

# Primary Sclerosing Cholangitis: Therapeutic Options and Surveillance Management

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**ABSTRACT:** Primary sclerosing cholangitis is a chronic immune-mediated liver disease. Though rare, it poses several clinical concerns for the managing physician. There are currently limited therapeutic options in the management of the condition and weak evidence base behind them. Endoscopic intervention is limited to those patients with obstructing stricture-related disease, and even liver transplantation has a risk of disease recurrence. Surveillance for inflammatory bowel disorders, metabolic bone disease, and malignancy is paramount when managing such patients. This article provides an overview of the condition with further focus on current therapeutic options and guidance on surveillance management.

**KEYWORDS:** cholangitis, surveillance, management, therapy

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## Introduction

Primary sclerosing cholangitis (PSC) is a chronic immune-mediated cholestatic liver disease characterized by inflammation and fibrosis of both intra- and extrahepatic bile ducts.<sup>1</sup> This results in progressive fibrostenotic strictures of the entire biliary tree, eventually leading to liver cirrhosis, portal hypertension, and end-stage liver disease.<sup>1</sup> The etiology is unknown, but it is more commonly seen in males with a median age of 40 years at presentation.<sup>2</sup> PSC is virtually always seen in nonsmokers.<sup>3</sup> Prevalence rates range from 6 to 16 cases per 100,000 in North America and Europe.<sup>4</sup> While the incidence of PSC is similar in North America and the Northern European countries, lower estimates are reported in Asia and Southern Europe.<sup>4</sup> Although PSC is a relatively uncommon disease, there has been an increase in incidence over time. As PSC can present subclinically with normal liver tests, thereby avoiding diagnosis, the incidence and prevalence are grossly underestimated.<sup>3</sup>

## Signs and Symptoms

The clinical presentation of PSC varies significantly. Fatigue and pruritis are common symptoms of the disease.<sup>5</sup> Fever, chills, and right upper quadrant pain may represent episodic bacterial cholangitis from biliary obstruction, whereas persistent jaundice, ascites, and variceal hemorrhage usually reflect advanced disease.<sup>1</sup>

Looking at the biochemical profile, serum alkaline phosphatase (ALP) is commonly elevated at the time of diagnosis with possible raised serum aminotransferase,<sup>5</sup> and in 10%–20%

of patients, a raised immunoglobulin G4 (IgG4) level is seen.<sup>6</sup> An unknown fraction of these patients with raised IgG4 level is likely to have autoimmune pancreatitis now known as IgG4-related sclerosing cholangitis, which has a better result for treatment.<sup>6</sup> Serum bilirubin levels tend to be in the normal range in the majority of patients.<sup>5</sup> Antismooth muscle, antinuclear, and antinuclear cytoplasmic antibodies can all be seen in up to >50% of patients with PSC; however, they are non-specific in diagnosis.<sup>7</sup>

Approximately 60%–80% of patients with PSC have concomitant inflammatory bowel disease (IBD), most commonly ulcerative colitis (UC).<sup>2</sup> IBD can be diagnosed at any time during the course of PSC.<sup>3</sup> Thus, it is recommended that all patients undergo a full colonoscopy with multiple biopsies at the time of diagnosis of PSC.<sup>8</sup> A total of 2.5%–7.5% of patients with IBD will eventually develop PSC, whereas 60%–70% of patients with PSC will develop IBD.<sup>3</sup> IBD can arise de novo even after successful liver transplantation for PSC, and PSC can develop even after curative colectomy for UC.<sup>3</sup>

