Review

Primary Sclerosing Cholangitis: From Pathogenesis to Medical Management

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Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterized by progressive inflammatory destruction of intrahepatic and extrahepatic bile ducts. It is strongly associated with inflammatory bowel disease, particularly ulcerative colitis. The pathogenesis of PSC remains unclear, however several hypotheses have been proposed that suggest roles for autoimmunity, genetic susceptibility, and the interaction between microorganisms and host immune response directed at the biliary system. A diagnosis of PSC is based on a constellation of clinical, biochemical, and typical cholangiographic features and usually without the need for liver histopathology. Complications of PSC include pruritus, portal hypertension, bone disease, end-stage liver disease, and cancers. Cholangiocarcinoma eventually develops in 8-15% of PSC patients. A variety of drugs have been evaluated as therapy for PSC, but no therapy has yet been proven to prolong survival or improve outcomes in PSC. Ursodeoxycholic acid (UDCA) has been intensively investigated to address its efficacy in PSC. A recent investigation noted that high-dose UDCA therapy in PSC did not confer benefit on combined clinical and survival endpoints. . Immunosuppressive agents are generally ineffective. Liver transplantation remains the only proven long-term treatment for advanced PSC, with approximately 20-25% risk of disease recurrence. Cancer surveillance, management of cirrhotic complications, and treatment of manifestations of cholestasis in those with PSC are clinically relevant. Further understanding of the pathogenesis of PSC is desperately required in order to effectively improve our current approaches to the management of this disease.
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Key Words: *primary sclerosing cholangitis, cholestasis, pruritus, inflammatory bowel disease, ulcerative colitis, pathogenesis, management, cholangiocarcinoma*

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by chronic inflammation and progressive obliterating fibrosis of the intrahepatic and extrahepatic bile ducts. It eventually leads to bile stasis, progressive hepatic fibrosis, and ultimately to cirrhosis, and the need for liver transplantation (LT). In addition, patients with PSC are at risk for the development of cholangiocarcinoma (CHCA) and other extrahepatic malignancies.[1-3] There is a strong but incompletely understood association between PSC and inflammatory bowel disease (IBD), particularly ulcerative colitis (UC). The pathogenesis of PSC has not been clearly elucidated; however it is thought to be mediated by immune dysregulation in patients with a genetic susceptibility. A diagnosis of PSC is based on a constellation of clinical, biochemical, and typical cholangiographic features. The management of PSC and its complications is challenging. The response to a variety of medical therapies for PSC has varied and, unfortunately, often ineffective.[4]

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EPIDEMIOLOGY

PSC is a rare disease in the general population. Three large population-based cohort epidemiologic studies from the UK, US, and Canada have reported an incidence of PSC to be 0.41, 0.90 and 0.92 cases per 100,000 person-years, respectively.[5-7] A geographic variation in the prevalence of PSC exists; the prevalence of PSC is lower in Middle East and Asia.[8] PSC generally affects the young and middle-aged individuals with male preponderance (male: female ratio ~2:1).[5-7,9] Interestingly, a recent cohort from the UK found that up to 50% of PSC patients presented after the age of 55 years and also demonstrated a trend toward increasing incidence of PSC, during the 10-year period.[6] PSC has been shown to be strongly associated with IBD and considered the most common hepatobiliary manifestation of IBD.[10] The majority of patients with PSC (70-81%) have associated IBD which can be diagnosed at any time during the course of PSC and vice versa.[3,4,6,10,11] Notably, a diagnosis of UC often precedes PSC. In patients with IBD and PSC, most cases (50-

90%) have UC and the remaining have Crohn's disease (CD), which usually involves the colon.[2,7,9,11] The reason for these differences in prevalence of PSC between the two IBD conditions is unclear. Conversely, the prevalence of PSC in those with IBD is much lower and ranges from 2.4-7.5% in patients with UC [9,12] and 1.4-3.4% in patients with CD.[9,11] More often, the features of UC in those with PSC, in comparison to those with UC but without-PSC, include pancolitis but with rectal sparing, backwash ileitis, pouchitis, and a higher incidence of colorectal cancer.[2,13]

