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Update in the Care and Management of Patients with Primary Sclerosing Cholangitis

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Abstract

Purpose of Review Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease for which specific medical therapy is not available. The goals of treatment are primarily early detection and management of complications. In this review, we discuss novel therapies under evaluation and provide the foundation for surveillance strategies.

Recent Findings Drugs under investigation include norursodeoxycholic acid, nuclear receptor agonists, anti-fibrotics, antibiotics, and anti-inflammatory drugs. Endoscopic therapy is indicated for symptomatic dominant strictures and in the work-up of malignancies. Recently, the use of stents was associated with an increased rate of complications compared to balloon dilatation; and long-term stenting should be avoided. Malignancies currently account for most of the PSC-related mortality.

Summary Many drugs are emerging for the treatment of PSC but liver transplantation is the only treatment modality shown to prolong survival. PSC recurrence occurs in up to 35% of transplanted allografts within a median of 5 years. Surveillance for hepatobiliary and colorectal malignancies is indicated.

Keywords Primary sclerosing cholangitis · Novel therapies · Endoscopy · Surveillance · Ursodeoxycholic acid · Antibiotics

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ACG	American College of Gastroenterology
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ATRA	All-trans-retinoic acid
BA	Bile acids
EASL	European Association for the Study of the Liver
ERCP	Endoscopic retrograde cholangiopancreatography
FISH	Fluorescence in situ hybridization
FGF	Fibroblast growth factor
FXR	Farsenoid X receptor
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
IgG4	IgG subclass 4
LOXL2	Lysyl oxidase homolog 2
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MRS	Mayo risk score
norUDCA	Norursodeoxycholic acid
OCA	Obeticholic acid
PPAR	Peroxisome proliferator-activated receptor
PSC	Primary sclerosing cholangitis
PXR	Pregnane X receptor
QOL	Quality-of-life
RCT	Randomized control trial
UC	Ulcerative colitis
UCDA	Ursodeoxycholic acid
VAP1	Vascular adhesion protein 1

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Overview of Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC), a fibrostenotic and idiopathic liver disease, is characterized by progressive inflammation, fibrosis, and stricturing of the intrahepatic and/or extrahepatic ducts [1]. The fibrostenotic disease eventually leads to biliary cirrhosis, portal hypertension, and liver failure. PSC is rare, with an estimated prevalence rate of 1–16 per 100,000

inhabitants [2••]. Although the pathogenesis of PSC has not been fully elucidated, a combination of genetic and environmental factors is thought to play a role. The strongest genetic associations lie within the human leukocyte antigen (HLA) complex on chromosome 6, suggesting that indeed PSC is an immune-mediated disease. However, while more than 20 susceptibility genes have been described to date, they contribute to less than 10% of overall PSC liability [1]. Other mechanisms implicated in the pathogenesis of PSC include the leakage of bacterial products through the inflamed gut, abnormal trafficking of lymphocytes from the gut to the liver, and accumulation of toxic bile. It is proposed that gut-derived pro-inflammatory bacterial products reach the portal circulation and trigger a strong adaptive immune response. In fact, the aberrant expression of adhesion molecules in the liver and abnormal homing of gut-derived lymphocytes to the liver support this hypothesis [3]. Finally, accumulation of cytotoxic bile and a defective bicarbonate umbrella also contribute to disease development and form the basis for bile acid therapy in PSC [4, 5].

One of the most striking features of PSC is its association with inflammatory bowel disease (IBD), noted in up to 75% of patients. The association is stronger with chronic ulcerative colitis (UC), although Crohn's disease and indeterminate colitis are also seen. Patients with PSC-IBD often have a specific IBD phenotype, termed IBD-PSC, characterized by pancolitis with rectal sparing and with ileal backwash [6]. The type of IBD, along with age at presentation, has a major influence on the course of PSC, with UC and older age at presentation being associated with worse progression [7••].