## Investigations

Endoscopic retrograde cholangiopancreatography (ERCP) was historically regarded as the gold standard diagnostic investigation for PSC;<sup>5</sup> however, magnetic resonance cholangiopancreatography (MRCP) has now become the imaging modality of choice due to its noninvasive nature, which avoids potentially serious complications, such as pancreatitis and bacterial cholangitis.<sup>9</sup> Additionally, it avoids radiation



exposure,<sup>4</sup> the need for prophylactic antibiotics,<sup>10</sup> and is more cost effective than ERCP.<sup>4</sup> A cholangiographic assessment of the biliary tree is useful to diagnose large duct PSC, and MRCP is the investigation of choice.<sup>5</sup> Classic features include multifocal annular structuring within the intrahepatic and/or extrahepatic bile ducts with alternating normal or slightly dilated segments.<sup>4</sup> A liver biopsy rarely adds to the diagnosis of PSC and can be nonspecific in the early stages.<sup>2</sup> The classic description of concentric ductal fibrosis, also known as onion skinning, involving the bile ducts within the portal tract areas is now rarely encountered.<sup>4</sup> It is, however, helpful in ruling out overlapping features of autoimmune hepatitis and diagnosing small duct disease.<sup>2</sup>

## Management

**Medical therapy.** Ursodeoxycholic acid (UDCA) has proved to be effective in primary biliary cirrhosis, but its efficacy has been controversial in PSC.<sup>6</sup> Low-dose UDCA (15–20 mg/kg/d) showed improvements in serum liver tests but not in symptoms. There was also no difference in treatment failure or progression of cirrhosis, development of varices, ascites, or encephalopathy.<sup>9,11</sup> A trial for high-dose UDCA was abandoned early due to an increased risk for the treatment group of serious adverse effects, including death and liver transplantation.<sup>9</sup> Randomized double-blind placebo-controlled trials using the lower end of higher doses of UDCA (30 mg/kg/d) failed to demonstrate efficacy and rather accelerated portal hypertension and variceal bleeding compared with placebo.<sup>12</sup> It is thought that the obstruction of bile ducts/ductules due to fibrotic strictures in PSC may have contributed to high-dose UDCA-induced disease progression and portal hypertension.<sup>13</sup> A recent study demonstrated that UDCA withdrawal leads to significant deterioration of liver biochemistry with varying symptom response but no real change to perceived quality of life.<sup>14</sup> The American Association for the Study of Liver Diseases (AASLD) currently recommends against UDCA use in patients with PSC,<sup>5</sup> whereas the European Association for the Study of Liver Guidelines (EASL) suggested that UDCA should only be offered to patients with PSC who also have advanced colitis.<sup>15</sup>

The use of immunosuppressive therapy in PSC has shown little impact with no evidence of long-term efficacy or delay in progression to end-stage PSC or complications.<sup>3</sup> Tacrolimus, azathioprine, and corticosteroids have shown modest improvements in liver biochemistry. These effects, however, were not sustained and did not show clinical benefit, and the outcomes were not assessed over prolonged periods to determine the progression to cirrhosis.<sup>16–18</sup> Corticosteroid therapy has been shown to be responsive in IgG4 cholangitis but does not have a role in PSC.<sup>7</sup> This response is defined as markedly improved biliary strictures allowing stent removal, reduction in liver enzymes, and significant decreases in serum IgG4 and CA19-9 levels.<sup>19</sup>

Antibiotics, specifically vancomycin, metronidazole, tetracycline, azithromycin, and minocycline, were explored to investigate the interrelationship between systemic and mucosal inflammation, gut microbiota, and bile acid metabolism.<sup>6,20,21</sup> Metronidazole has been shown to reduce pruritic symptoms.<sup>20</sup> In a specific trial, at 12 weeks, vancomycin led to a reduction in ALP and low dose metronidazole showed significant reduction in bilirubin.<sup>21</sup>

Fenofibrates also showed reduction in ALP levels; however, further studies are needed to assess the association of hepatitis with this medication.<sup>21</sup> There are ongoing studies with rifaximin, nor-UDCA, retinoic acid, simtuzumab, and an apical sodium-dependent bile salt transporter blocker.

