosely defined as stenoses with a diameter of no more than 1.5 mm in the common bile duct or no more than 1 mm in a hepatic duct. DSs develop in approximately 45% of patients with PSC and may present (although not always) with progressive jaundice, pruritus, right upper quadrant pain, and/or acute cholangitis. It is recommended that patients with clinical signs and symptoms attributable to a DS undergo evaluation; ERC with or without cholangioscopy is typically necessary in this scenario to further examine the biliary tree, obtain specimens (eg, intraductal brushings and/or biopsies), and perform therapeutic maneuvers (mainly balloon dilation). Short-term biliary stenting may also be performed, although the available data do not support this as a routine practice due to increased risk of treatment-related adverse events.[103]

Satisfactory remediation of DSs may require multiple ERC sessions, following which a subset of patients will demonstrate biochemical and symptomatic improve-

Table 4. Clinical Trials in Progress for the Treatment of PSC

Therapeutic Agent	Study Characteristics and Outcome
Cenicriviroc (inhibitor of CCR2 and CCR5)	• NCT02653625 (open-label, phase 2) • Outcome: % change in ALP from baseline
BTT1023 (vascular adhesion protein-1 inhibitor)	• NCT02239211 (open-label, phase 2) • Outcome: % change in ALP from baseline
Curcumin (anti-inflammatory, antifibrotic, antisenescent)	• NCT02978339 (open-label, phase 2) • Outcome: % change in ALP from baseline
NGM282 (fibroblast growth factor 19 analog)	• NCT02704364 (randomized, placebo-controlled, phase 2) • Outcome: % change in ALP from baseline
GS-9674 (farnesoid X receptor agonist)	• NCT02943460 (randomized, placebo-controlled, phase 2) • Outcome: % change in ALP from baseline
UDCA in pediatric PSC	• NCT01088607 (open-label, phase 1) • Outcome: % change in GGT and ALT from baseline
Vancomycin in pediatric PSC	• NCT01802073 (open-label, phase 3) • Outcome: % change in ALT, GGT, MRCP findings, and biopsy findings from baseline
Mitomycin C (antineoplastic)	• NCT01688024 (randomized, placebo-controlled, phase 2) • Outcome: change in Mayo risk score from baseline
LUM001 (apical sodium-dependent bile-acid transporter inhibitor)	• NCT02061540 (open-label, pilot, phase 2) • Outcome: Safety change in fasting serum bile acid from baseline
Fecal microbiota transplantation	• NCT02424175 (open-label, pilot, phase 1 and 2) • Outcome: change in gut microbial profile, ALP, AST, ALT, and bilirubin from baseline

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCR, C-C chemokine receptor; GGT, gamma-glutamyl transpeptidase; MRCP, magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

ments.[104,105] Therefore, it is thought that endoscopic therapy for DSs may offer long-term benefit (at least in some patients) in addition to short-term benefit. However, it remains unclear which patients with PSC are most likely to experience long-term benefit from endoscopic intervention.[106] Therefore, further research is needed.

Surgical Management

PSC is a common indication for LT globally and is the leading indication in Northern European countries. LT is the only potentially curative treatment currently available for PSC. Compared to PBC, for which the rate of LT has declined, the trend for LT for PSC has persisted. Specific indications for LT relatively unique to patients with PSC include recurrent acute cholangitis and refractory PSC-related symptoms (specifically fatigue and pruritus).[107] In select, highly specialized centers, patients with PSC complicated by CCA meeting specific criteria are also candidates for LT.[108]

Recurrent PSC (rPSC) is an enduring clinical dilemma. It occurs in 1.8% to 36.8% of LT recipients and is associated with a greater need for repeat LT, a 4-fold increased risk of death, and decreased overall survival compared to patients who remain rPSC-free.[109] Potential risk factors include the presence of IBD, use of a living related donor, young age, sex, and colectomy prior to LT.[110-113]

Associated Disorders and Complications

Symptoms

Data from referral centers have found that 45% to 55% of patients with PSC are symptomatic at the time of PSC diagnosis,[114] and up to 22% of asymptomatic patients will develop symptoms of PSC, mainly fatigue and pruritus, within 5 years.[114] Patients with PSC who have symptoms at the time of diagnosis have significantly worse survival and impaired health-related quality of life (HRQOL) than those who are asymptomatic at the time of PSC diagnosis.[114] Significant reduction in HRQOL in terms of physical and social functioning, general and mental health, and bodily pain have been well described in PSC.[115]

Inflammatory Bowel Disease

The robust association between PSC and IBD has been known for decades, but the mechanism(s) by which these

2 diseases are related remains elusive. Several theories have been proposed, many of which involve crosstalk between the inflamed colon and the liver in susceptible individuals[116,117] or a connection to the enteric microbiome, as discussed earlier.[62-64,66]

It is worth mentioning that even in the absence of concomitant PSC, abnormalities of serum liver biochemistries are frequently encountered in patients with IBD; 29% to 55% of patients with IBD have been reported to have concomitant serum liver test abnormalities.[118] This is clinically important, as this subset of patients has a 4.8-fold higher risk of death compared to patients with IBD who have normal serum liver test results.[118]