The most commonly reported symptoms in PSC include fatigue, jaundice, pruritus, and abdominal pain; however, up to 40% are asymptomatic at diagnosis. The biochemical hallmark of PSC is an elevation in serum alkaline phosphatase (ALP), usually between three and ten times the upper limit of normal. Other laboratory abnormalities include elevation in serum transaminases and immunoglobulin G (IgG) and presence of autoantibodies [8]. In approximately 10% of patients with PSC, an elevation of IgG subclass 4 (IgG4) is noted [9], making it important to differentiate PSC from IgG4-sclerosing cholangitis (IgG4-SC), which is the biliary manifestation of IgG4-related disease.

IgG4-related disease is a systemic process characterized by involvement of multiple organs with a lymphocytic infiltrate and an abundance of IgG4-positive plasma cells. The disease is diagnosed based on the HISORt criteria—histopathological, imaging, serological (serum IgG4 levels), other organ involvement (pancreas, salivary glands, kidneys, etc.), and response to treatment [10]. The magnitude of IgG4 elevation and the ratio of IgG4/IgG1 help in the differential diagnosis of PSC versus IgG4-SC. Markedly elevated IgG4 levels of greater than 2.8 g/L are suggestive of IgG4-SC, whereas elevated levels between 1.4 g/L and 2.8 g/L are equivocal and require further evaluation [11]. In this subgroup of patients, an IgG4/IgG1 ratio > 0.24 suggests Ig4-SC [12].

Typically, the diagnosis of PSC is suspected in a patient with a cholestatic pattern of liver biochemistries and findings of multifocal strictures and dilatations of the biliary tree on cholangiogram. Importantly, other causes of secondary sclerosing cholangitis must be excluded. Cholangiography can be performed using magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), or percutaneous transhepatic cholangiogram, but MRCP is recommended as the initial diagnostic modality [13]. MR-based elastography and vibration-controlled elastography can be used to estimate the presence of advanced fibrosis/cirrhosis and non-invasively stage PSC [14, 15].

Approximately 10% of patients with sclerosing cholangitis will have the same biochemical and histological characteristics of classic PSC but with a normal cholangiogram. These patients are classified as small-duct PSC and are known to have a more benign clinical course, with longer transplant-free survival and lower rates of cholangiocarcinoma compared to large-duct PSC. Importantly, approximately 25% of patients with small-duct PSC progress to large-duct PSC within an average of 8 years [16, 17].

Currently, specific medical therapy for PSC is not available. The goals of treatment are primarily early detection and management of complications (Fig. 1). In addition to biliary cirrhosis, complications of PSC include dominant strictures of the bile ducts, bacterial cholangitis, cholangiocarcinoma, colon cancer (in patients with concomitant IBD), gallbladder cancer, and extra-hepatic complications of cholestasis, such as metabolic bone disease. The median survival time from diagnosis of PSC to liver transplant or PSC-related death is around 21 years [2••]. Liver transplantation is the only effective treatment modality shown to prolong survival; however, PSC can recur in up to 35% of the transplanted allografts within a median of 5 years [18–22].

Treatment Modalities for PSC

Medical Therapy

Updates on UDCA

Despite being the most widely studied medical therapy in PSC since the 1980s, the role of UDCA is still controversial. UDCA is a hydrophilic secondary bile acid thought to increase the hydrophilicity of circulating BA, stimulate the hepatobiliary secretion of BA, reduce the hepatocyte/cholangiocyte injury induced by BA and cytokines, and play an anti-inflammatory and immunomodulatory role [23]. Furthermore, UDCA in cholestasis augments epithelial membrane stability and stimulates BA excretion and a bicarbonate-rich choleresis [24].

