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Eric Gochanour

*Liver Care Network and Organ Care Research Swedish Medical Center Seattle WA*

Channa Jayasekera

Kris V Kowdley

*Liver Care Network and Organ Care Research Swedish Medical Center Seattle WA*

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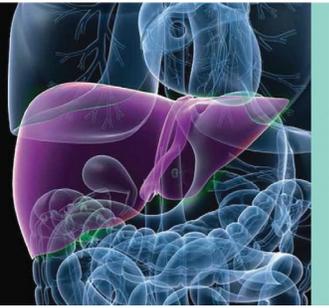
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# Primary Sclerosing Cholangitis: Epidemiology, Genetics, Diagnosis, and Current Management

*Eric Gochanour, M.D.,\* Channa Jayasekera, M.D.,†  
and Kris Kowdley, M.D.\**

Primary sclerosing cholangitis (PSC) is a rare, idiopathic, and progressive biliary tract disease that can lead to liver fibrosis and cirrhosis. PSC is characterized by inflammation and destruction of intrahepatic and extrahepatic bile ducts, leading to progressive hepatic fibrosis.<sup>1</sup> The etiology of PSC is unknown, although several genes are associated with its development and clinical course.<sup>2,3</sup> There is a strong association between inflammatory bowel disease (IBD) of the colon and PSC.<sup>1,2</sup> An overlap syndrome of autoimmune hepatitis and PSC is an additional, well-established presentation, particularly in younger patients. The diagnosis of PSC relies heavily on characteristic cholangiographic features in the setting of cholestatic liver enzyme abnormalities.<sup>2</sup> Patients with PSC are at increased risk for cholangiocarcinoma and gallbladder cancer, as well as colon cancer in those with concurrent IBD.<sup>4</sup> Screening for malignancies involving the gallbladder, bile ducts, and colon is therefore a critical

component of PSC management. Liver transplantation is by far the most effective treatment, although a posttransplant recurrence rate of approximately 20% is reported. This review aims to highlight the most salient aspects of identifying and managing this unique cholestatic liver disease.

## EPIDEMIOLOGY

PSC is a rare disorder with regional variation in prevalence.<sup>3</sup> The prevalence in the United States is estimated to be 1 to 16 per 100,000.<sup>1</sup> An estimated 80% of patients diagnosed with PSC have concurrent IBD.<sup>2</sup> There is a 2:1 male predominance when PSC is associated with IBD and a slight female predominance in the absence of IBD (Table 1).<sup>1</sup> Average age at diagnosis is typically 30 to 40 years old.<sup>1</sup> In patients with IBD, the prevalence rate of PSC is estimated to be approximately 5%.<sup>3</sup>

Abbreviations: ERC, endoscopic retrograde cholangiography; IBD, inflammatory bowel disease; MRC, magnetic resonance cholangiography; PSC, primary sclerosing cholangitis.

From the \*Liver Care Network and Organ Care Research Swedish Medical Center, Seattle, WA; and †Department of Gastroenterology, Kaiser Permanente Washington, Seattle, WA.

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**TABLE 1. PSC EPIDEMIOLOGY**

Characteristics

Sex: Men (2:1)  
 Age at Diagnosis: Fourth to fifth decade of life  
 IBD in PSC: 80%  
 PSC in IBD: 5%

**GENETICS**

The pathogenesis of PSC remains unclear, although multiple genes have been implicated in its development.<sup>3</sup> An immunologically mediated process is supported by known associations with human leukocyte antigens.<sup>3</sup> Another theory involves bacterial translocation to the biliary tree based on an animal model of bacterial overgrowth and link with ulcerative colitis.<sup>3,4</sup> Certain gene mutations including cystic fibrosis transmembrane receptor (CFTR) mutations have also been associated with the development of PSC.<sup>3,4</sup>

**DIAGNOSIS**

Patients with PSC are often asymptomatic early in the disease course; usually they are identified through a persistent cholestatic pattern of elevated liver enzymes.<sup>2</sup> Fatigue and pruritus are common symptoms, but many patients are asymptomatic. Biliary tract obstruction may lead to acute pruritus and/or cholangitis, presenting with jaundice, fever, and abdominal pain. Patients with PSC-IBD may present with abnormal bowel habits, abdominal pain, and intestinal bleeding, with concurrent liver enzyme abnormalities.

The differential diagnosis of PSC includes secondary sclerosing cholangitis, immunoglobulin G4-associated cholangitis, autoimmune hepatitis, primary biliary cholangitis, ischemic cholangiopathy, papillary tumors, cholangiocarcinoma, cholangiolithiasis, and HIV cholangiopathy.<sup>3</sup> These causative factors should be evaluated during the diagnostic workup.

Liver biopsy is usually unnecessary in diagnosing PSC, but it is helpful to evaluate PSC-autoimmune hepatitis overlap syndrome and small-duct PSC.<sup>3</sup> Characteristic features of PSC on histology include concentric periductal “onion skinning” fibrosis, although this distinctive feature is insensitive.<sup>3</sup> Similarly, there are no known sensitive serological assays for PSC.

**THE ROLE OF IMAGING IN PSC**

Given the limitations of liver histology and absence of sensitive serological assays, it is essential to perform cholangiography when PSC is suspected. Magnetic resonance cholangiography (MRC) is now recommended by all major professional societies as the initial diagnostic modality of choice<sup>2,3,5,6</sup> (Table 2).