Portal Hypertension

Portal hypertension is a frequent complication of PSC. For example, esophageal varices develop at a rate of 5% every year in patients with PSC, including parastomal varices in patients with ileostomy (or other stomas).[119,120] The management of portal hypertension and its related complications in patients with PSC is no different than in non-PSC patients, as outlined in societal guidelines.[121]

Hepatic Osteodystrophy

Bone loss is a common complication of PSC and other cholestatic liver diseases.[122] Severe osteoporosis has been found to be 6.1 times more prevalent in patients with PSC than in matched healthy controls.[122] Age at least 54 years, body mass index no more than 24, and presence and duration of IBD have all been found to correlate with the presence of osteoporosis in patients with PSC.[122] Moreover, patients with PSC (especially middle-aged patients) have been found to have a high rate of nonvertebral fracture, which in turn has a negative impact on physical and mental aspects of HRQOL.[123,124] Patients with PSC should be screened at the time of diagnosis and then at regular intervals (every 1-5 years per the European Association for the Study of the Liver and every 2-3 years per the American Association for the Study of Liver Diseases [AASLD]).[125,126] Calcium and vitamin D supplements (for osteopenia) and bisphosphonates (for osteoporosis) are also recommended.

Cancer Risk

Compared to the general population, there is a 2-fold increased risk of any cancer and a 40-fold increase in the risk of liver cancer in patients with PSC.[127] Moreover, PSC confers a 400-fold increased risk of CCA, and nearly one-third of all-cause mortality in patients with PSC is from CCA.[128] The risk of CRC in PSC is nearly an order of magnitude higher compared to that of the general population and even higher (nearly 30-fold) in patients with PSC-IBD.[129]

Surrogate Endpoints

Serum, imaging, and other biomarkers that could potentially be used in clinical trials as surrogate endpoints in PSC represent an area of need and active study. ALP has perhaps been the most commonly investigated biomarker and appears to be promising for prognostic purposes as well as a surrogate endpoint for therapeutic response in PSC.[130-134] A joint workshop (AASLD-FDA) in March 2016 recommended the use of a biliary-specific blood test (ALP) and measurement of hepatic stiffness and fibrosis by transient elastography or, ideally, histology when designing clinical trials in PSC.[134-137]

Several prognostic models have been proposed for predicting major outcomes of PSC using parameters such as age, sex, hepatomegaly, splenomegaly, albumin, bilirubin, cholangiography, and histology.[114,138-141] More recently, a spleen length of more than 120 mm has been found to be predictive of adverse outcomes (hepatic decompensation, liver-related death, and need for LT).[142]

Summary

PSC is an important global cause of morbidity and mortality. Currently, there is no effective pharmacotherapy for PSC that prevents major adverse outcomes (eg, progression to cirrhosis, carcinogenesis, or need for LT). The rarity of PSC, limited understanding of its etiopathogenesis, paucity of validated surrogate markers, and long natural history are barriers to developing effective medical therapies. LT, the only treatment shown to extend the survival of patients with PSC, is reserved for highly select patients, and even then, rPSC can be problematic. There are several experimental agents in the pharmacologic pipeline, some of which have demonstrated encouraging results and are currently being evaluated in phase 2 (or higher) trials. Overall, there continues to be progress in the understanding and management of this disease, with potential on the horizon.

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References

1. O'Hara SP, Tabibian JH, Splinter PL, LaRusso NF. The dynamic biliary epithelia: molecules, pathways, and disease. *J Hepatol*. 2013;58(3):575-582.
2. Tabibian JH, Lindor KD. Primary sclerosing cholangitis: a review and update on therapeutic developments. *Expert Rev Gastroenterol Hepatol*. 2013;7(2):103-114.
3. Tabibian JH, O'Hara SP, Splinter PL, Trussoni CE, LaRusso NF. Cholangiocyte senescence by way of N-ras activation is a characteristic of primary sclerosing cholangitis. *Hepatology*. 2014;59(6):2263-2275.
4. Lazaridis KN, Strazzabosco M, Larusso NF. The cholangiopathies: disorders of biliary epithelia. *Gastroenterology*. 2004;127(5):1565-1577.
5. Olsson R, Danielsson A, Järnerot G, et al. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. *Gastroenterology*. 1991;100(5 pt 1):1319-1323.