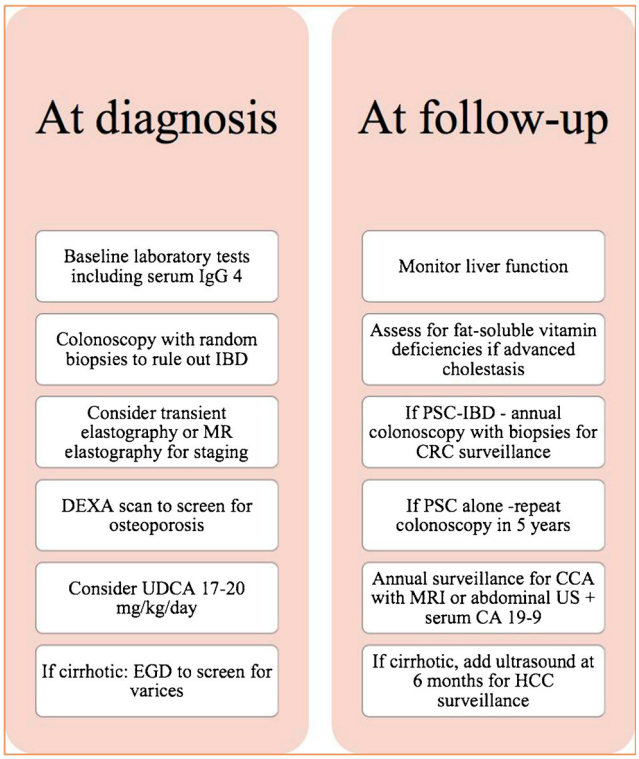

Fig. 1 Management recommendations at diagnosis and follow-up of a patient with primary sclerosing cholangitis (PSC); IgG4 immunoglobulin G subclass 4, IBD inflammatory bowel disease, MR magnetic resonance, DEXA dual-energy X-ray absorptiometry, UDCA ursodeoxycholic acid, EGD esophago-gastric duodenoscopy, CRC colorectal cancer, CCA cholangiocarcinoma, HCC hepatocellular carcinoma. With annual surveillance for CCA, we are automatically surveying the gallbladder as well

UDCA has been studied at a variety of doses as well as in combination with other therapies. To summarize, there is strong evidence against the use of high-dose UDCA (> 28 mg/kg/day) in the treatment of PSC. In fact, patients on high-dose UDCA were found to have worse outcomes including decompensated cirrhosis/death/transplant and colorectal neoplasia compared to patients on placebo [25–27]. In that regard, one study reported that the increased risk of adverse events with high-dose UDCA treatment is only significant in patients with early histological stage disease or normal total bilirubin [25].

With the exception of high-dose UDCA, which should not be used, the evidence for or against lower doses of UDCA is not quite so clear. The various randomized control trials (RCT) examining the use of UDCA have been compiled in three meta-analyses which conclude that low-dose UDCA (13–15 mg/kg/day) may result in clinical and biochemical improvement but does not impact survival, whereas medium-dose UDCA (17–23 mg/kg/day) induces a biochemical and histological response with an uncertain impact on survival and no increased rate of adverse events [28, 29].

Whether improvements in laboratory markers of cholestasis can be translated into clinical benefit is unclear. Recent studies have shown that normalization, or significant reduction, of serum ALP was associated with better prognosis [30–34]. However, they also reported that this normalization of ALP may not be driven by UDCA treatment and a rather high proportion of newly diagnosed PSC patients will experience spontaneous normalization of ALP, which correlates with an improved 10-year prognosis [35, 36]. In a Nordic population, treatment with UDCA was associated with lower incidence of cholangiocarcinoma in PSC patients awaiting liver transplantation [37]. Despite all these findings, no single RCT has shown a statistically significant survival benefit of UDCA in PSC.

With respect to chemoprophylaxis, three small retrospective studies reported a decrease in the incidence of dysplasia and colorectal carcinoma in patients with PSC and IBD being treated with UDCA [38–40]. A meta-analysis examining the efficacy of UDCA in preventing colonic neoplasia in patients with UC and PSC reported no statistically significant improvement in adenoma or colon cancer occurrence [41].

In light of all these controversial findings, Wunsch et al. sought to prospectively evaluate the effect of UDCA withdrawal on various clinical, laboratory, and quality-of-life (QOL) parameters in a cohort of 29 PSC patients [42]. Cessation of long-term treatment with UDCA resulted in a significant, rapidly deteriorating biochemical cholestasis which was accompanied by an increase in Mayo Risk Score (MRS) [42]. Of note, the MRS is a prognostic index used to predict survival in non-transplanted patients suffering from PSC. Additionally, there was a trend toward deterioration in QOL parameters as well as worsening pruritus [42]. However, patients were only followed for 3 months, which is likely insufficient time to exclude a transient rebound effect. Moreover, the study did not report how the cohort was selected, whether or not these patients had demonstrated an initial therapeutic response, and whether or not withdrawal of UDCA affected patients with and without cirrhosis differently.

