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# Pathogenesis of Primary Sclerosing Cholangitis and Advances in Diagnosis and Management

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## Abstract

Primary sclerosing cholangitis (PSC), first described in the mid-1850's, is a complex liver that is heterogeneous in its presentation. PSC is characterized by chronic cholestasis, associated with chronic inflammation of the biliary epithelium, resulting in multi-focal bile duct strictures that can affect the entire biliary tree. Chronic inflammation leads to fibrosis involving the hepatic parenchyma and biliary tree, which can lead to cirrhosis and malignancy. The etiology of PSC is not fully understood which in part explains a lack of effective medical therapy for this condition. However, we have begun to better understand the molecular pathogenesis of PSC. The recognition of specific clinical subtypes and their pattern of progression could improve phenotypic and genotypic classification of the disease. We review our current understanding of this enigmatic disorder and discuss important topics for future studies.

### Keywords

cholestatic liver disease; cholangiocarcinoma; autoimmune disease; inflammatory bowel disease

## Epidemiology and Natural History

Prevalence rates for PSC in North America and Europe range from 6 to 16 cases per 100,000 inhabitants.[1–3] Studies of population-based cohorts have estimated incidence of PSC in many North American locations to be approximately 1 per 100,000 persons.[3, 4] The incidence of PSC appears similar in North American and Northern European countries.[5] However, the incidence and prevalence vary worldwide, with lower estimates reported from Asia and Southern Europe.[6, 7] Although PSC may be an uncommon disease, the reported incidence has increased over time.[5]

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The median age of patients diagnosed with PSC is 41 y, and it appears to be more common among men.[5] Patients are often diagnosed incidentally and nearly 50% are asymptomatic. Despite being asymptomatic at the time of diagnosis, patients with PSC have shorter average times of survival, compared to matched controls from the general population.[8] Five years after diagnosis of asymptomatic PSC, approximately 22% show clinical symptoms, and after 6 y, up to 76% have some evidence of disease progression (biochemical, symptomatic, or radiographic).[8, 9] Fatigue is often present at the time of diagnosis. Other presenting signs and symptoms include abdominal pain (37%), jaundice (30%), and fever (17%).[9] When patients are symptomatic upon presentation, the median time of survival until death or liver transplantation is 9 y (compared to 12–18 y for all PSC patients, regardless of symptoms).[8–10]

PSC can present during child-bearing years, yet little is known about PSC progression during pregnancy or its effects on the fetus and mother. In a case series, fertility was not reduced among women with PSC, nor was there a higher proportion of fetal loss or adverse fetal outcomes, compared to the general population. Although no serious maternal outcomes were noted, there was an increase in liver enzymes among 20% of pregnant women with PSC.[11]

The major risk factor for development of PSC is inflammatory bowel disease (IBD). Sixty to eighty percent of patients with PSC have concurrent IBD (typically ulcerative colitis, UC), and about 4% of patients with UC have coexisting PSC.[12, 13] Individuals with PSC are most frequently male, and in rare cases, have a family history of the disease. Smoking has been reported to protect against PSC, even after controlling for underlying UC.[5, 14, 15]

Several prognostic scores for PSC have been developed. The revised Mayo risk score is based on a combination of patient's age; levels of bilirubin, aspartate aminotransferase, and albumin; and the presence of variceal bleeding. These factors can predict survival times, without the need for liver biopsy.[16] However, the use of prognostic models is not recommended for management of individual patients with PSC, given the significant variations in disease course.[10, 12] Complications related to PSC such as intermittent episodes of cholangitis can occur in 10%–15% of patients.[17] Portal hypertension and cirrhosis, metabolic bone disease, associated malignancies, and co-existing conditions such as IBD add to the disease burden.

## Diagnosis of PSC

### Serum Markers

An increased serum level of alkaline phosphatase is the most common biochemical abnormality detected in patients with PSC. In some cases, it is the only biochemical alteration observed, such as in patients with intrahepatic or diffuse involvement with PSC.[12] However, the level of alkaline phosphatase can vary throughout the disease course and may be normal.[18] Although serum levels of aminotransferase are frequently normal, in some patients they are reduced to 3–4-fold below the upper limit of normal.[12] Higher values indicate acute biliary obstruction or even an overlap syndrome with autoimmune hepatitis (AIH). Serum levels of total bilirubin are typically normal, and increased only among patients with significant structuring. Serum levels of albumin, international normalized ratios, and platelet counts are typically normal unless cirrhosis and portal hypertension have developed.

Patients with IBD who have increased liver test values which suggest an underlying cholestatic liver disease should immediately raise the suspicion of concurrent PSC. In rare cases, subjects with IBD undergoing computed tomography or magnetic resonance (MR)

enterography have been found to have unsuspected intrahepatic bile duct dilatation, even though they had normal results from biochemical analyses of serum samples for liver function. Subsequent MR cholangiopancreatography (MRCP) identified changes associated with PSC in these subjects.

PSC is associated with a high proportion of non-specific auto-antibodies.[19] Unlike primary biliary cirrhosis, there is no diagnostic serologic test that is specifically associated with PSC. Serologic tests might be useful for patients suspected of having PSC and AIH, or immunoglobulin (Ig)G4-associated cholangitis (IAC) in association with autoimmune pancreatitis (AIP).

## Imaging

Cholangiography is the best way to identify patients with PSC (Figure 1). The classic features include multi-focal anular structuring within the intrahepatic and/or extrahepatic bile ducts, with alternating normal or slightly dilated segments.[20] Typically there is diffuse involvement. However, up to 25% of individuals have only intrahepatic disease.[20] Although endoscopic retrograde cholangiopancreatography (ERCP) is used to evaluate symptomatic patients with suspected biliary obstruction or cholangiocarcinoma, MR cholangiopancreatography (MRCP) has largely replaced ERCP as a diagnostic tool, due to improvements in imaging and software-processing technology. Pooled analyses have reported good to excellent diagnostic performance for MRCP, compared to ERCP, for detection of PSC.[21] MRCP is noninvasive, avoids radiation, and is more cost effective than ERCP in diagnosis.[22, 23] With stronger magnetic fields and availability of 3D image reprocessing, the ability to visualize 3$^{rd}$- and 4$^{th}$-order intrahepatic ducts is now possible, which improves the sensitivity of MRCP when no extrahepatic biliary strictures are present. It is reasonable to consider patient referral if quality MRCP images are not available, to exclude or confirm the presence of PSC.

## Liver Histology

Typically, a liver biopsy is not required to diagnose PSC, unless small-duct PSC is suspected or if there are concerns that a patient also has AIH. Histologic features of PSC are often nonspecific and prone to sampling variations, due to the heterogeneous involvement of the biliary tree.[24] Unfortunately, the classic description of concentric ductal fibrosis (“onion skinning”) involving bile ducts within portal tract areas is rarely encountered in clinical practice (Figure 2).[25] Use of histologic analysis to determine the stage of liver fibrosis requires a specialized scoring system (Batts-Ludwig).[26] However, noninvasive methods to assess fibrosis and cirrhosis, such as elastography imaging, are emerging as useful tools for subjects with PSC.[27]

## Distinguishing IAC from PSC

IAC was identified during seminal studies to codify the diagnosis and treatment for AIP. IAC and AIP are each manifestations of a systemic inflammatory condition associated with IgG4 production and deposition within the biliary system and pancreas, respectively[28, 29] IAC is often diagnosed based on the HISORt criteria (Table 1). [30] However, other criteria have recently been proposed.[31] Although biliary strictures can develop in patients with PSC or IAC, IAC appears to have distinct clinical, biochemical and histologic features from PSC (Table 1). Some individuals believed to have traditional PSC could actually have IAC, so it is recommended that serum levels of IgG4 are measured and cross-sectional imaging is used to evaluate the pancreas.[12]

Based on findings from retrospective studies, it is not clear whether some patients with PSC and increased serum levels of IgG4 actually have IAC or a unique subtype of PSC.[32, 33] For

example, Bjornsson et al. reviewed data from 285 patients diagnosed with classic PSC; 12% had increased serum levels of IgG4 (>140 mg/dL). However, only 17% of these individuals had pancreatic involvement suggestive of IAC or AIP, and few subjects were assessed by histologic analysis to identify tissue infiltration with IgG4. Mendes et al. found that patients with features of typical PSC and increased serum levels of IgG4 had a shorter time to liver transplantation, compared to patients with normal IgG4 levels, indicating a more aggressive disease course.[33]

Conversely, 23% of liver explants from patients undergoing liver transplantation for PSC had infiltration with IgG4 positive cells—these patients had a more aggressive disease course and increased risk for recurrent PSC. Interestingly, an estimated 50% of subjects with increased serum levels of IgG4 had normal did not have IgG4 positive tissue.[34] Importantly, some patients with PSC and ductal cholangiocarcinoma also have increased levels of total IgG4. Increased production of IgG4 might therefore indicate a more aggressive disease course, rather than serve as marker of patients who should be considered for treatment with corticosteroids.[35] Therefore, it is important to carefully exclude the presence of malignancy.[30] Future studies should help clarify the prevalence and outcomes of PSC patients with increased levels of IgG4 who do not meet the criteria for IAC.