6. Schrumpf E, Elgjo K, Fausa O, Gjone E, Kolmannskog F, Ritland S. Sclerosing cholangitis in ulcerative colitis. *Scand J Gastroenterol*. 1980;15(6):689-697.
7. Gulamhusein AF, Eaton JE, Tabibian JH, Atkinson EJ, Juran BD, Lazaridis KN. Duration of inflammatory bowel disease is associated with increased risk of cholangiocarcinoma in patients with primary sclerosing cholangitis and IBD. *Am J Gastroenterol*. 2016;111(5):705-711.
8. Angulo P, Batts KP, Jorgensen RA, LaRusso NA, Lindor KD. Oral budesonide in the treatment of primary sclerosing cholangitis. *Am J Gastroenterol*. 2000;95(9):2333-2337.
9. Angulo P, Bharucha AE, Jorgensen RA, et al. Oral nicotine in treatment of primary sclerosing cholangitis: a pilot study. *Dig Dis Sci*. 1999;44(3):602-607.
10. Beuers U, Spengler U, Kruis W, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo-controlled trial. *Hepatology*. 1992;16(3):707-714.
11. Bharucha AE, Jorgensen R, Lichtman SN, LaRusso NF, Lindor KD. A pilot study of pentoxifylline for the treatment of primary sclerosing cholangitis. *Am J Gastroenterol*. 2000;95(9):2338-2342.
12. Duchini A, Younossi ZM, Saven A, Bordin GM, Knowles HJ, Pockros PJ. An open-label pilot trial of cladibrine (2-cholordeoxyadenosine) in patients with primary sclerosing cholangitis. *J Clin Gastroenterol*. 2000;31(4):292-296.
13. Hommes DW, Erkelens W, Ponsioen C, et al. A double-blind, placebo-controlled, randomized study of infliximab in primary sclerosing cholangitis. *J Clin Gastroenterol*. 2008;42(5):522-526.
14. LaRusso NF, Wiesner RH, Ludwig J, MacCarty RL, Beaver SJ, Zinsmeister AR. Prospective trial of penicillamine in primary sclerosing cholangitis. *Gastroenterology*. 1988;95(4):1036-1042.
15. Lindor KD, Jorgensen RA, Anderson ML, Gores GJ, Hofmann AF, LaRusso NF. Ursodeoxycholic acid and methotrexate for primary sclerosing cholangitis: a pilot study. *Am J Gastroenterol*. 1996;91(3):511-515.
16. Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology*. 2009;50(3):808-814.
17. Lindor KD, Wiesner RH, Colwell LJ, Steiner B, Beaver S, LaRusso NF. The combination of prednisone and colchicine in patients with primary sclerosing cholangitis. *Am J Gastroenterol*. 1991;86(1):57-61.
18. 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(5):1464-1472.
19. Olsson R, Broomé U, Danielsson A, et al. Colchicine treatment of primary sclerosing cholangitis. *Gastroenterology*. 1995;108(4):1199-1203.
20. Silveira MG, Torok NJ, Gossard AA, et al. Minocycline in the treatment of patients with primary sclerosing cholangitis: results of a pilot study. *Am J Gastroenterol*. 2009;104(1):83-88.
21. Tabibian JH, Gossard A, El-Youssef M, et al. Prospective clinical trial of rifaximin therapy for patients with primary sclerosing cholangitis. *Am J Ther*. 2017;24(1):e56-e63.
22. Talwalkar JA, Angulo P, Keach JC, Petz JL, Jorgensen RA, Lindor KD. Mycophenolate mofetil for the treatment of primary sclerosing cholangitis. *Am J Gastroenterol*. 2005;100(2):308-312.
23. Talwalkar JA, Gossard AA, Keach JC, Jorgensen RA, Petz JL, Lindor RN. Tacrolimus for the treatment of primary sclerosing cholangitis. *Liver Int*. 2007;27(4):451-453.
24. van Hoogstraten HJ, Vleggaar FP, Boland GJ, et al; Belgian-Dutch PSC Study Group. Budesonide or prednisone in combination with ursodeoxycholic acid in primary sclerosing cholangitis: a randomized double-blind pilot study. *Am J Gastroenterol*. 2000;95(8):2015-2022.
25. Van Thiel DH, Carroll P, Abu-Elmagd K, et al. Tacrolimus (FK 506), a treatment for primary sclerosing cholangitis: results of an open-label preliminary trial. *Am J Gastroenterol*. 1995;90(3):455-459.
26. Vleggaar FP, Monkelbaan JF, van Erpecum KJ. Probiotics in primary sclerosing cholangitis: a randomized placebo-controlled crossover pilot study. *Eur J Gastroenterol Hepatol*. 2008;20(7):688-692.
27. 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(5):1364-1369.
28. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol*. 2012;56(5):1181-1188.
29. Toy E, Balasubramanian S, Selmi C, Li CS, Bowlus CL. The prevalence, incidence and natural history of primary sclerosing cholangitis in an ethnically diverse population. *BMC Gastroenterol*. 2011;11:83.
30. Liang H, Manne S, Shick J, Lissoos T, Dolin P. Incidence, prevalence, and natural history of primary sclerosing cholangitis in the United Kingdom. *Medicine (Baltimore)*. 2017;96(24):e7116.
31. Escorsell A, Parés A, Rodés J, Solís-Herruzo JA, Miras M, de la Morena E; Spanish Association for the Study of the Liver. Epidemiology of primary sclerosing cholangitis in Spain. *J Hepatol*. 1994;21(5):787-791.