Currently, the American Association for the Study of Liver Diseases (AASLD) recommends against the use of UDCA therapy in PSC patients while the European Association for the Study of the Liver (EASL) states there is insufficient evidence to make clear recommendations [8, 43]. The American College of Gastroenterology (ACG) issued a recent set of guidelines recommending against the use of high-dose UDCA (> 28 g/kg/day) but leaving further decisions regarding use of median-dose UDCA at the discretion of the treating physician based on impact on serum ALP [44].

UDCA has also been utilized in combination with other adjuvant therapies including several immunosuppresants and antibiotics. Glucocorticoids, budesonide, azathioprine, methotrexate, cylclosporine, tacrolimus, D-penicillamine, colchicine, and pentoxifylline have shown no benefit in PSC [44].

Novel Therapies Under Evaluation

Antibiotics Although the relationship between the gut microbiota and PSC is incompletely understood; it is well known that the microbiome directly affects BA homeostasis and other metabolic pathways [45]. Furthermore, the composition of gut microbiota is distinct in patients with PSC-IBD compared to IBD alone, showing reduced bacterial diversity and altered composition. As an example, investigators found an abundance of the *Veillonella* genus in patients with PSC, a genus that is possibly associated with progressive fibrotic disorders [46••]. The use of antibiotics in PSC seeks to alter the gut microbiota to suppress hepatobiliary inflammation and fibrosis.

Various antibiotics have been investigated, but the two most promising thus far have been vancomycin and metronidazole [47]. In a recent RCT investigating the safety and efficacy of low- and high-dose oral vancomycin and metronidazole, only the low- and high-dose vancomycin groups showed a significant decrease in serum ALP, which was the study's primary endpoint [48]. The MRS decreased significantly in the low-dose vancomycin group and the low-dose metronidazole group. The high-dose metronidazole group had improvement in itching scores but did not meet the primary endpoint and had too many drop-outs due to adverse events [48]. In an older study, the addition of metronidazole to low-dose UDCA treatment was shown to more significantly reduce serum ALP levels and MRS as well as improve both stage and grade of liver histology [49].

In the pediatric population, use of vancomycin has been associated with marked improvement in symptoms and liver biochemistries in addition to showing beneficial immunomodulatory effects, particularly in non-cirrhotic patients [50]. Ongoing studies are investigating the role of oral vancomycin in PSC-IBD patients (NCT01802073).

A recent pilot study of 16 patients reported a significant decrease in ALP levels and MRS with the use of minocycline, at the expense of an increased rate of adverse events [51]. Finally, a pilot study of fecal microbiota transplantation for the treatment of PSC is underway (NCT02424174). Preliminary results indicate that fecal transplantation can significantly improve the microbiome diversity while lowering serum ALP in PSC patients [52]. Table 1 summarizes available studies of antibiotics in PSC.

24-Norursodeoxycholic Acid The synthetic bile acid homolog of UDCA, norursodeoxycholic acid (norUDCA), has superior anti-inflammatory, anti-fibrotic, and anti-proliferative effects when compared to UDCA, with a highly potent choleretic profile [55]. The chemical properties of norUDCA enable cholehepatic shunting, that is, the recycling of BA between hepatocytes and cholangiocytes through the periductular capillary plexus. This process leads to induction of BA-dependent flow and flushing of the bile ducts [56]. A recent proof-of-concept phase II clinical study investigated the role of norUDCA in the treatment of PSC, using reduction in ALP as the primary endpoint. Patients were randomized to placebo or one of three active treatment arms—500, 100, and 1500 mg norUDCA daily; after the 12-week treatment period, patients on norUDCA had a dose-dependent reduction in ALP with a very promising safety profile [57••]. Phase III studies are underway in Europe (EudraCT 003367–19).