### IBD in Patients with PSC

IBD is a common feature of PSC.[36] Patients diagnosed with PSC should undergo colonoscopy and biopsies to determine if they have IBD—even when there are no symptoms.[12] A recent study found that the chronologic order of diagnosis has switched in past decades. In a recent cohort (2003–2007), most patients were diagnosed with PSC first; in an earlier cohort (1993–1997), most patients were diagnosed with IBD first.[37]

Most patients with PSC and IBD have chronic UC (PSC-UC). PSC-UC may have a different phenotype than UC. Several studies have reported that pancolitis is more common in patients with PSC-UC. Although early studies associated with PSC-UC with backwash ileitis or rectal sparing, these findings have not always been reproduced.[38–40] Furthermore, subjects with PSC and IBD can have minimal endoscopic activity despite the presence of more active histologic inflammation.[41] Those with PSC-UC have an increased cumulative risk for colorectal neoplasia, compared to individuals with UC alone, an increased risk for of pouchitis, and a higher risk of peristomal varices following proctocolectomy with ileostomy.[42–44]

PSC can be diagnosed following a colectomy just as IBD can develop after liver transplantation.[36, 45] Similarly, patients diagnosed with PSC without IBD can still develop this disease and colorectal cancer, at a later time. Thus, a colonoscopy every 5 y following the diagnosis of PSC to exclude or confirm the development of IBD has been suggested.[46]

Recent observations have suggested an inverse prognostic relationship between PSC and IBD. Progressive PSC requiring a transplant appears to be associated with UC that is more quiescent and less likely to require a colectomy. In contrast, individuals without progressive PSC were found to have an increased need for colectomy, more severe histologic inflammation and increased risk of colorectal neoplasia.[47,48] These observations indirectly support a model of PSC and IBD pathogenesis that involves aberrant lymphocyte homing.[47]

## PSC Subtypes

### Small-Duct PSC

Among cases with suspected PSC and normal cholangiography, liver biopsy analysis is recommended, to rule out small-duct PSC.[12] Nearly 6% of patients with chronic cholestasis,

a normal cholangiogram, and IBD have concurrent small-duct PSC.[49] Individuals with small-duct PSC have symptoms and laboratory results similar to those of subjects with classic PSC.[49] However, patients with small-duct PSC survive longer and have a lower cumulative risk for cholangiocarcinoma than patients with large-duct involvement.[50, 51] An estimated 20% of subjects with small-duct PSC develop large-duct PSC (intra or extrahepatic) over a 7–10 y period.[50, 51]

### Overlap Between AIH and PSC

AIH-PSC has been reported to occur in 6% or less of patients with PSC but the true prevalence is unknown.[52, 53] Similar to classic PSC, IBD is often associated with AIH-PSC.[54, 55] The simplified International Autoimmune Hepatitis Group scoring system can aid in diagnosis of AIH, but it is not recommended for diagnosis of AIH-PSC.[56] AIH-PSC should be suspected for patients with abnormal cholangiograms that indicate PSC, biochemical features of AIH (increased antibody titers or levels of transaminases), lymphoplasmacytic portal-based infiltrates, and significant interface hepatitis (based on liver biopsy analysis), or for patients with AIH that becomes refractory to therapy.[12, 55] Patients with AIH-PSC could have shorter survival times (or time to liver transplantation), compared to patients with AIH alone or other overlap syndromes such as AIH and Primary Biliary Cirrhosis.[52]

## Pathogenesis

The pathogenic mechanisms of PSC are incompletely understood, but the process is likely multifactorial. A number of hypotheses have emerged; studies of these could clarify pathologic mechanisms and identify potential therapeutic targets. PSC likely occurs in genetically susceptible individuals, perhaps after exposure to environmental triggers. These could initiate a series of events that involve complex interactions between the innate and adaptive immune systems, ultimately leading to lymphocyte migration, cholangiocyte damage, and progressive fibrosis. Several important observations, coupled with the strong association between certain human leukocyte antigen (HLA) haplotypes and frequency of concurrent extrahepatic autoimmune disorders, support the concept that PSC is an immune-mediated phenomenon.[57]

### Genetic Predisposition

Patients who have a first-degree relative with PSC have a 9- to 39-fold increase in risk for the development of the disease. [14] In the past 2 decades, candidate gene studies associated specific HLAs with PSC, including the haplotypes HLA-DRB1*1501-DQB1*0602, HLA-DRB1*1301-DQB1* 0603, and HLA-A1-B8-DRB1*0301-DQB1*0201.[58–61]

Recent, genome-wide association studies have also reported that the strongest genetic risk to PSC lies within the MHC, where the heritability represented by these loci is twice that of all other risk loci combined. [62] Several other loci have been associated with PSC; these contain genes that regulate immune self-recognition and adaptive immunity. [63] To date, 12 non-MHC risk loci have been associated with PSC. Most of these loci have a stronger association with PSC than IBD, indicating the overlapping yet unique genetic architecture between PSC and IBD.[64] However, the picture of genetic predisposition to PSC is not complete; large genetic studies are underway to identify variants associated with PSC and to better determine its association with IBD.

### Bacteria, Molecular Patterns and the Innate Immune System

Translocation of microbial flora across an inflamed, permeable gut with subsequent activation of the immune system and inflammation of the biliary tree is a hypothesized

mechanism for the development of PSC.[65] Small intestinal bacterial overgrowth and introduction of bacterial antigens to the portal circulation cause pericholangitis in animal models.[66–68] However, studies in humans have suggested portal venous bacteremia is uncommon in UC.[69] Blood samples from patients with PSC have staining patterns for atypical perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) that differ from those of patients with other vasculitides.[70] Atypical p-ANCA appears to cross react with human β-tubulin isotype 5 and the bacterial protein FtsZ, which is expressed by intestinal flora.[71] PSC patients might therefore have an aberrant immune response to intestinal microbes.

Although some antibiotics have been shown to reduce serum levels of alkaline phosphatase and Mayo Risk scores, the long-term effects of antibiotics on PSC progression are not clear.[72, 73] Growing interest in the relationship between the human microbiome and chronic disease will undoubtedly lead to studies in patients with PSC.