32. Ang TL, Fock KM, Ng TM, Teo EK, Chua TS, Tan JY. Clinical profile of primary sclerosing cholangitis in Singapore. *J Gastroenterol Hepatol*. 2002;17(8):908-913.
33. Ngu JH, Gearry RB, Frampton CM, Stedman CA. Mortality and the risk of malignancy in autoimmune liver diseases: a population-based study in Canterbury, New Zealand. *Hepatology*. 2012;55(2):522-529.
34. Liu K, Wang R, Kariyawasam V, et al. Epidemiology and outcomes of primary sclerosing cholangitis with and without inflammatory bowel disease in an Australian cohort. *Liver Int*. 2017;37(3):442-448.
35. Deneau M, Jensen MK, Holmen J, Williams MS, Book LS, Guthery SL. Primary sclerosing cholangitis, autoimmune hepatitis, and overlap in Utah children: epidemiology and natural history. *Hepatology*. 2013;58(4):1392-1400.
36. Weismüller TJ, Trivedi PJ, Bergquist A, et al; International PSC Study Group. Patient age, sex, and inflammatory bowel disease phenotype associate with course of primary sclerosing cholangitis. *Gastroenterology*. 2017;152(8):1975-1984.e8.
37. Lunder AK, Hov JR, Borthne A, et al. Prevalence of sclerosing cholangitis detected by magnetic resonance cholangiography in patients with long-term inflammatory bowel disease. *Gastroenterology*. 2016;151(4):660-669.e4.
38. Fraga M, Fournier N, Safroneeva E, et al; Swiss IBD Cohort Study Group. Primary sclerosing cholangitis in the Swiss Inflammatory Bowel Disease Cohort Study: prevalence, risk factors, and long-term follow-up. *Eur J Gastroenterol Hepatol*. 2017;29(1):91-97.
39. Schaeffer DF, Win LL, Hafezi-Bakhtiari S, Cino M, Hirschfield GM, El-Zimaity H. The phenotypic expression of inflammatory bowel disease in patients with primary sclerosing cholangitis differs in the distribution of colitis. *Dig Dis Sci*. 2013;58(9):2608-2614.
40. Boonstra K, van Erpecum KJ, van Nieuwkerk KM, et al. Primary sclerosing cholangitis is associated with a distinct phenotype of inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18(12):2270-2276.
41. Feldstein AE, Perrault J, El-Youssif M, Lindor KD, Freese DK, Angulo P. Primary sclerosing cholangitis in children: a long-term follow-up study. *Hepatology*. 2003;38(1):210-217.
42. Miloh T, Arnon R, Shneider B, Suchy F, Kerkar N. A retrospective single-center review of primary sclerosing cholangitis in children. *Clin Gastroenterol Hepatol*. 2009;7(2):239-245.
43. Tabibian JH, Trussoni CE, O'Hara SP, Splinter PL, Heimbach JK, LaRusso NF. Characterization of cultured cholangiocytes isolated from livers of patients with primary sclerosing cholangitis. *Lab Invest*. 2014;94(10):1126-1133.
44. 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(8):901-908.
45. Tabibian JH, O'Hara SP, Trussoni CE, et al. Absence of the intestinal microbiota exacerbates hepatobiliary disease in a murine model of primary sclerosing cholangitis. *Hepatology*. 2016;63(1):185-196.
46. Trussoni CE, Tabibian JH, Splinter PL, O'Hara SP. Lipopolysaccharide (LPS)-induced biliary epithelial cell NRas activation requires epidermal growth factor receptor (EGFR). *PLoS One*. 2015;10(4):e0125793.
47. Mueller T, Beutler C, Picó AH, et al. Enhanced innate immune responsiveness and intolerance to intestinal endotoxins in human biliary epithelial cells contributes to chronic cholangitis. *Liver Int*. 2011;31(10):1574-1588.
48. Yokoyama T, Komori A, Nakamura M, et al. Human intrahepatic biliary epithelial cells function in innate immunity by producing IL-6 and IL-8 via the TLR4-NF-kappaB and -MAPK signaling pathways. *Liver Int*. 2006;26(4):467-476.
49. Haruta I, Kikuchi K, Hashimoto E, et al. Long-term bacterial exposure can trigger nonsuppurative destructive cholangitis associated with multifocal epithelial inflammation. *Lab Invest*. 2010;90(4):577-588.
50. Hobson CH, Butt TJ, Ferry DM, Hunter J, Chadwick VS, Broom MF. Enterohepatic circulation of bacterial chemotactic peptide in rats with experimental colitis. *Gastroenterology*. 1988;94(4):1006-1013.
51. Lichtman SN, Okoruwa EE, Keku J, Schwab JH, Sartor RB. Degradation of endogenous bacterial cell wall polymers by the muralytic enzyme mutanolysin prevents hepatobiliary injury in genetically susceptible rats with experimental intestinal bacterial overgrowth. *J Clin Invest*. 1992;90(4):1313-1322.
52. Lichtman SN, Wang J, Clark RL. A microcholangiographic study of liver disease models in rats. *Acad Radiol*. 1995;2(6):515-521.
53. Yamada S, Ishii M, Liang LS, Yamamoto T, Toyota T. Small duct cholangitis induced by N-formyl L-methionine L-leucine L-tyrosine in rats. *J Gastroenterol*. 1994;29(5):631-636.
54. Hiramatsu K, Harada K, Tsuneyama K, et al. Amplification and sequence