### Symptom management.

**Pruritis.** Pruritis can be detrimental to patient's quality of life leading to depression and sleep deprivation. In severe cases, it can lead to suicidal ideation.<sup>22</sup> It tends to be worse at night and in warm, humid climates. Without appropriate symptom control, it may lead to excoriations from scratching and other dermatologic complications. Mild pruritis can be managed with skin emollients and antihistamines. More severe pruritis is managed with bile acid sequestrants, such as cholestyramine.<sup>7</sup> Other medical interventions include rifampicin (to be used in caution as increases risk of hepatotoxicity), naltrexone or naloxone, sertraline, or phenobarbital.<sup>7,22,23</sup> There are limited data on the efficacy of these medications, and approximately 5%–10% of patients have severe pruritis, that is, refractory to medical therapy.<sup>22</sup> If there is a dominant stricture, then therapeutic intervention should be considered for symptom alleviation.<sup>7</sup>

**Fatigue.** Fatigue is common in PSC and is also very difficult to treat as well. UDCA has shown to improve fatigue in a few studies but with limited evidence.<sup>23</sup> It is thought that fatigue may be a symptom of depression, which is commonly found in chronic diseases;<sup>24</sup> however, a recent study by van Os et al<sup>25</sup> failed to demonstrate an increased frequency of depression in PSC. Currently, there is no recommended therapy to improve fatigue in PSC, as recent studies in antidepressants have not yet proved any beneficial effect of quality of life or fatigue.<sup>26</sup> It is important, however, to exclude any associated conditions that can cause or worsen fatigue, such as depression, anemia, adrenal insufficiency, sleep disorders, and hypothyroidism.<sup>23</sup>

**Endoscopic intervention.** The main objective of an endoscopic or percutaneous therapeutic approach to the management of patients with PSC is to relieve biliary obstruction secondary to stricturing disease. The AASLD recommends that patients who would derive maximal benefit from this procedure are those with symptoms from dominant strictures, such as cholangitis, jaundice, pruritis, right upper quadrant pain, and worsening biochemical indices.<sup>5</sup> If dominant strictures are present, initial management should be with endoscopic dilatation with or without stenting.<sup>27</sup> AASLD also



recommends that prior to endoscopic therapy, brush cytology and/or endoscopic biopsy should be obtained to exclude a superimposed malignancy.<sup>5</sup> Due to the invasive nature of the procedure, 7.3%–20% are at risk for complications postendoscopy, including pancreatitis, cholangitis, biliary tract perforation, and hemorrhage.<sup>5,28</sup>

**Liver transplantation.** PSC is the fifth most common indication for liver transplantation in the United States<sup>29</sup> and accounts for 4%–5% of all liver transplants performed each year.<sup>30</sup> As with all patients with chronic liver disease, indications for liver transplantation are portal hypertension refractory to medical therapy, impaired quality of life, and chronic liver failure.<sup>4,5</sup> Additional indications for patients with PSC include recurrent bacterial cholangitis and cholangiocarcinoma.<sup>5,6</sup> Refractory pruritis may rarely be an indication for liver transplant<sup>22</sup> only after all therapeutic options have been exhausted, and psychiatric comorbidity potentially worsening the pruritis has been excluded.<sup>31</sup> The one-year survival rate posttransplant exceeds 90%,<sup>32</sup> and the five-year survival rate for deceased donor allografts is 85% with disease recurrence occurring in 20%–25% after 5–10 years.<sup>33</sup> A Roux-en-Y choledochojejunostomy is typically the method of choice for biliary reconstruction during liver transplant.<sup>34</sup> Complications of liver transplant include early acute cellular rejection (within 30 days), hepatic artery thrombosis, anastomotic biliary stricture, and recurrence.<sup>4</sup> Unlike chronic ductopenic rejection, early acute rejection responds well to systemic corticosteroids and has shown to have no effect on graft survival.<sup>32</sup>