Normally, biliary epithelial cells are exposed to common intestinal pathogen-associated molecular patterns such as lipopolysaccharide and lipoteichoic acid. However, exposure to lipopolysaccharide may disrupt tight junctions in colonic and biliary epithelial cells, through Toll-like receptor (TLR)4-dependent mechanisms.[74, 75] Alteration of such barriers could expose cholangiocytes to a variety of substances, such as bile acids, that could promote injury and inflammation. Disruption of cholangiocyte tight junctions is an important step in the development of PSC in animal models.[76, 77] For example, mice with altered cholangiocyte tight junctions leak bile acid into the portal tract. This leads to an inflammatory response that involves CD8+ and CD4+ T cells and upregulation of tumor necrosis factor (TNF)α, transforming growth factor β1, and interleukin (IL)1β. This inflammatory infiltrate causes myofibroblast activation and fibrosis.[76]

Despite exposure to such common pathogen-associated molecular patterns, the innate immune system of patients without PSC does not appear to be as upregulated by these endotoxins.[78, 79] For example, in liver explants from patients with PSC, biliary epithelial cells express higher levels of TLR, nucleotide-binding oligomerization domain, the MyD88/IRAK complex, TNFα, interferon (INF)γ, and IL8 than cells from individuals without PSC. Early-stage PSC samples express lower levels of IL8, TNFα, and TLR than late-stage samples. After repeated exposure to endotoxins, biliary epithelial cells from patients with PSC continued to secrete high levels of IL8, indicating a lack of tolerance to repeated endotoxin exposure. This hyper-responsiveness could be mediated by increases in IFNγ and TNFα, which stimulate TLR4-mediated intake of endotoxin by biliary epithelial cells and ongoing TLR4 signaling in patients with PSC.[78] In addition, pathogens could stimulate TLR5 or TLR7 to induce T-helper (Th)17 cells, which produce IL17, in PSC patients.[80]

These findings indicate that patients with PSC have an increased immune response to intestinal endotoxins, which could contribute to chronic biliary inflammation. The common association between bacteria and dominant biliary strictures could further promote this response in advanced stages.[81] Some researchers have proposed that the innate immune system is also involved in the early stages of PSC development. This process could involve activation of macrophages, natural killer cells, and dendritic cells by pathogen-associated molecular patterns via pattern recognition receptors such as TLRs.[82]

## Adhesion Molecules and Lymphocyte Recruitment

The interaction between adhesion molecules and lymphocyte recruitment to the liver is emerging as an important step in the pathogenesis of PSC. Inflammatory mediators appear to upregulate a variety of adhesion molecules during development of PSC, including intercellular adhesion molecules, vascular cell adhesion molecule-1 (VCAM-1), and mucosal addressin cellular adhesion molecule 1 (MAdCAM-1).[83] Typically, MAdCAM-1 is

expressed in the mucosal vessels of the intestine. However, under conditions of inflammation, it can be expressed by hepatic endothelium.[84, 85] Patients with PSC have also been observed to have altered expression of chemokines such as CCL 25, CCL 28, CXCL12, and CXCL 16. Upregulation of CCL 25 and 28 leads to activation of α4β7 integrins, which increases lymphocyte binding to MAdCAM-1. CCL 28 also appears to activate α4β1 integrin and increase its adhesion to VCAM-1, which is primarily expressed in the portal and sinusoidal endothelial cells of the liver. Once lymphocytes have entered the portal tract, CXCL12 and CXCL16 may facilitate lymphocyte binding to the bile duct epithelium.[83]

The observation that PSC can still develop after colectomy, and IBD can still develop after liver transplantation has led some to suggest that aberrant homing of lymphocytes between the intestine and liver could be involved in the pathogenesis of PSC.[86] In this hypothesis, activated intestinal lymphocytes undergo enterohepatic circulation and persist as memory cells that cause hepatic inflammation. Chemokines and adhesion molecules that are shared by the intestine and liver could contribute to binding of immune cells at both sites.[86] Vascular adhesion protein (VAP)1 is found in endothelial cells of the liver and in the mucosal vessels. In patients with IBD, the chronic inflammation appears to upregulate VAP-1 expression in intestinal venules.[87] Activation of VAP-1 has been shown to increase the expression of MAdCAM-1 in hepatic vessels, which ultimately promotes recruitment of effector lymphocytes to the liver.[88] However, upregulation of hepatic MAdCAM-1 has been described in other chronic liver disease, so it might not be a specific feature of PSC.[84]

Long-lived memory cells that are primed in the intestine and circulate to the liver might lead to PSC after colectomy. Interestingly, it appears that α4β7+CCR9+ CD8+ T cells that infiltrate the liver in PSC appear to be primed by dendritic cells in the intestine, rather than antigen-presenting cells in the liver, through a process that requires retinoic acid.[89] These observations support a role for aberrant lymphocyte trafficking in the pathogenesis of PSC. Further studies are needed to clarify these findings and investigate the roles of specific adhesion molecules in the pathogenesis of PSC.

## Antibodies and T Cells

A high proportion of patients with PSC have nonspecific autoantibodies[19], as well as autoantibodies that bind to biliary epithelial cells.[90] These biliary autoantibodies have been shown to bind biliary epithelial cells and activate the innate immune system by inducing expression of transcription factor ERK1/2 and upregulating TLRs, leading to production of inflammatory cytokines.[91] The autoantibodies also increase expression of IL6 and adhesion molecules such as CD44, and could thereby promote lymphocyte proliferation, Ig production, and cell adhesion.[90, 91]

An influx of lymphocytes, particularly T cells, has been observed in the portal tracts of PSC patients.[83] In addition to the portal area, the proportion of circulating T cells, such as γδ+ T cells, is increased and also co-express CD45RO and IL2, indicating an activated memory phenotype.[82] Regulatory T cells are believed to participate in the pathogenesis of a variety of autoimmune diseases. The observation that patients with PSC-UC have a higher proportion of CD4+CD25+ regulatory T cells than patients with only UC warrants further study.[92] Th17 cells have also been implicated in autoimmune diseases.[93] Compared to patients with autoimmune hepatitis or fatty liver disease, livers of patients with PSC contain higher number of Th17 cells—possibly a response to microbes.[80]

### Transporter Defects

Multidrug resistance protein (MDR)3 is an ATP-binding cassette transporter that is required for biliary excretion of phosphatidylcholine.[94] Defects in MDR3 have been associated with several cholestatic syndromes, in addition to drug-induced cholestasis.[95] Mdr2 (the rodent analogue to MDR3) knockout mice have features of sclerosing cholangitis.[76] Decreased bile concentrations of phosphatidylcholine might increase the toxicity of other bile acids.[76] Patients with cystic fibrosis may develop biliary cholangiographic features analogous to those of patients with PSC.[96] Variants and functional mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) have been described in PSC patients.[97] However, it is not clear how mutations in MDR3 and CFTR contribute to PSC in the majority of patients.

### Animal Models

A reliable and reproducible single animal model for PSC is needed. A classification scheme for animal models was eloquently described by Pollheimer et al. In these animals, cholangitis is induced by enteric bacteria cell wall components, infectious agents (such as *Cryptosporidium parvum*), biliary obstruction, chemicals (such as lithocholic acid), knockout of genes such as *Mdr2* or *Cftr* (in mice), or primary biliary and endothelial cell injury.[57] Mice injected with death receptor 5 agonists have also provided insight into apoptosis in cholestatic liver disease.[98] Given the heterogeneity of PSC and the many factors that contribute to its pathogenesis, a single animal model will be challenging to develop. Consequently, multiple models may be required to examine the various aspects of PSC development.

## Pharmacologic Agents

### UDCA

All randomized controlled trials of agents designed to prevent PSC progression have produced negative results, despite promising results from open-label precursor studies. The most commonly studied agent is ursodeoxycholic acid (UDCA), which significantly slows progression of other chronic biliary diseases, such as primary biliary cirrhosis (Table 2).[99–103] A European study did not demonstrate increased survival times of patients with PSC given 17–23 mg/kg/day UDCA, compared to placebo.[102] However, this study was underpowered and concerns were raised about noncompliance among subjects given the test article. Unexpectedly, a North American study was stopped early because 28–30 mg/kg/day UDCA increased the risk of disease progression 2-fold, compared with placebo; study endpoints included cirrhosis, varices, cholangiocarcinoma, liver transplantation, or death. [103] The increase in adverse events appeared to primarily occur in patients with early-stage disease compared to similar patients in the placebo group.[104] Furthermore, high-dose UDCA was associated with an increased risk for colorectal neoplasia among patients with UC, providing further evidence for the toxicity of UDCA at this weight-based dosing range.[105]

A meta-analysis of 8 trials determined that UDCA did not slow PSC progression.[106] Although there is no clear role for UDCA therapy this time, the safety profile of moderate-dose UDCA (17–23 mg/kg/day) indicates that it could be worth further examination in prospective trials. The American Association for the Study of Liver Diseases (AASLD) recommends against UDCA therapy for PSC, whereas the European Association for the Study of Liver Diseases does not recommend for or against treatment with UDCA, based on the limited data.[12, 107]

### Immunosuppressive Agents

Corticosteroids, etanercept, tacrolimus, cyclosporine, azathioprine, methotrexate, and infliximab have not demonstrated clinical benefits for subjects with PSC.[108, 109] Immunosuppressants therefore have no role in the treatment of classic PSC and are not recommended.[12]

Individuals with evidence for AIH-PSC should be treated with immunosuppressive therapies, as recommended for AIH. Treatment with azathioprine can reduce corticosteroid-related adverse effects. Dosing schedules and duration of therapy are similar to those for AIH.[12] The recent interest in budesonide for AIH will likely result in its use for AIH-PSC, yet its efficacy for this condition is unknown.[110] There is no clear role for UDCA in the treatment of AIH-PSC.