analysis of partial bacterial 16S ribosomal RNA gene in gallbladder bile from patients with primary biliary cirrhosis. *J Hepatol*. 2000;33(1):9-18.
55. Mistilis SP, Skyring AP, Goulston SJ. Effect of long-term tetracycline therapy, steroid therapy and colectomy in pericholangitis associated with ulcerative colitis. *Australas Ann Med*. 1965;14(4):286-294.
56. Olsson R, Björnsson E, Bäckman L, et al. Bile duct bacterial isolates in primary sclerosing cholangitis: a study of explanted livers. *J Hepatol*. 1998;28(3):426-432.
57. Pohl J, Ring A, Stremmel W, Stiehl A. The role of dominant stenoses in bacterial infections of bile ducts in primary sclerosing cholangitis. *Eur J Gastroenterol Hepatol*. 2006;18(1):69-74.
58. Sasatomi K, Noguchi K, Sakisaka S, Sata M, Tanikawa K. Abnormal accumulation of endotoxin in biliary epithelial cells in primary biliary cirrhosis and primary sclerosing cholangitis. *J Hepatol*. 1998;29(3):409-416.
59. Kummen M, Holm K, Anmarkrud JA, et al. The gut microbial profile in patients with primary sclerosing cholangitis is distinct from patients with ulcerative colitis without biliary disease and healthy controls. *Gut*. 2017;66(4):611-619.
60. Quraishi MN, Sergeant M, Kay G, et al. The gut-adherent microbiota of PSC-IBD is distinct to that of IBD. *Gut*. 2017;66(2):386-388.
61. Ruhlemann MC, Heinsen FA, Zenouzi R, Lieb W, Franke A, Schramm C. Faecal microbiota profiles as diagnostic biomarkers in primary sclerosing cholangitis. *Gut*. 2017;66(4):753-754.
62. Sabino J, Vieira-Silva S, Machiels K, et al. Primary sclerosing cholangitis is characterised by intestinal dysbiosis independent from IBD. *Gut*. 2016;65(10):1681-1689.
63. Torres J, Bao X, Goel A, et al. The features of mucosa-associated microbiota in primary sclerosing cholangitis. *Aliment Pharmacol Ther*. 2016;43(7):790-801.
64. Bajer L, Kverka M, Kostovcik M, et al. Distinct gut microbiota profiles in patients with primary sclerosing cholangitis and ulcerative colitis. *World J Gastroenterol*. 2017;23(25):4548-4558.
65. Torres J, Palmela C, Brito H, et al. The gut microbiota, bile acids and their correlation in primary sclerosing cholangitis associated with inflammatory bowel disease. *United European Gastroenterol J*. 2018;6(1):112-122.
66. Rossen NG, Fuentes S, Boonstra K, et al. The mucosa-associated microbiota of PSC patients is characterized by low diversity and low abundance of uncultured Clostridiales II. *J Crohns Colitis*. 2015;9(4):342-348.
67. 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(8):939-943.
68. Karlsen TH, Franke A, Melum E, et al. Genome-wide association analysis in primary sclerosing cholangitis. *Gastroenterology*. 2010;138(3):1102-1111.
69. Chapman RW, Varghese Z, Gaul R, Patel G, Kokinon N, Sherlock S. Association of primary sclerosing cholangitis with HLA-B8. *Gut*. 1983;24(1):38-41.
70. Donaldson PT, Norris S. Evaluation of the role of MHC class II alleles, haplotypes and selected amino acid sequences in primary sclerosing cholangitis. *Autoimmunity*. 2002;35(8):555-564.
71. Norris S, Kondeatis E, Collins R, et al. Mapping MHC-encoded susceptibility and resistance in primary sclerosing cholangitis: the role of MICA polymorphism. *Gastroenterology*. 2001;120(6):1475-1482.
72. Yang X, Cullen SN, Li JH, Chapman RW, Jewell DP. Susceptibility to primary sclerosing cholangitis is associated with polymorphisms of intercellular adhesion molecule-1. *J Hepatol*. 2004;40(3):375-379.
73. Wiencke K, Louka AS, Spurkland A, Vatn M, Schrumpf E, Boberg KM; IBSEN Study Group. Association of matrix metalloproteinase-1 and -3 promoter polymorphisms with clinical subsets of Norwegian primary sclerosing cholangitis patients. *J Hepatol*. 2004;41(2):209-214.
74. Folseraas T, Melum E, Rausch P, et al. Extended analysis of a genome-wide association study in primary sclerosing cholangitis detects multiple novel risk loci. *J Hepatol*. 2012;57(2):366-375.
75. Sebode M, Peiseler M, Franke B, et al. Reduced FOXP3(+) regulatory T cells in patients with primary sclerosing cholangitis are associated with IL2RA gene polymorphisms. *J Hepatol*. 2014;60(5):1010-1016.
76. Ellinghaus D, Folseraas T, Holm K, et al. Genome-wide association analysis in primary sclerosing cholangitis and ulcerative colitis identifies risk loci at GPR35 and TCF4. *Hepatology*. 2013;58(3):1074-1083.
77. Liu JZ, Hov JR, Folseraas T, et al; UK-PSCSC Consortium; International PSC Study Group; International IBD Genetics Consortium. Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis. *Nat Genet*. 2013;45(6):670-675.
78. Alberts R, de Vries EMG, Goode EC, et al; International PSC Study Group, The UK PSC Consortium. Genetic association analysis identifies variants associated with disease progression in primary sclerosing cholangitis [published online August 4, 2017]. *Gut*. doi:10.1136/gutjnl-2016-313598.