**Recurrent PSC.** PSC has shown to recur in 20%–25% of liver transplant recipients over 10 years.<sup>4</sup> A large study showed that patients with IBD and an intact colon were at increased risk for PSC recurrence.<sup>35</sup> There is a hypothesis of an interrelationship between posttransplant IBD activity requiring intensified corticosteroid treatment leading to increased PSC recurrence rates.<sup>36</sup> A rise in serum alkaline phosphatase can indicate recurrence with confirmation on cholangiography, showing the typical features of PSC in the original liver.<sup>4</sup> Unfortunately, no medical therapy has yet been shown to effectively prevent PSC recurrence or stop disease progression. Retransplant may be successful, but the disease can continue to recur.<sup>4</sup>

### Prognostic Indicators

Recent studies have shown that normal range ALP levels are significantly associated with a better prognosis.<sup>37</sup> Lindstrom's prospective randomized control trial demonstrated that patients who have reduced (by 40% or more from initial diagnosis) or normal levels of ALP have longer survival times than patients without reductions in ALP. This did not vary in patients who were also given UDCA.<sup>38</sup> Al Mamari et al's<sup>39</sup> study showed that an improvement in ALP to below 1.5, the upper limit of normal, was associated with a better outcome and a reduced risk of cholangiocarcinoma in PSC.

### Cancer Surveillance in Patients with PSC

Patients with PSC have an increased incidence of colorectal, hepatobiliary, and gallbladder malignancies. As a result, cancer surveillance is recommended in this patient cohort.

**Colorectal neoplasia.** The prevalence of colorectal neoplasia in patients with PSC and IBD is thought to be as high as 60%–80% in Western countries.<sup>6</sup> Therefore, at the time of diagnosing PSC and five yearly thereafter, colonoscopy and biopsy to exclude IBD is advised.<sup>2</sup> Both the EASL and the AASLD recommend annual or biannual surveillance of patients found to have concomitant PSC and IBD. The risk of colorectal cancer is not reduced postliver transplant, and surveillance should continue thereafter.<sup>4</sup>

Recent studies are investigating whether there are medications that may prevent the development of dysplasia and thus prevent cancer. As it is thought that chronic inflammation leads to malignant transformation, the use of maintenance anti-inflammatory therapy should constitute primary chemoprevention.<sup>40</sup> Thus, 5-aminosalicylate compounds, immunomodulators, UDCA, and folic acid have been identified as possible chemopreventive agents.<sup>41</sup> 5-Aminosalicylate compounds and immunomodulators have anti-inflammatory properties and are used as maintenance therapy in patients with UC.<sup>41</sup> Although the mechanisms of these drugs have biological plausibility, results thus far are conflicting in whether they prevent malignancy.<sup>40,41</sup> Raised levels of bile acids have been implicated as a carcinogen, which is cytotoxic to colonic epithelial cells, inducing hyperproliferation.<sup>41</sup> Thus, it is hypothesized that UDCA should reduce the risk of CRC in IBD. Some retrospective studies reported a favorable effect of low-dose UDCA, although there are no prospective controlled trials, demonstrating a benefit for UDCA for chemoprevention against colonic dysplasia in IBD associated with PSC.<sup>7</sup> A retrospective analysis showed that the long-term use of high-dose UDCA was actually associated with an increased risk of colorectal neoplasia in patients with UC and PSC.<sup>41</sup> Folate deficiency is associated with the alteration of the normal DNA methylation process and changes in chromosome and chromatin. Patients with IBD are at risk of folate deficiency as some of the medications used for IBD lead to impaired folate absorption. Similar to the above, however, results are variable, and recent studies have failed to make an association with folic acid supplementation and cancer prevention.<sup>41</sup>

**Hepatobiliary malignancy.** The lifetime risk of cholangiocarcinoma in patients with PSC is 5%–10%,<sup>42</sup> and up to 50% are diagnosed within the first year of diagnosis of PSC.<sup>15</sup> After the first year of diagnosis, the yearly incidence rate is 0.5%–1.5%.<sup>15</sup> Advanced fibrosis is not a prerequisite to its development.<sup>42</sup> The guidance for surveillance is less clear in the case of hepatobiliary malignancies than in colorectal neoplasia. AASLD recommends CA19-9 levels with either annual magnetic resonance (MR) imaging and MRCP or ultrasound examinations to diagnose or exclude cholangiocarcinoma if