## Endoscopic Therapy

New or worsening symptoms in patients with PSC typically warrant investigation to exclude a dominant extrahepatic biliary stricture. A dominant stricture is defined as a stenosis ≤ 1.5 mm in the common bile duct or ≤1 mm in the hepatic duct.[12] When present, it should raise the concern for cholangiocarcinoma. Although the prevalence of dominant strictures in patients with PSC is unknown, it has been approximated at 50%[111] Symptomatic dominant strictures are less common, forming in approximately 10%–30% of patients.[111, 112] Bacteria are often found in bile from patients with a dominate stricture (more than 40% of cases), in contrast to those without dominant strictures.[81]

Expansion of dominant strictures by dilatation alone or dilation and stent placement can provide long-term biliary drainage and reduce symptoms.[112] However, there are no data from randomized, controlled studies to compare these methods. Importantly, the combination of stenting and dilation was associated with more complications than dilation alone in a large retrospective study.[112] Biliary endoprosthetic stent placement should therefore be reserved for cases in which dilatation is unable to maintain lumen patency. [112] The required duration of stenting varies; 6–8 weeks is probably the safest interval to avoid superimposed complications such as cholangitis. Some patients require stenting with regular exchanges for as long as 6–12 months before strictures resolve.

Oral antibiotics for a minimum of 5 days after dilatation and/or stenting can reduce the risk for cholangitis.[12] Brush cytology and/or biopsy samples should be obtained to exclude the possibility of cholangiocarcinoma.[12] Post-ERCP pancreatitis and cholangitis have been reported in 5%–7% and 1% of patients, respectively.[113, 114] Factors that predict post-ERCP complications include the presence of cirrhosis, Crohn's disease, AIH, level of operator experience, and the performance of a sphincterotomy or biliary dilation.[113] Although therapeutic endoscopy can reduce symptoms and prevent and treat cholangitis, its role in modifying disease progression is unclear.

## Liver Transplantation

PSC is a leading indication for liver transplantation in some Scandinavian countries, and it is the fifth-most frequent indication for liver transplantation in the United States.[115] With 1- and 5-year rates of survival exceeding 90% and 80%, respectively, patients with PSC have among the most successful outcomes following liver transplantation.[116] Typically, a Roux-en-Y choledochojejunostomy is the method of choice for biliary reconstruction during liver transplant.[117]

Indications for transplants from deceased or living donors are similar to those for other chronic liver diseases, including complications of portal hypertension that are refractory to

medical therapies. Patients with disease-related complications such as refractory pruritus and recurrent bacterial cholangitis increasingly receive liver transplants from living donors, because of their low priority for livers from deceased donors, based on Model for End-Stage Liver Disease (MELD) scores.

PSC patients are more likely to receive a transplant from a living donor than patients with other chronic liver diseases—this trend has increased since the MELD score came into use.[118] However, the practice of referral for liver transplantation from a living donor or granting exception points for a perceived increased risk in mortality secondary to cholangitis was questioned by a study that did not find an increased risk of waitlist removal for death or clinical deterioration secondary to cholangitis.[119]

Individuals who have undergone liver transplantation for PSC have an increased risk for early (within 30 days) acute cellular rejection, which typically responds to systemic corticosteroids and does not appear to affect graft survival.[116] Although chronic ductopenic rejection is becoming less common, it can occur and has deleterious effects on patient and graft survival.[116] Other complications include hepatic artery thrombosis, anastomotic biliary stricture, and recurrent disease.

### Liver Transplantation for Cholangiocarcinoma

Specific patients with perihilar cholangiocarcinoma, recognized through exceptional criteria established by the United Network of Organ Sharing, can receive a liver from a deceased donor. Previously considered an absolute contra-indication, patients with unresectable early-stage (stage I–II) peri-hilar cholangiocarcinoma that is 3 cm or less might benefit from liver transplantation.[12, 120] These individuals receive neoadjuvant therapy with external beam radiation, radiosensitizing chemotherapy, endoscopic brachytherapy, and oral capecitabine before exploratory laparotomy, to verify their candidacy for liver transplantation.[120] The 5 y rate of recurrence-free survival was 65% when this method was used at dozen transplant centers—all had similar survival rates.[120] More patients with PSC appeared to remain free of recurrence compared to those without PSC, though this was not statistically significant.[120]

### Diagnosis and Management of Recurrent PSC

PSC is estimated to recur in 20%–25% of recipients over a 10 y period after liver transplantation.[12] The definition of recurrent PSC requires the exclusion of other confounding events that could cause non-anastomotic biliary strictures, including incompatible blood types, cytomegalovirus infection, and hepatic artery thrombosis.[121] Typically, PSC recurs more than 90 days after liver transplantation.[122] Interestingly, a large study showed that patients with IBD and an intact colon were at increased risk for PSC recurrence.[122]

Increasing serum levels of alkaline phosphatase can indicate PSC recurrence; the diagnosis is secured when cholangiography shows features typical of PSC in the original liver.[121, 122] Histologic analysis has a secondary role in diagnosis, as it may be performed to exclude rejection. Notably, ductopenia can accompany recurrent PSC in the absence of rejection, making cholangiography necessary.[122, 123] No medical therapy has been shown to prevent PSC recurrence or stop disease progression. Hepatic re-transplantation is successful for specific patients with recurrent PSC, but the disease can continue to recur.

## Cancer Surveillance in Patients with PSC

Cholangiocarcinoma occurs in 1%–2% of patients annually following a diagnosis of PSC, with a lifetime risk of 5%–10%.[124] Cholangiocarcinoma is frequently detected within the

first 1–3 years after the initial diagnosis of PSC.[125] The presence of advanced fibrosis is not required for cholangiocarcinoma development, unlike hepatocellular carcinoma, which is typically found in conjunction with cirrhosis. Increased levels of bilirubin, duration of IBD, and history of IBD-associated colorectal neoplasia have been proposed as risk factors.[124, 126, 127]

Cholangiocarcinoma is difficult to diagnose—particularly in trying to distinguish a benign dominant stricture from ductal cholangiocarcinoma. Often the diagnosis requires the use of multiple serum, imaging, and endoscopic tests over time. Furthermore, there are no risk stratification criteria to identify a high-risk group within the PSC population for enhanced surveillance. In the absence of systematic data, a rational approach to cholangiocarcinoma surveillance has been proposed and is currently in use at the Mayo Clinic.[128] This approach involves annual MR imaging and MRCP or ultrasound examinations, plus measurement of serum carbohydrate antigen 19-9 (CA19-9). ERCP assessment is reserved for individuals with increasing levels of CA-19-9 and/or imaging evidence for dominant strictures. [128] Although tests for serum levels of CA 19-9 alone are not sensitive or specific enough to facilitate detection of cholangiocarcinoma, values above 130 U/L in the absence of bacterial cholangitis detect cholangiocarcinoma with 79% sensitivity and 98% specificity.[129] The value of measuring serum CA 19-9 to detect asymptomatic or early-stage cholangiocarcinoma, however, has never been proven. The advantage of combining serum CA 19-9 measurements with imaging is therefore to improve our ability to detect worrisome extrahepatic strictures that could be cholangiocarcinomas. Alternatively, a normal level of CA 19-9 with evidence of dominant structuring would also raise suspicion for cholangiocarcinoma.