79. Fickert P, Pollheimer MJ, Beuers U, et al; International PSC Study Group (IPSCSG). Characterization of animal models for primary sclerosing cholangitis (PSC). *J Hepatol*. 2014;60(6):1290-1303.
80. Fickert P, Wagner M, Marschall HU, et al. 24-norUrsodeoxycholic acid is superior to ursodeoxycholic acid in the treatment of sclerosing cholangitis in Mdr2 (Abcb4) knockout mice. *Gastroenterology*. 2006;130(2):465-481.
81. Popov Y, Patsenker E, Fickert P, Trauner M, Schuppan D. Mdr2 (Abcb4)-/- mice spontaneously develop severe biliary fibrosis via massive dysregulation of pro- and antifibrogenic genes. *J Hepatol*. 2005;43(6):1045-1054.
82. Fickert P, Pollheimer MJ, Silbert D, et al. Differential effects of norUDCA and UDCA in obstructive cholestasis in mice. *J Hepatol*. 2013;58(6):1201-1208.
83. Fickert P, Fuchsbichler A, Marschall HU, et al. Lithocholic acid feeding induces segmental bile duct obstruction and destructive cholangitis in mice. *Am J Pathol*. 2006;168(2):410-422.
84. Fickert P, Stöger U, Fuchsbichler A, et al. A new xenobiotic-induced mouse model of sclerosing cholangitis and biliary fibrosis. *Am J Pathol*. 2007;171(2):525-536.
85. Wunsch E, Trottier J, Milkiewicz M, et al. Prospective evaluation of ursodeoxycholic acid withdrawal in patients with primary sclerosing cholangitis. *Hepatology*. 2014;60(3):931-940.
86. Lindor KD; Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. Ursodiol for primary sclerosing cholangitis. *N Engl J Med*. 1997;336(10):691-695.
87. van Hoogstraten HJ, Wolfhagen FH, van de Meeberg PC, et al. Ursodeoxycholic acid therapy for primary sclerosing cholangitis: results of a 2-year randomized controlled trial to evaluate single versus multiple daily doses. *J Hepatol*. 1998;29(3):417-423.
88. Mitchell SA, Bansi DS, Hunt N, Von Bergmann K, Fleming KA, Chapman RW. A preliminary trial of high-dose ursodeoxycholic acid in primary sclerosing cholangitis. *Gastroenterology*. 2001;121(4):900-907.
89. Ali AH, Tabibian JH, Lindor KD. Update on pharmacotherapies for cholestatic liver disease. *Hepatol Commun*. 2016;1(1):7-17.
90. Fickert P, Hirschfield GM, Denk G, et al; European PSC norUDCA Study Group. norUrsodeoxycholic acid improves cholestasis in primary sclerosing cholangitis. *J Hepatol*. 2017;67(3):549-558.
91. Ali AH, Carey EJ, Lindor KD. Recent advances in the development of farnesoid X receptor agonists. *Ann Transl Med*. 2015;3(1):5.
92. Nevens F, Andreone P, Mazzella G, et al; POISE Study Group. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med*. 2016;375(7):631-643.
93. Vadasz Z, Kessler O, Akiri G, et al. Abnormal deposition of collagen around hepatocytes in Wilson's disease is associated with hepatocyte specific expression of lysyl oxidase and lysyl oxidase like protein-2. *J Hepatol*. 2005;43(3):499-507.
94. Muir A, Goodman Z, Levy C, et al. Efficacy and safety of simtuzumab for the treatment of primary sclerosing cholangitis: results of a phase 2b, dose-ranging, randomized, placebo-controlled trial. *J Hepatol*. 2017;66(1):S73.
95. 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(2):397-406.
96. Davies YK, Cox KM, Abdullah BA, Safta A, Terry AB, Cox KL. Long-term treatment of primary sclerosing cholangitis in children with oral vancomycin: an immunomodulating antibiotic. *J Pediatr Gastroenterol Nutr*. 2008;47(1):61-67.
97. Rahimpour S, Nasiri-Toosi M, Khalili H, Ebrahimi-Daryani N, Nouri-Taromlou MK, Azizi Z. A triple-blinded, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of oral vancomycin in primary sclerosing cholangitis: a pilot study. *J Gastrointestin Liver Dis*. 2016;25(4):457-464.
98. Tabibian JH, Weeding E, Jorgensen RA, et al. Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis—a pilot study. *Aliment Pharmacol Ther*. 2013;37(6):604-612.
99. Buness C, Lindor KD, Miloh T. Oral vancomycin therapy in a child with primary sclerosing cholangitis and severe ulcerative colitis. *Pediatr Gastroenterol Hepatol Nutr*. 2016;19(3):210-213.
100. Färkkilä M, Karvonen AL, Nurmi H, et al. Metronidazole and ursodeoxycholic acid for primary sclerosing cholangitis: a randomized placebo-controlled trial. *Hepatology*. 2004;40(6):1379-1386.
101. Allegretti J, Kassam Z, Carrellas M, et al. Fecal microbiota transplantation improves microbiome diversity and liver enzyme profile in primary sclerosing cholangitis. Presented at World Congress of Gastroenterology at ACG2017; October 13-18, 2017; Orlando, FL. Abstract P1425.
102. Dave M, Elmunzer BJ, Dwamena BA, Higgins PD. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of MR cholangiopancreatography. *Radiology*. 2010;256(2):387-396.