Nuclear Receptor Agonists Another approach to adjust BA secretion is by regulating genetic expression of the constituents involved in the process. Nuclear receptors are ligand-activated transcription factors that affect the expression of hepatic transporters thereby modulating the enterohepatic circulation of BA. Various novel therapies for PSC involve modulation of nuclear receptors including the Farnesoid X receptor (FXR), peroxisome proliferator-activated receptor (PPAR), pregnane X receptor (PXR), and glucocorticoid receptor.

FXR activation leads to increased expression of (FGF)19, which results in downregulation of BA synthesis, and modulation of several BA transporters, leading to a choleretic effect. Furthermore, in vitro models and animal models of FXR activation suggest anti-inflammatory and anti-fibrotic properties [58]. *Obeticholic acid* (OCA), a synthetic chenodeoxycholic acid analog that is an extremely potent FXR agonist, demonstrated anti-cholestatic, anti-inflammatory, and anti-fibrotic effects in preclinical and clinical studies [59, 60]. AESOP is a 24-week, double-blind, placebo-controlled, dose-ranging trial evaluating the efficacy and safety of OCA compared to placebo in 77 patients with PSC (NCT 102177136). Patients were randomized to one of three treatment groups: placebo, OCA 1.5–3 mg, and OCA 5–10 mg (with dose titration occurring at the 12-week midpoint). Patients receiving 5 mg of OCA daily with the option to titrate to 10 mg achieved a statistically significant reduction in ALP as compared to placebo at week 24 (-22% vs. $+1\%$, $p < 0.05$) [61]. A 2-year open-label extension phase is currently ongoing.

All-trans-retinoic acid (ATRA) is a permissive activator of FXR. In a recent pilot study, addition of ATRA to low-dose UDCA was shown to significantly reduce alanine aminotransferase (ALT) and the BA intermediate C4, a marker for BA synthesis, suggesting a reduction in hepatic inflammation [62]. However, no statistically significant reduction in ALP was observed.

NGM282, an engineered variant of FGF19, has strong anti-inflammatory and anti-fibrotic properties in mouse models of cholestatic liver diseases [63]. NGM282 was investigated for the treatment of PSC in a small RCT involving 62 patients, but results are not yet available (NCT02704363).

PPAR activation regulates BA excretion from hepatocytes and its stimulation has a strong anti-cholestatic and anti-inflammatory effect. The *fibrates* are PPAR agonists, and both

Table 1 Studies evaluating the role of antibiotics in PSC

Drug	Year	*N*	Antibiotic dose	Treatment duration	Change in ALP	Other
Metronidazole [44]	2004	80	600–800 mg/day	36 months	−52%	50% on MTZ/UDCA had AEs
Minocycline [46••]	2009	16	200 mg/day	12 months	−20%	25% discontinued due to AEs
Vancomycin [45]	2008	14	50 mg/kg (kids)	Up to 54 months		Normalization of GGT and ALT in noncirrhotics
Vancomycin vs. metronidazole [43]	2013	18 vs. 17	Vancomycin 125 or 250 mg QID MTZ 250 or 550 mg TID	12 weeks	42–10%	6 patients discontinued study due to AE, 4 in MTZ group
Vancomycin [53]	2016	29	125 mg QID	12 weeks	−45%	
Rifaximin [54]	2017	16	550 mg BID	12 weeks	No change	Only negative study with antibiotics in PSC

N sample size, *ALP* alkaline phosphatase, *MTZ* metronidazole, *UDCA* ursodeoxycholic acid, *AE* adverse events, *GGT* gamma-glutamyl transferase, *ALT* alanine aminotransferase, *QID* 4 times per day, *TID* 3 times per day, *BID* 2 times per day

fenofibrate and bezafibrate have been evaluated for PSC. Mizuno et al. reported on the benefit of bezafibrate use [64] and two small studies from France and the USA reported on use of fenofibrate for a total of 21 patients, both with significant improvement in ALP and other liver biochemistries [65, 66]. A well-designed RCT has not yet been conducted.

Finally, PXR regulates the expression of proteins involved in the detoxification and metabolism of BA. An example of a potent PXR agonist is rifampin, often used for the management of cholestatic itch. However, the use of rifampin has been limited by its potential hepatotoxicity.