The efficacy of this approach, with several recall mechanisms for enhanced surveillance based on ERCP cytology results, is currently under investigation at the Mayo Clinic. It should be noted that the 2010 AASLD guidelines for PSC do not comment on cholangiocarcinoma screening. However, they do propose diagnostic imaging and assessment of cholangiocarcinoma by measurement of CA19-9 and imaging if a clinical indication develops (deterioration in either clinical status or liver test results).[12]

## Cytology and Fluorescence in situ hybridization (FISH)

Routine brush cytology analysis alone detects cholangiocarcinoma with low levels of sensitivity (40% or less), although the specificity is nearly 100%.[12] FISH has been shown to be more sensitive than, and as specific as cytology.[130] FISH requires a probe set that is applied to subpopulations of cells with chromosome amplifications, to assess aneusomy. In the presence on aneusomy, the additional copies of chromosomes detected by the FISH probes (typically targeting peri-centromeric regions of chromosomes 3, 7, and 17 and band 9p21) are highlighted; manual counting allows one to describe the extent of aneusomy.[131] At the Mayo Clinic, FISH results are assigned to 1 of 3 categories: negative, trisomy (10 or more cells show 3 copies of chromosomes 7 or 3, and 1 or 2 copies of the other probes) or tetrasomy (10 or more cells show 4 copies of all probes), and polysomy (5 or more cells have gained 2 or more chromosomes).[131]

In a large study of 235 PSC patients, individuals with polysomy (compared to those with trisomy or tetrasomy or negative FISH results) had similar outcomes to those with proven cholangiocarcinoma (Figure 3).[131] Among patients with PSC and a dominant stricture, the presence of polysomy identified those with an eventual diagnosis of cholangiocarcinoma with 88% specificity.[131] The value of FISH was confirmed by the finding that 75% of individuals with persistent polysomy in more than one test develop cholangiocarcinoma after 3 years.[132] Proteomic analyses of urine and bile, along with a variety of serologic markers, are being examined to aid in the diagnosis of cholangiocarcinoma.[133–135]

### Gallbladder Neoplasia

Gallbladder disease such as cholelithiasis is common among patients with PSC. [136] In addition, PSC patients have an increased risk of gallbladder neoplasia. Although the exact prevalence of neoplasia is not known, one series described among PSC patients that underwent a cholecystectomy, 14% had a gallbladder mass which was malignant in 57% of cases.[137] Current AASLD guidelines recommend an annual ultrasound to detect lesions in the gallbladder, and cholecystectomy if lesions are detected, regardless of size.[12] Despite this recommendation, the likelihood of malignancy in small gallbladder polyps is unclear. One study did not find neoplasia in polyps less than 0.8 cm but reported 40% morbidity associated with cholecystectomy in PSC patients—particularly among those with advanced liver disease.[138] Although there have been rare reports of small polyps harboring malignancies, physicians should weigh the risks and benefits of a cholecystectomy (vs monitoring) for patients with small polyps and advanced liver disease from PSC, without other high-risk features.[15]

### Colorectal Neoplasia

The combination of PSC and UC is associated with a 4-fold increase in risk of colorectal neoplasia (CRN), compared to UC alone.[42] PSC patients with Crohn's disease also have an increased risk of CRN.[139] It is common to detect CRN shortly after the 2 conditions are discovered.[140]

### Colonoscopic Surveillance

With the initial diagnosis of PSC in subjects with IBD, immediate and annual surveillance colonoscopy and biopsy analysis, throughout the colon, is recommended.[12, 140] The risk is not reduced by liver transplantation, so annual surveillance should continue following this procedure.[12] Surveillance biopsies provide limited information, because only a small surface area of the entire colon is examined. Researchers are therefore investigating the ability of other modalities, such as chromoendoscopy, to increase rates of neoplasia detection in this population. In clinical practice, we increase the frequency of surveillance and use chromoendoscopy for patients with indefinite or low-grade dysplasia (LGD) who elect not to undergo colectomy. Raised areas that are suspected to be neoplastic should be removed (if possible), and surrounding biopsies should be collected to evaluate for colitis and endoscopically flat neoplasia.

Following ileal–anal pouch anastomosis in patients with PSC-IBD, the pouch is still at risk for cancer. [141] Some clinicians have proposed annual surveillance of the pouch for patients with PSC, although there is little evidence to support this strategy.[142]

### Indications for Colectomy

Indications for colectomy in PSC-IBD patients include cancer, high-grade dysplasia, and unresectable LGD.[128, 143] Although few data are available from patients with PSC-IBD about sporadic adenomas (identified by endoscopic examination, raised lesions outside regions of colitis, with normal surrounding tissue based on biopsy analysis), it may be reasonable to follow these individuals with endoscopic examinations—the typical practice for patients with only UC, particularly if only a small, single sporadic adenoma is detected.[144] Notably, these lesions are rarely encountered, due to the high prevalence of pancolitis.[38] The fate of unifocal or multi-focal LGDs (flat or raised) in regions of colitis are not well defined in PSC-IBD patients. However, the 1 y cumulative incidence of high-grade dysplasia or cancer in patients with PSC-UC and a diagnosis of flat or adenoma-like dysplasia is 25%, whereas multifocal LGD was associated with neoplasia recurrence or

progression.[145] These findings support the recommendation of colectomy for patients with multi-focal LGD that is flat and found in areas of colitis.

### Evidence for UDCA as Chemoprevention Agent

UDCA has been proposed to decrease the risk of CRN in patients with PSC and UC,[146, 147] based on results from retrospective studies. However, these studies had inconsistent results, so UDCA has not been recommended a chemopreventative agent for patients with PSC-IBD.[12, 105, 148–150]

## Future Directions

### Novel Pharmacological Therapies

Thus far, antibodies against TNF have been ineffective in patients with PSC.[108, 151] The role of biologic agents such as ustekinumab and vedolizumab in the treatment of IBD is being investigated, and their role in treatment of PSC-IBD remains to be seen. [152, 153] Given the possible role of lymphocyte trafficking in the pathogenesis of PSC, monoclonal antibodies that alter this process could have a potential therapeutic benefit.

Janus kinase (JAK) is a tyrosine kinase component of signaling pathways for many cytokines.[154] Tofacitinib is a JAK inhibitor that decreases signaling by inflammatory cytokines, T-cell differentiation, and lipopolysaccharide-induced innate immune responses.[155–157] JAK kinase signaling is therefore a therapeutic target for many autoimmune and inflammatory disorders.[154] Recently, tofacitinib was examined for the treatment of UC.[155]

Inhibiting progressive fibrosis is an attractive target, and tyrosine kinase receptors appear to have important roles in fibrosis.[158] Imatinib is a tyrosine kinase inhibitor that has anti-fibrotic properties in livers of animal models.[159] In the clinic, it is used to treat gastrointestinal stromal tumors and chronic myelogenous leukemia. Imatinib has been reported to have hepatotoxic effects, and the safety of this agent in PSC patients is unknown.[160] Other agents with potential anti-fibrotic properties include angiotensin receptor blockers, colchicine, and pentoxifylline.[161, 162] However colchicine and pentoxifylline have not shown benefit in patients with PSC.[163, 164] The combination of all-trans retinoic acid and UDCA has been shown to reduce bile duct proliferation and fibrosis in animal models.[165] The efficacy of this combination is under investigation.

Farnesoid X receptor (FXR) is a nuclear receptor that regulates bile acid homeostasis.[166, 167] When activated, FXR limits hepatic bile acid accumulation and upregulates bilirubin and phospholipid export pumps. FXR activation is also involved in anti-bacterial defense and protects against inflammation.[167] Obeticholic acid is an FXR agonist under investigation for primary biliary cirrhosis. FXR agonists have potent choleretic activity, so in patients with downstream obstructions (biliary strictures), they might worsen liver disease by increasing biliary pressure.[166] Studies of FXR agonists in patients with PSC should therefore be performed with great care.