103. Kaya M, Petersen BT, Angulo P, et al. Balloon dilation compared to stenting of dominant strictures in primary sclerosing cholangitis. *Am J Gastroenterol*. 2001;96(4):1059-1066.
104. van Milligen de Wit AW, Rauws EA, van Bracht J, et al. Lack of complications following short-term stent therapy for extrahepatic bile duct strictures in primary sclerosing cholangitis. *Gastrointest Endosc*. 1997;46(4):344-347.
105. Wagner S, Gebel M, Meier P, et al. Endoscopic management of biliary tract strictures in primary sclerosing cholangitis. *Endoscopy*. 1996;28(7):546-551.
106. Björnsson E, Lindqvist-Ottosson J, Asztely M, Olsson R. Dominant strictures in patients with primary sclerosing cholangitis. *Am J Gastroenterol*. 2004;99(3):502-508.
107. Martin P, DiMartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology*. 2014;59(3):1144-1165.
108. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology*. 2012;143(1):88-98.e3.
109. Ravikumar R, Tsochatzis E, Jose S, et al. Risk factors for recurrent primary sclerosing cholangitis after liver transplantation. *J Hepatol*. 2015;63(5):1139-1146.
110. Dvorchik I, Subotin M, Demetris AJ, et al. Effect of liver transplantation on inflammatory bowel disease in patients with primary sclerosing cholangitis. *Hepatology*. 2002;35(2):380-384.
111. Vera A, Moledina S, Gunson B, et al. Risk factors for recurrence of primary sclerosing cholangitis of liver allograft. *Lancet*. 2002;360(9349):1943-1944.
112. Cholongitas E, Shusang V, Papatheodoridis GV, et al. Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. *Liver Transpl*. 2008;14(2):138-143.
113. Alabraba E, Nightingale P, Gunson B, et al. A re-evaluation of the risk factors for the recurrence of primary sclerosing cholangitis in liver allografts. *Liver Transpl*. 2009;15(3):330-340.
114. Broomé U, Olsson R, Lööf L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut*. 1996;38(4):610-615.
115. Zakharia K, Tabibian A, Lindor KD, Tabibian JH. Complications, symptoms, quality of life and pregnancy in cholestatic liver disease. *Liver Int*. 2018;38(3):399-411.
116. Eksteen B, Miles AE, Grant AJ, Adams DH. Lymphocyte homing in the pathogenesis of extra-intestinal manifestations of inflammatory bowel disease. *Clin Med (Lond)*. 2004;4(2):173-180.
117. Eksteen B, Mora JR, Haughton EL, et al. Gut homing receptors on CD8 T cells are retinoic acid dependent and not maintained by liver dendritic or stellate cells. *Gastroenterology*. 2009;137(1):320-329.
118. Mendes FD, Levy C, Enders FB, Loftus EV Jr, Angulo P, Lindor KD. Abnormal hepatic biochemistries in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2007;102(2):344-350.
119. Treeprasertsuk S, Kowdley KV, Luketic VA, et al. The predictors of the presence of varices in patients with primary sclerosing cholangitis. *Hepatology*. 2010;51(4):1302-1310.
120. Tabibian JH, Abu Dayyeh BK, Gores GJ, Levy MJ. A novel, minimally invasive technique for management of peristomal varices. *Hepatology*. 2016;63(4):1398-1400.
121. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2017;65(1):310-335.
122. Angulo P, Grandison GA, Fong DG, et al. Bone disease in patients with primary sclerosing cholangitis. *Gastroenterology*. 2011;140(1):180-188.
123. Raszeja-Wyszomirska J, Kucharski R, Zygmunt M, Safranow K, Miazgowski T. The impact of fragility fractures on health-related quality of life in patients with primary sclerosing cholangitis. *Hepat Mon*. 2015;15(4):e25539.
124. Guichelaar MM, Schmoll J, Malinchoc M, Hay JE. Fractures and avascular necrosis before and after orthotopic liver transplantation: long-term follow-up and predictive factors. *Hepatology*. 2007;46(4):1198-1207.
125. Chapman R, Fevery J, Kalloo A, et al; American Association for the Study of Liver Diseases. Diagnosis and management of primary sclerosing cholangitis. *Hepatology*. 2010;51(2):660-678.
126. European Association for the Study of the Liver. EASL clinical practice guidelines: management of cholestatic liver diseases. *J Hepatol*. 2009;51(2):237-267.
127. Card TR, Solaymani-Dodaran M, West J. Incidence and mortality of primary sclerosing cholangitis in the UK: a population-based cohort study. *J Hepatol*. 2008;48(6):939-944.
128. Boonstra K, Weersma RK, van Erpecum KJ, et al; EpiPSCPBC Study Group. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology*. 2013;58(6):2045-2055.
129. Broomé U, Löfberg R, Veress B, Eriksson LS. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology*. 1995;22(5):1404-1408.