Anti-fibrotics *Simtuzumab*, a monoclonal antibody against lysyl oxidase homolog 2 (LOXL2), an enzyme involved in liver fibrosis, was shown to be safe and have possible anti-inflammatory and anti-fibrotic effects in preclinical and clinical studies [67, 68]. Simtuzumab was investigated in a large multi-center RCT involving 234 patients with PSC treated for 2 years (NCT 01672853). Unfortunately, use of simtuzumab had no effect on fibrosis progression nor on serum levels of liver biochemistries [69].

Vascular adhesion protein 1 (VAP1) is involved in the inflammatory process that drives fibrogenesis in liver disease; it is suggested that VAP1 may serve as a target for reduction in inflammation and reversal of liver damage [70]. *Timolumab*, a monoclonal antibody against VAP1, is being examined in a single arm clinical trial (NCT 02239211).

Other Therapies *Vedoluzimab* is a selective humanized monoclonal antibody to the α4 β7 integrin expressed in lymphocytes, approved for the treatment of moderate to severe IBD. This α4 β7 integrin binds to an adhesion molecule selectively expressed on intestinal endothelial vessels (MADCAM1) and therefore modulates lymphocyte trafficking to the gut. MADCAM1 is also aberrantly expressed in the peribiliary plexus in certain liver diseases, including PSC. Thus, it is postulated that vedoluzimab could interrupt abnormal lymphocyte trafficking to the liver and modulate hepatic inflammation in PSC. A recent retrospective study evaluated the effect of vedoluzimab on liver biochemistries in 28 patients with PSC-IBD at weeks 14 and 30 after initiation of the infusions and failed to demonstrate any change in liver enzymes or MRS [71]. One patient had to stop vedoluzimab due to worsening of liver biochemistries. Larger studies are awaited.

LUM001, now named *Maralixibat*, is an inhibitor of the apical sodium-dependent BA transporter known to prevent intestinal absorption of BA. It has been shown to significantly decrease fasting serum BA levels. An open-label pilot study of Maralixibat treated 27 patients with PSC for 12 weeks but results of this trial have not yet been published (NCT02061540).

Cenicriviroc, an anti-inflammatory agent which antagonizes CCR2 and CCR5, is also currently being evaluated in a clinical trial in patients with PSC (NCT02653625).

Endoscopic Therapy

Endoscopic management of PSC has been proposed to improve survival and prolong transplant-free survival based on retrospective studies, but this has never been demonstrated prospectively [72, 73]. ERCP serves primarily as a therapeutic modality and should only be reserved for diagnosis in patients who cannot undergo MRCP or whose MRCP was negative despite a high clinical suspicion. The main indications for ERCP include (1) clinical suspicion for cholangitis, (2) concern for biliary obstruction manifesting with worsening biochemistries and/or pruritus, and (3) management of severe stricturing disease (Table 2) [74••]. ERCP allows for cholangiographic imaging, obtaining brushings/biopsies of the biliary tree for cytology and/or fluorescence in situ hybridization (FISH), and direct visualization with cholangioscopy. Combining these three methods to diagnose cholangiocarcinoma markedly improves sensitivity and specificity versus cytology alone [75]. The use of cholangioscopy not only

Table 2 Indications for endoscopic intervention in PSC

Indications for therapeutic endoscopy in PSC
Significant stricture identified at MRCP with symptoms likely to improve after intervention:
Cholangitis
Pruritus
Suspicion for cholangiocarcinoma-new or progressive stricture associated with:
Worsening cholestasis
New or worse itching
Weight loss
Elevated CA 19-9
Enhancing mass lesion seen on MRI

enables better visualization of the biliary tree but also offers a multitude of additional therapeutic modalities, including lithotripsy when choledocholithiasis is discovered during ERCP, which is otherwise missed in up to 30% of patients [76].