24-norUrsodeoxycholic acid is a derivative of UDCA.[168] It has been shown to improve liver test results and histologic features, compared to UDCA, in animal models of PSC.[169] Phase 2 clinical trials are underway to determine the efficacy of this agent in PSC patients.

The therapeutic potential of the above agents is largely speculative. Preclinical and small pilot studies are needed to investigate their mechanisms of action, safety, and potential efficacy.

### Validation of Common and Novel Clinical Trial Endpoints

PSC is a rare, slowly progressive disease, so it is a challenge to design clinical trials powered to capture differences in relevant clinical endpoints. Validated markers of disease progression are important. A retrospective study associated normalization of alkaline phosphatase level with an improved prognosis.[18] Another retrospective study associated reduction of alkaline phosphatase levels to below 1.5-fold the upper limit of normal with better outcomes including a decrease in the development of cholangiocarcinoma.[170] Additional biomarkers would improve the sensitivity and specificity of algorithms that predict disease progression and outcome of these subjects. Other approaches to monitor disease progression and response to therapy include MR and CT cholangiography and measurements of liver stiffness with elastography.

## Conclusions

PSC is a rare but important cholestatic liver disease that reduces patients survival and quality of life. Management of patients involves early recognition of the disorder, implementation of routine screening protocols to identify complications (Figure 4), and treating comorbid conditions. In the absence of effective medical therapy for the disease itself, treatment centers on endoscopic management and referral for liver transplantation, when necessary.

Although our understanding of PSC and its comorbid conditions has improved, much is left to learn about its pathogenesis. Animal models and genomic-based approaches will increase our understanding of the pathophysiology, and hopefully lead to new therapeutic strategies.

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## Abbreviations

| | |
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| **PSC** | primary sclerosing cholangitis |
| **IBD** | inflammatory bowel disease |
| **UC** | ulcerative colitis |
| **AIH** | autoimmune hepatitis |
| **ERCP** | endoscopic retrograde cholangiopancreatography |
| **MRCP** | magnetic resonance cholangiopancreatography |
| **IAC** | IgG4-associated sclerosing cholangitis |
| **AIP** | autoimmune pancreatitis |
| **VCAM-1** | vascular cell adhesion molecule-1 |
| **M MAdCAM-1** | mucosal addressin cellular adhesion molecule 1 |
| **MDR3** | multidrug resistance protein 3 |
| **CFTR** | Cystic fibrosis transmembrane conductance regulator |
| **CA 19-9** | carbohydrate antigen 19-9 |
| **HLA** | human leukocyte antigen |
| **MELD** | Model for End-Stage Liver Disease |

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|---|---|
| **FISH** | fluorescence in situ hybridization |
| **CRN** | colorectal neoplasia |
| **LGD** | low-grade dysplasia |
| **IL** | interleukin |
| **JAK** | janus kinase |
| **FXR** | farnesoid X receptor |

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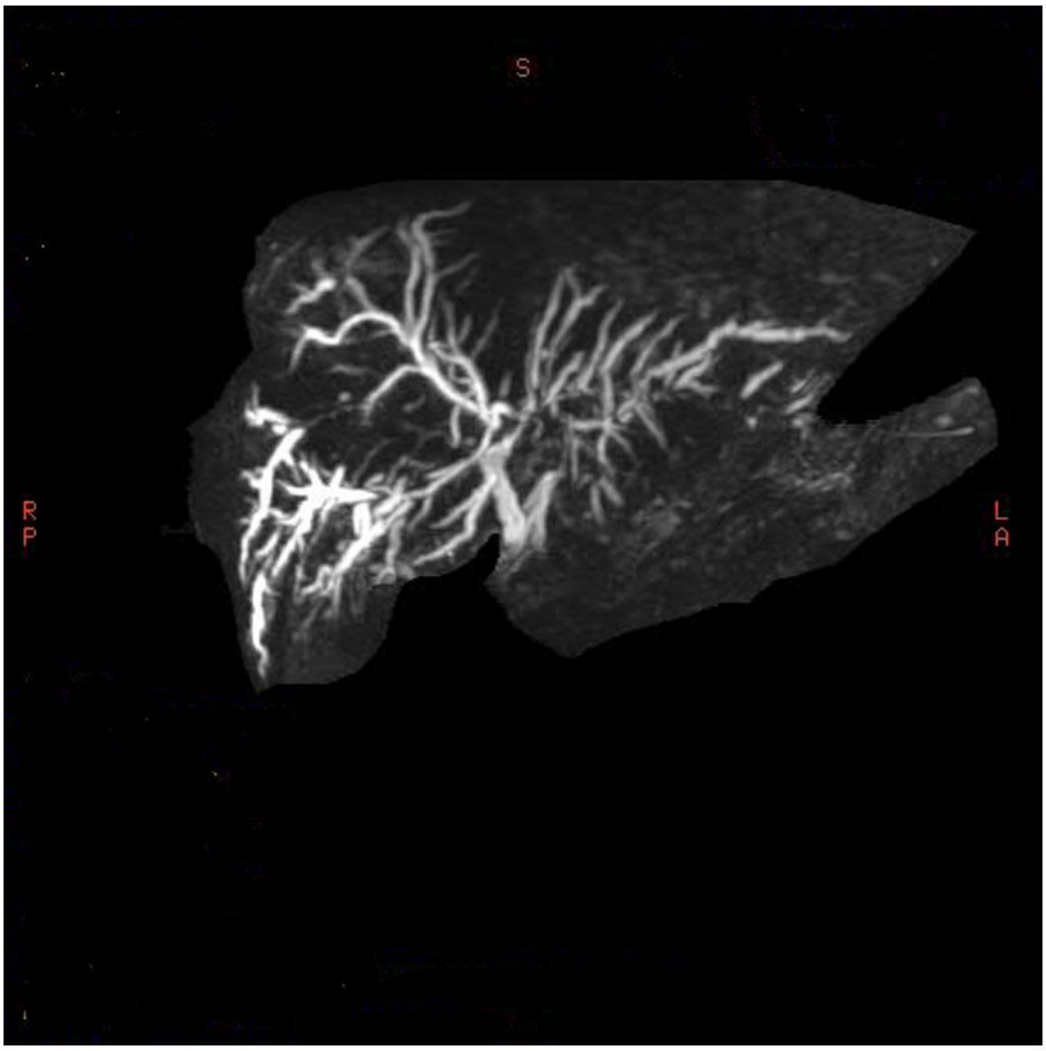


**Figure 1.**
A 3D Post-Processing Image From MR Cholangiography
Diffusely dilated intrahepatic ducts with multifocal narrowing with diffuse ductal wall thickening and enhancement.