130. Stanich PP, Björnsson E, Gossard AA, Enders F, Jorgensen R, Lindor KD. Alkaline phosphatase normalization is associated with better prognosis in primary sclerosing cholangitis. *Dig Liver Dis*. 2011;43(4):309-313.
131. Lindström L, Hultcrantz R, Boberg KM, Friis-Liby I, Bergquist A. Association between reduced levels of alkaline phosphatase and survival times of patients with primary sclerosing cholangitis. *Clin Gastroenterol Hepatol*. 2013;11(7):841-846.
132. Al Mamari S, Djordjevic J, Halliday JS, Chapman RW. 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(2):329-334.
133. Hilscher M, Enders FB, Carey EJ, Lindor KD, Tabibian JH. Alkaline phosphatase normalization is a biomarker of improved survival in primary sclerosing cholangitis. *Ann Hepatol*. 2016;15(2):246-253.
134. Ponsioen CY, Chapman RW, Chazouillères O, et al. Surrogate endpoints for clinical trials in primary sclerosing cholangitis: review and results from an International PSC Study Group consensus process. *Hepatology*. 2016;63(4):1357-1367.
135. Corpechot C, Gaouar F, El Naggar A, et al. Baseline values and changes in liver stiffness measured by transient elastography are associated with severity of fibrosis and outcomes of patients with primary sclerosing cholangitis. *Gastroenterology*. 2014;146(4):970-979.
136. Vesterhus M, Hov JR, Holm A, et al. Enhanced liver fibrosis score predicts transplant-free survival in primary sclerosing cholangitis. *Hepatology*. 2015;62(1):188-197.
137. Ponsioen CY, Lindor KD, Mehta R, Dimick-Santos L. Design and endpoints for clinical trials in primary sclerosing cholangitis [published online March 25, 2018]. *Hepatology*. doi:10.1002/hep.29882.
138. Farrant JM, Hayllar KM, Wilkinson ML, et al. Natural history and prognostic variables in primary sclerosing cholangitis. *Gastroenterology*. 1991;100(6):1710-1717.
139. Ponsioen CY, Vrouenraets SM, Prawirodirdjo W, et al. Natural history of primary sclerosing cholangitis and prognostic value of cholangiography in a Dutch population. *Gut*. 2002;51(4):562-566.
140. Tischendorf JJ, Hecker H, Krüger M, Manns MP, Meier PN. Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: a single center study. *Am J Gastroenterol*. 2007;102(1):107-114.
141. Wiesner RH, Grambsch PM, Dickson ER, et al. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. *Hepatology*. 1989;10(4):430-436.
142. Ehlken H, Wroblewski R, Corpechot C, et al. Spleen size for the prediction of clinical outcome in patients with primary sclerosing cholangitis. *Gut*. 2016;65(7):1230-1232.
143. Knox TA, Kaplan MM. A double-blind controlled trial of oral-pulse methotrexate therapy in the treatment of primary sclerosing cholangitis. *Gastroenterology*. 1994;106(2):494-499.
144. Epstein MP, Kaplan MM. A pilot study of etanercept in the treatment of primary sclerosing cholangitis. *Dig Dis Sci*. 2004;49(1):1-4.
145. Sterling RK, Salvatori JJ, Luketic VA, et al. A prospective, randomized-controlled pilot study of ursodeoxycholic acid combined with mycophenolate mofetil in the treatment of primary sclerosing cholangitis. *Aliment Pharmacol Ther*. 2004;20(9):943-949.
146. Cox KL, Cox KM. Oral vancomycin: treatment of primary sclerosing cholangitis in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 1998;27(5):580-583.
147. Davies YK, Tsay CJ, Caccamo DV, Cox KM, Castillo RO, Cox KL. Successful treatment of recurrent primary sclerosing cholangitis after orthotopic liver transplantation with oral vancomycin. *Case Rep Transplant*. 2013;2013:314292.
148. Mizuno S, Hirano K, Isayama H, et al. Prospective study of bezafibrate for the treatment of primary sclerosing cholangitis. *J Hepatobiliary Pancreat Sci*. 2015;22(10):766-770.
149. Assis DN, Abdelghany O, Cai SY, et al. Combination therapy of all-trans retinoic acid with ursodeoxycholic acid in patients with primary sclerosing cholangitis: a human pilot study. *J Clin Gastroenterol*. 2017;51(2):e11-e16.
150. Kowdley KV, Bowlus CL, Levy C, et al. The AESOP trial: a randomized, double-blind, placebo-controlled, phase 2 study of obeticholic acid in patients with primary sclerosing cholangitis. *Hepatology*. 2017;66(6):1254A. Abstract LB-2.
151. Muir A, Goodman Z, Levy C, et al. Efficacy and safety of simtuzumab for the treatment of primary sclerosing cholangitis: results of a phase 2b, dose-ranging, randomized, placebo-controlled trial. *J Hepatol*. 2017;66(1 suppl):S73.