Dominant strictures, defined as stenosis with a diameter < 1.5 mm in the common bile duct or < 1 mm in the hepatic ducts within 2 cm from the bifurcation, can be treated with balloon dilatation or stenting [72, 77–82]. However, the use of stents is associated with a higher rate of complications when compared to balloon dilatation without stenting, especially post-ERCP pancreatitis. This was well demonstrated by DILSTENT, the only study comparing the two treatment modalities in a randomized controlled fashion and which failed to demonstrate any difference in survival between the two groups [83]. Currently, both AASLD and EASL recommend against the routine use of biliary stenting as primary therapy for dominant strictures. When stents are placed, their removal is recommended within 2 weeks due to an increased risk of cholangitis. To further minimize the risk of post-ERCP complications, guidelines recommend administering prophylactic antibiotics, considering use of rectal indomethacin pre-procedure, aspiration of bile prior to injection of contrast media, and performing biliary sphincterotomy in cases of difficult cannulation [74••, 84].

Surveillance for Malignancies

PSC is associated with a major lifetime risk of hepatobiliary and gastrointestinal malignancies, most commonly cholangiocarcinoma, gallbladder adenocarcinoma, occasionally hepatocellular carcinoma, and, in the PSC-IBD phenotype, colorectal carcinoma. In a large Swedish study, the risk for hepatobiliary malignancies and colorectal carcinoma was 161 times and ten times increased compared to the general population, respectively [85]. The overall frequency of malignancies was estimated to be 13%. More than 40% of the mortality in PSC patients is attributed to the associated malignancies, which far exceeds the mortality caused by end-stage liver disease [2••, 85, 86]. With such a high disease burden and very limited treatment options, it is reasonable to establish surveillance recommendations.

Cholangiocarcinoma

Cholangiocarcinoma is a rare gastrointestinal malignancy in the general population; for the PSC patient, it is the leading cause of death. The lifetime risk of cholangiocarcinoma in PSC patients is 10–15% [85]. Potential risk factors for the development of cholangiocarcinoma include old age at PSC diagnosis, male gender, a MRS greater than four, history of variceal bleeding, long duration of IBD, presence of colorectal neoplasia, and elevated total serum bilirubin [87, 88]. Additionally, certain genetic variants, smoking, and alcohol consumption have been identified as major risk factors [8, 89]. More recently, in an international study including more than 7000 PSC patients, Weismueller et al. confirmed that older age and male gender were important risk factors for cholangiocarcinoma in PSC [7••]. The presence of dominant strictures, found in up to 50% of PSC patients should raise concern for cholangiocarcinoma, although fewer than 25% of these dominant strictures are malignant [90]. Given that a third of cholangiocarcinomas are diagnosed within 12 months of PSC diagnosis, newly diagnosed patients should be under close surveillance [7••, 43].

Although specific surveillance guidelines are not universally accepted, experts agree that patients with PSC should undergo annual cross-sectional imaging with magnetic resonance imaging (MRI)/MRCP or a liver ultrasound, along with measurement of serum CA19-9 (Fig. 1). Despite being the tumor marker most commonly associated with cholangiocarcinoma, serum CA 19-9 does not perform well as a screening test. Using a cut-off value of 129 U/mL provided a sensitivity of 78% and specificity of 98% [91]. However, it is well known that approximately a third of patients with PSC and elevated CA 19-9 do not harbor a malignancy [92]. Using lower cut-off values, such as 20 U/mL, leads to a substantial increase in false-positive tests [93]. As a result of the poor accuracy of CA 19-9, guidelines are purposefully evasive and do not provide a clear recommendation on specific cut-offs to be used. For patients with high CA 19-9 and no evidence of dominant strictures, it may be appropriate to repeat imaging with MRI/MRCP at a shorter interval.

Patients with a new dominant stricture or one that occurs in association with worsening symptoms, change in serum cholestatic parameters, or with rapidly increasing or persistently elevated CA19-9 should undergo ERCP with brush cytology and FISH. Although the diagnostic yield of this procedure is low, with negative brushings not providing absolute

reassurance of the absence of cancer, techniques such as FISH, digital image analysis, or direct visualization of the biliary tree via digital cholangioscopy have provided significant improvement. To that end, finding of polysomy on FISH, especially when serial (from specimens collected from multiple ERCPs) or multifocal (in multiple areas of the biliary tree), is associated with greater likelihood of diagnosing cholangiocarcinoma [7••, 94].