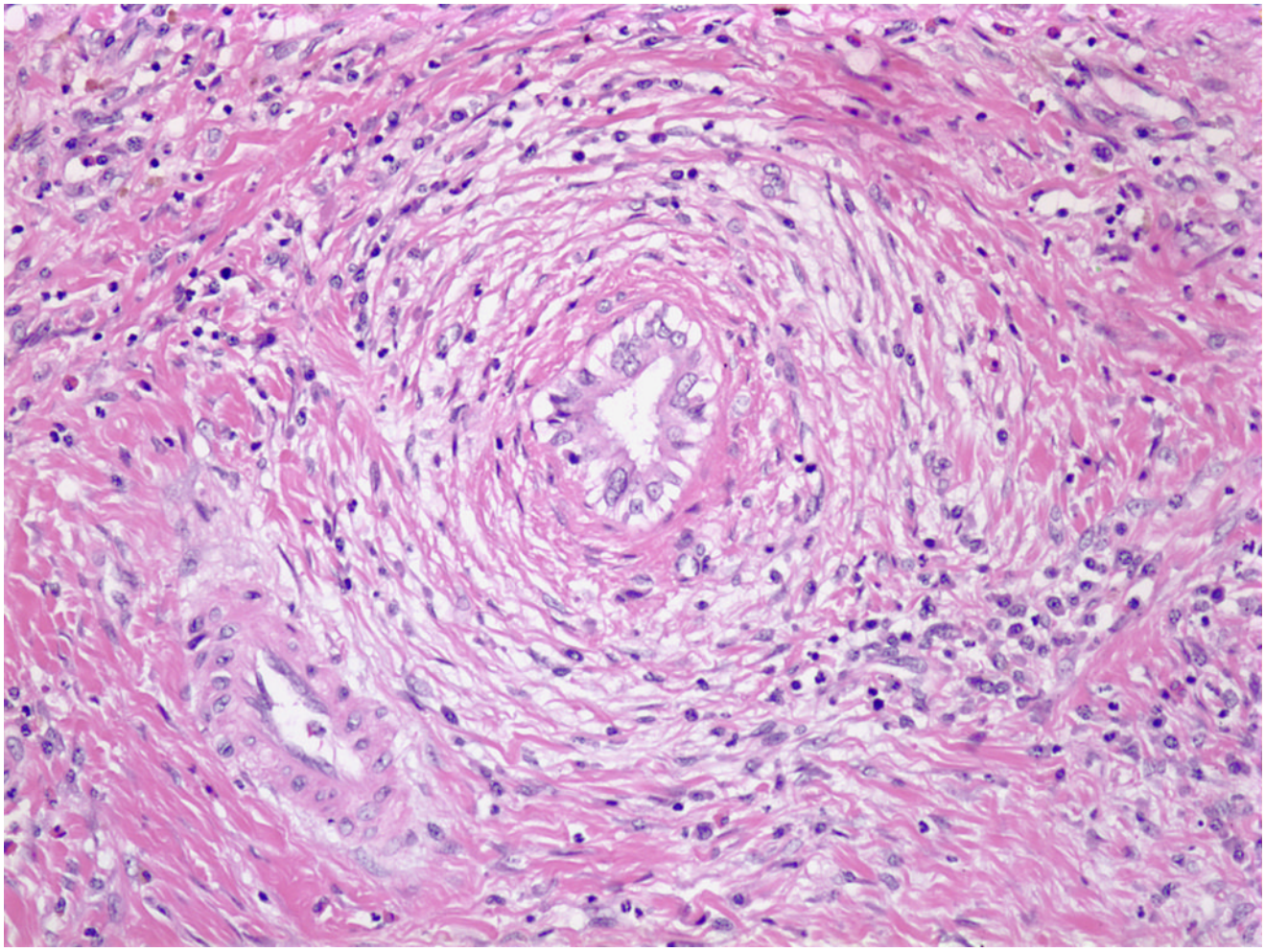

**Figure 2.**
Histologic Features of PSC
Concentric ductal fibrosis.

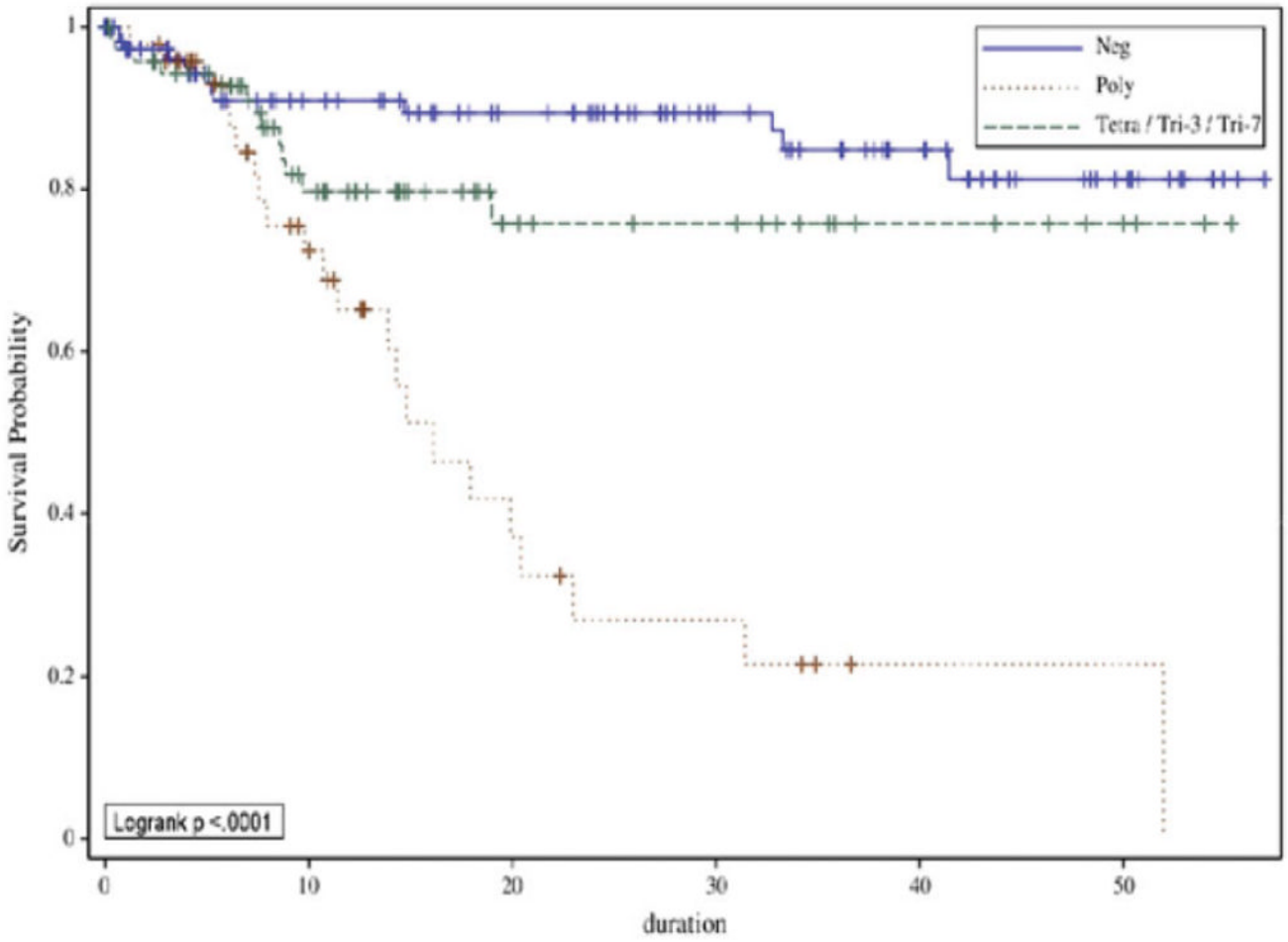


**Figure 3.**
Survival of Patients with PSC with Polysomy, Trisomy 3/7 or Tetrasomy, or no Chromosome Amplifications, Based on FISH Analysis.
Reused with permission from Lindor and colleagues.[131]