Even though MRC is highly sensitive and specific (0.86 and 0.94, respectively) in detecting the multifocal biliary stricturing and peripheral pruning phenotype of large-duct PSC, indeterminate cases warrant consideration of endoscopic retrograde cholangiography (ERC), which remains the reference standard for cholangiography (Fig. 1). Isolated involvement of peripheral ductules (small-duct

**TABLE 2. DIAGNOSING PSC**

MRCP	ERCP	Liver Biopsy
Noninvasive	Greater sensitivity	Used to rule out overlapping conditions
Less expensive	Allows for therapeutic intervention	
No radiation exposure		
Eliminates risk for pancreatitis		



**FIG 1** Endoscopic retrograde cholangiography demonstrating focal strictures and dilations creating characteristic “beading” appearance of intrahepatic bile ducts.

**TABLE 3. COMPLICATIONS OF PSC**

Cholangitis  
 Gastrointestinal malignancies  
 Fat-soluble vitamin deficiencies  
 Bone diseases  
 Cirrhosis and portal hypertension

PSC) is seen in less than 10% of cases, necessitating liver biopsy because both MRC or ERC are insensitive for small-duct changes.<sup>7</sup> Although useful for diagnosis, neither baseline nor serial cholangiographic features predict disease progression or prognosis in PSC.

The increased risk for clinically significant biliary obstruction, cholelithiasis, hepatolithiasis, cholangiocellular dysplasia and cholangiocarcinoma, hepatocellular carcinoma, polyps and cancer of the gallbladder, and colon cancer drives the vital role of regular imaging in the long-term management of PSC (Table 3).

### Screening for Malignancy and Premalignant States

Despite the modest positive predictive values, most professional societies and expert opinion support screening for cholangiocarcinoma with ultrasonography, MRC, and ERC, with or without serum CA 19-9 every 6 to 12 months.<sup>2,3,5</sup> Annual ultrasonography is the recommended modality for gallbladder polyp and cancer screening. As with patients without PSC, the presence of advanced (stage 3) liver fibrosis or cirrhosis warrants hepatocellular carcinoma screening every 6 months, with ultrasonography, computed tomography, or magnetic resonance imaging, with or without serum alpha-fetoprotein. Elastography modalities (e.g., FibroScan, magnetic resonance elastography) for fibrosis staging in PSC require further validation. Even in asymptomatic individuals, colonoscopy to screen for IBD is recommended in all patients at PSC diagnosis. Presence of concurrent PSC and IBD warrants colon cancer screening with colonoscopy every 1 to 2 years.<sup>2,5</sup> European guidelines additionally recommend colonoscopy with random colonic biopsies for IBD screening every 5 years in patients with PSC who do not have concurrent IBD.<sup>5</sup>

### Imaging Directed by Clinical Features

Differentiating malignant and benign dominant biliary strictures is difficult. Nevertheless, the development of dominant biliary strictures should prompt an exhaustive evaluation for cholangiocarcinoma. Despite very high specificity, sensitivity for cholangiocarcinoma of brush cytology

obtained on ERC is only 43%.<sup>8</sup> The addition of fluorescent *in situ* hybridization increases sensitivity to 68%, although specificity decreases to 70%.<sup>8,9</sup> Pooled data from small studies of endoscopic retrograde cholangioscopy with targeted biopsy demonstrate a 65% sensitivity and 97% specificity.<sup>10</sup>

## CURRENT MANAGEMENT

There are no approved pharmacological therapies for PSC. Ursodeoxycholic acid is the best studied, although the role of this therapy in PSC remains unclear.<sup>3</sup> High-dose ursodeoxycholic acid (>28 mg/kg/day) is associated with increased adverse clinical outcomes and should be avoided.<sup>11</sup> Despite enthusiasm about its use as a possible therapy for PSC, recent studies with oral vancomycin have not shown significant benefit, and randomized clinical trials are needed.<sup>3</sup> Patients with decompensated cirrhosis caused by PSC or with refractory cholangitis may be best treated with liver transplantation. Liver transplantation has shown success for selected patients with hilar cholangiocarcinoma caused by PSC.<sup>12</sup> Recurrent PSC is estimated to occur in approximately 20% of patients.<sup>3</sup>

As with other cholestatic liver diseases, osteopenia may be a complication of PSC, and bone density screening at diagnosis and at 2- to 4-year intervals is suggested.<sup>3</sup> Fat-soluble vitamin deficiencies may occur.<sup>3</sup>

## PROGNOSIS

The disease course of PSC is highly variable. Serum alkaline phosphatase levels <1.5x upper limit of normal have been associated with improved survival in patients with PSC,<sup>13</sup> whereas patients with alkaline phosphatase levels  $\geq 2.4$ x upper limit of normal are more likely to die or require liver transplantation.<sup>14</sup>

## CONCLUSION

PSC is a rare idiopathic cholestatic liver disease with no approved treatment, although a number of agents are currently showing promise in clinical trials. The disease course is variable, and management is focused on mitigating several life-threatening complications, including hepatic and extra-hepatic malignancies, with emphasis on early consideration of liver transplantation in appropriately selected patients; liver transplantation is an effective treatment for end-stage liver disease. Disease recurrence has been reported but does not reduce favorable long-term outcomes.

## CORRESPONDENCE

Kris Kowdley, M.D., Liver Care Network and Organ Care Research Swedish Medical Center, 1124 Columbia Street, Suite 600, Seattle, WA, 98104. E-mail: kris.kowdley@swedish.org

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