there is a clinical indication, such as a deterioration in the patient's clinical condition or liver function tests.<sup>5</sup> They do not, however, suggest routine surveillance. Recent American College of Gastroenterology guidelines on PSC advise to consider screening for cholangiocarcinoma with regular ultrasound or MR and serial CA19-9 every 6–12 months.<sup>7</sup> EASL guidelines acknowledge that it is difficult to distinguish between benign and malignant changes with all imaging modalities and suggest that CA19-9 combined with cross-sectional liver imaging may be useful as a screening strategy.<sup>15</sup> CA19-9 levels of >130 U/L are 79% sensitive and 98% specific for cholangiocarcinoma in the absence of bacterial cholangitis;<sup>43</sup> the presence of CA19-9 at this level in patients with PSC warrants further investigation. Brush cytology sampling and biopsy during ERCP is specific but very insensitive (18%–40%).<sup>7</sup> Fluorescence in situ hybridization of cell samples will increase the sensitivity and add to the diagnostic accuracy of cholangiocarcinoma.<sup>7,15</sup>

**Gallbladder malignancies.** In patients with PSC, gallbladder cancer risk is 10 times higher than in the general population. Male gender and age under 60 years are additional risk factors.<sup>44</sup> The EASL guidelines recommend annual ultrasound scanning to exclude gallbladder masses.<sup>15</sup> Though what is to be done if a mass lesion is detected is a contentious issue. AASLD recommends cholecystectomy regardless of the size of the lesion,<sup>5</sup> and EASL guidelines recommend cholecystectomy with a gallbladder mass even <1 cm in diameter.<sup>15</sup> However, undergoing cholecystectomy is not without risk, especially in patients with PSC; one study put the morbidity at 40% for cholecystectomies in this cohort and found no malignant changes in polyps <8 mm in size.<sup>45</sup> American College of Gastroenterology thus recommends cholecystectomy for patients with gallbladder polyps >8 mm in size to prevent the development of gallbladder adenocarcinoma.<sup>7</sup> As the incidence of gallbladder malignancies in PSC is markedly lower than that of hepatobiliary malignancies, EASL guidelines does not currently recommend regular screening.<sup>15</sup> However, annual abdominal ultrasonography should be considered for any detected gallbladder abnormalities.<sup>15</sup>

### Metabolic Bone Disease

Chronic liver disease generally can cause metabolic bone disease (termed hepatic osteodystrophy), and as such this can develop in patients with PSC. It presents as osteopenia or osteoporosis, which is defined as dual energy X-ray absorptiometry (DEXA) scan *T*-scores of 1–2.5 or greater than 2.5 standard deviations below the density of normal adult bones, respectively. The incidence of osteoporosis is 4%–10% in PSC, with increasing age, duration of PSC, and decreasing body mass index being additional risk factors.<sup>46</sup> It is recommended that patients with PSC and confirmed osteopenia receive calcium and vitamin D; in the case of osteoporosis, bisphosphonates should be added.<sup>47</sup> It is also suggested that parenteral bisphosphonates are used in those with esophageal varices as

esophageal ulceration is a recognized problem in patients taking oral bisphosphonates.<sup>5</sup>

### Conclusion

PSC is a progressive disease that reduces patients' survival and quality of life. As of yet, there are no effective medical therapy and management centers on early recognition of the disorder and implementation of routine screening protocols to identify complications and treat any concomitant conditions. Specific management focuses on endoscopic emphasis and appropriate referral for liver transplant when necessary.

### Author Contributions

Conceived and designed the experiments: AK and AP. Analyzed the data: AK, DW, and AP. Wrote the first draft of the manuscript: AK and DW. Contributed to the writing of the manuscript: AK, DW, and AP. Agree with manuscript results and conclusions: AK, DW, and AP. Jointly developed the structure and arguments for the paper: AK, DW, and AP. Made critical revisions and approved final version: AK and AP. All authors reviewed and approved of the final manuscript.

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