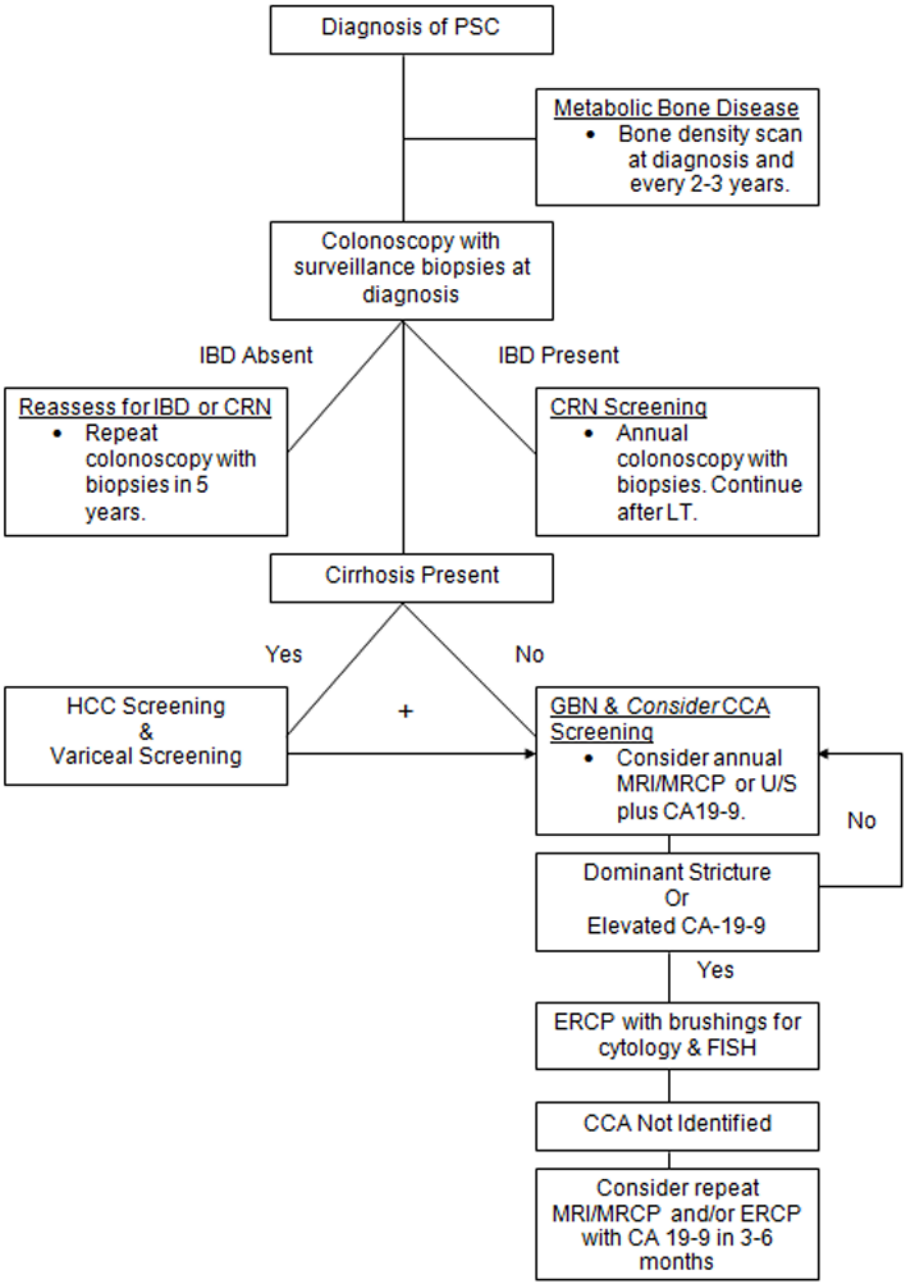


**Figure 4.**

Surveillance of Co-Morbid Conditions in Patients with PSC.

Abbreviations: PSC (primary sclerosing cholangitis); IBD (inflammatory bowel disease); CRN (colorectal neoplasia); HCC (hepatocellular carcinoma); GBN (gallbladder neoplasia); CCA (cholangiocarcinoma); ERCP (endoscopic retrograde cholangiopancreatography); MRCP (magnetic resonance cholangiopancreatography); FISH (fluorescence in situ hybridization).

**Table 1**

Diagnostic Classification of Typical PSC, Small-Duct PSC, AIH-PSC, and IAC

| | Cholangiography | Pathology | Diagnosis | Management [a] | Other Features |
|---|---|---|---|---|---|
| **Typical PSC** | • Multifocal intrahepatic &/or extrahepatic stricturing. | • Concentric ductal fibrosis classic but uncommon.<br>• Histology often nonspecific, nondiagnostic.<br>• Stage determined by Ludwig classification. | • MRCP (preferred over ERCP unless intervention necessary) with typical features.<br>• Exclusion of CCA, secondary causes of cholangitis.<br>• Cholestatic liver test elevations are supportive. | • Screening for and treatment of comorbid conditions.<br>• Endoscopic management of dominant strictures (balloon dilatation preferred over stenting when feasible). | • 70–80% coexisting IBD.<br>• PSC-IBD may be unique phenotype.<br>• Increased risk of CCA, GBN, HCC (after development of cirrhosis).[b]<br>• Increased risk of CRN in PSC-IBD.[b] |
| **Small-Duct PSC** | • Normal cholangiogram. | • Same as classic. | • Liver biopsy.<br>• Cholestatic liver test elevations are supportive. | • Same as classic, except need for endoscopic management is rare. | • May progress to classic PSC.<br>• Coexisting IBD common.<br>• Improved survival and less risk of CCA compared to classic. |
| **AIH-PSC** | • Same as classic | • LPC infiltrate, interface hepatitis. | • Biochemical & histologic evidence of AIH plus cholangiographic changes of PSC. | • Pharmacotherapy similar to AIH: Prednisone or budesonide, & Azathioprine.<br>• Endoscopic management of strictures. | • Improved prognosis compared to classic but worse prognosis than AIH alone.<br>• Suspect if: AIH refractory to |

| | Cholangiography | Pathology | Diagnosis | Management [a] | Other Features |
|---|---|---|---|---|---|
| | | | | | therapy, AIH with IBD, or PSC with laboratory testing suggestive of AIH. |
| **IAC** | • Similar to classic plus may have intra-pancreatic involvement.<br>• Strictures may be fleeting and responsive to steroids. | • Bile duct has LPC infiltrate with > 10 IgG4 positive cells per hpf. | • Biliary strictures with either:<br>**a.** Definitive features:<br>**i.** pancreatic/ biliary resection or core pancreatic biopsy with supporting pathology.<br>OR<br>**ii.** Classic radiographic features of AIP plus elevated serum IgG4 (>140 mg/dL).<br>**b.** Probable IAC (2 or more of the following):<br>**i.** elevated serum IgG4<br>**ii.** Other organ involvement (ex. Retroperitoneal fibrosis).<br>**iii.** Supporting bile duct biopsy.<br>**iv.** Suggestive pancreatic imaging findings.<br>• Malignancy must be excluded. | • For definitive IAC, corticosteroids for 11 weeks and consideration of azathioprine for maintenance of remission.<br>• For probable IAC, corticosteroids for 4 weeks, if responsive then continue to treat as definitive IAC. | • Coexisting IBD is uncommon. |

[a] Referral for liver transplantation when appropriate is key component of management for all PSC subtypes.

[b] At this time we recommend surveillance for CRN in the setting of IBD, GBN, CCA and HCC (in those with cirrhosis) regardless if they have classic PSC or another PSC subtype.

Abbreviations: PSC (primary sclerosing cholangitis); AIH (autoimmune hepatitis); IAC (IgG4 associated cholangitis); AIP (autoimmune pancreatitis); LPC (lymphoplasmacytic); CRN (colorectal neoplasia); CCA (cholangiocarcinoma); GBN (gallbladder neoplasia); HCC (hepatocellular carcinoma); hpf (high-power field).

**Table 2**

Key Randomized Placebo-Controlled Trials of UDCA for PSC

| Year (reference) | Dose UDCA | Follow up | Number of Patients | Outcomes |
|---|---|---|---|---|
| 1997 (99) | 13–15 mg/kg/day | 2.2 years | 105 | • No difference in treatment failure (time to transplant, histology, etc)<br>• Liver tests improved in UDCA group. |
| 2001 (100) | 20 mg/kg/day | 2 years | 26 | • UDCA had improvement in liver tests, histology and cholangiography. |
| 2001 (101) | 25–30 mg/kg/day | 1 year | 30 | • UDCA group had improved liver tests, improved Mayo Risk Score at 1 year and better predicted 4 year survival than placebo.<br>• Higher dose UDCA had improved Mayo Risk score compared to patients enrolled in lower dose UDCA trial [99]. |
| 2005 (102) | 17–23 mg/kg/day | 5 years | 219 | • No difference in death or liver transplant, cholangiocarcinoma or liver tests. |
| 2009 (103) | 28–30 mg/kg/day | 6 years | 150 | • UDCA improved liver tests but was associated with more adverse events including time to death or liver transplant. |