Once cholangiocarcinoma is diagnosed, treatment options are very limited. In rare cases of limited stage, unresectable, perihilar cholangiocarcinoma, patients may undergo neoadjuvant therapy and be eligible for liver transplantation under a very strict protocol [95]. In the vast majority of otherwise unresectable tumors, palliative treatments including endoscopic stenting, photodynamic therapy, and chemotherapy may be pursued.

Gallbladder Carcinoma

Gallbladder carcinoma is diagnosed in up to 3.5% of patients with PSC, [53] compared to 0.35% in the general population. In addition, the frequency of other gallbladder abnormalities including gallstones, cholecystitis, and benign lesions is increased in patients with PSC [53, 54, 96–98]. Predictors for malignancy in gallbladder lesions or polyps include size, rapid and sessile growth, imaging features of vascularity and local invasion, chronic inflammation, infections, and old age at time of identification. Since patients are already under surveillance for cholangiocarcinoma, no additional testing is required for gallbladder cancer surveillance.

Currently, both the AASLD and the EASL guidelines recommend cholecystectomy for all gallbladder lesions in PSC regardless of size [8, 43]. A gallbladder polyp >8 mm is considered the best cut-off for detection of neoplasia [98]. In the case of smaller gallbladder lesions, it is unclear whether PSC patients would benefit from cholecystectomy rather than close surveillance alone. Unfortunately, cholecystectomy performed in PSC patients, with or without cirrhosis, is associated with increased morbidity rate when compared to patients without PSC. The risk is further increased for patients with Child-Pugh score ≥ 7 [98]. Therefore, for patients with Child B cirrhosis and small gallbladder polyps <8 mm, an alternative strategy may be to repeat ultrasound imaging in shorter intervals of 3 to 6 months.

Hepatocellular Carcinoma

Although the prevalence of hepatocellular carcinoma is not well established in PSC, patients afflicted with cirrhosis secondary to PSC have a higher risk of developing hepatocellular carcinoma with an estimated incidence of 1.5% per year [99]. Bergquist et al. determined that in a large cohort of PSC patients undergoing orthotopic liver transplantation, up to 4% had hepatocellular carcinoma [85]. Surveillance for hepatocellular carcinoma in PSC is not widely recommended; however, surveillance for other hepatobiliary malignancies will serve dual purpose. The recommendations for diagnostic tools for hepatocellular carcinoma surveillance are not different than for other liver disease. AFP and ultrasound imaging are widely used. Strong evidence for the frequency of screening is lacking; however, in the cirrhotic PSC patient, biannual ultrasound imaging is recommended [100].

Colorectal Carcinoma

In patients with PSC-IBD, the 20-year risk of colorectal carcinoma is 20–30% compared to 5% in patients with UC alone. A large meta-analysis comparing the risk of colorectal carcinoma in PSC-UC subjects versus UC alone determined that PSC serves as an independent risk factor for colonic dysplasia [101]. This also holds true in Crohn's colitis, however, with a less profound association. With that being said, at the time of PSC diagnosis, patients should undergo colonoscopy with biopsies to determine whether or not IBD is present (Fig. 1). If PSC-IBD is diagnosed, either annual (EASL) or biannual (AASLD) colonoscopy with 4-quadrant biopsies every 10 cm should be pursued [8, 43]. The specific timing and frequency of repeat colonoscopy when IBD is not diagnosed is unclear. Currently, it is suggested that patients undergo repeat colonoscopy with biopsies every 5 years.

Conclusion

The progressive nature of PSC and the lack of an effective medical therapy make this disease one of the leading indications for liver transplantation. In addition to biliary cirrhosis, these patients are plagued with a number of biliary and extra-hepatic complications as well as malignancies, for which surveillance is indicated. Recently, an improved understanding of the regulation of BA homeostasis and the pathogenesis of cholestatic diseases has contributed to new therapeutic targets being explored for PSC, with promising preliminary results.

Compliance with Ethical Standards

Conflict of Interest Cynthia Levy reports grants and personal fees from Intercept Pharmaceuticals, grants from Tobira, grants from Gilead, grants from NGM, grants from Shire (formerly LUMENA), grants from High Tide, grants from DURECT, outside the submitted work.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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