Most of these epidemiological data have been derived from IBD-specialized Centers in Northern America and Northern Europe. Nevertheless, the data from other regions of the World appear to be different and vary substantially. Although not as high as in certain regions in the Northern Hemisphere, the prevalence of IBD in patients with PSC has been reported to be 21-32% in Japan,[14,15] 44% in Spain,[16] 50% in India,[17] and 62% in the UK.[18] The reasons for this variation remain unclear, but possibly due to multiple factors such as differences in genetic predilection, and in the rates of performing colonoscopy with multiple biopsies in PSC patients across different centers, which may then possibly translate into the under- and over-estimation of colitis.[13] In addition, in some regions with a high prevalence of IgG4-associated disease such as in Japan, the reported cases of PSC and IgG4-associated cholangitis may somewhat overlap.[19]

PATHOGENESIS

The pathogenesis of PSC has been extensively investigated, but not complete elucidated. A variety of concepts have been implicated, however no single hypothesis has explained all the pathological and clinical features of this condition.[1,20-22] Currently, the interaction between microorganisms and host immune response related to the biliary system, particularly in the background of genetic susceptibility, seems to be the most convincing concept.[4]

Autoimmunity

Evidence of immune dysregulation in PSC is suggested indirectly by the presence of a variety of autoantibodies, which are often detected in the serum of patients with PSC. The prevalence of autoantibodies in a significant proportion of patients with PSC has been reported; anti-nuclear cytoplasmic antibody (ANCA) 50-88%, anti-nuclear antibody 7-77%, anti-smooth muscle antibody 13-20%, anti-endothelium antibody 35%, anti-cardiolipin antibody 4-66%, thyroglobulin antibodies 4%, and rheumatoid factor 15%.[2,23] Anti-nuclear specific antibodies seem to be the most attention autoantibodies in PSC that can be detected in up to 88% of patients.[23] Notably, the immunofluorescence microscopic patterns of these antibodies are distinct from that produced by c-ANCA or classic p-ANCA in vasculitic diseases.[23] This atypical p-ANCA (so-called anti-neutrophil nuclear antibody or ANNA) are non-specific and can be detected in patients with UC (40-87%) and autoimmune hepatitis type 1 (50-96%).[23] A recent study suggested that a target autoantigen for atypical p-ANCA is a neutrophil envelop protein called beta-tubulin isotype 5 (TTB-5).[24]

Extrahepatic autoimmune disorders, such as type I diabetes mellitus and Grave's disease, are common in PSC-IBD patients which may further suggest the role of autoimmunity in PSC. Approximately 25% of patients with PSC had concurrent autoimmune diseases, compared to 9% of patients with IBD alone.[25] In addition, PSC patients have an increased frequency of the HLA B8, DR3, and DC2 haplotypes, which are also common to several autoimmune diseases.[21] However, PSC is more common in men, in contrast to female predominance in the majority of other autoimmune diseases, and also does not respond to corticosteroids. Further, the autoantibodies in PSC are generally present at low levels, and the specific antibodies against biliary system have not been identified.[2,21] Taken together, PSC is not a classic autoimmune disease, but several evidences suggest a pivotal role for immune-mediating processes in the pathogenesis of PSC.

Role of Genetic Susceptibility

The prevalence of PSC in first-degree relatives and siblings is 0.7% and 1.5%, respectively, which are nearly 100-fold increases compared with general populations.[26] In genetic terms, PSC is considered a complex trait whereby polymorphisms in several genes together with environmental factors are required for disease development.[22] The major histocompatibility complex (MHC) on the short arm of chromosome 6 encodes the HLA molecules having a critical role in T cell response, and along with MHC class I chain-like (MIC) α-molecules involved in the innate immune function may play a role in the pathogenesis.[1] An association between the haplotypes HLA A1-B8-DR3 (particularly with the presence of MICA5.1 and MICB24), DR6 and DR2 and susceptibility to PSC is well-documented, whereas HLA DR4, DR11, MICA*002 may be protective.[20-22]

Whether or not PSC and IBD share similar genetic susceptibility remains inconclusive. A large Scandinavian cohort found that IBD-associated polymorphisms in the CARD15, TLR-4, CARD4, SLC22, DLG5, and MDR1 genes failed to demonstrate their role in patients with PSC.[27] HLA associations found in PSC have been mostly distinct from those seen in UC and no significant differences were noted between PSC patients with or without concurrent UC.[28] Recently, 3 genome-wide association studies identified 9 PSC risk loci outside the HLA complex including 2q13, 2q16, 2q35, 3p21, 4q27, 6p21, 9q34, 10p15, and 13q3.[29-31] Several of these loci are also reported to be associated with UC, and harbor the putative candidate genes REL, IL2, CARD9, and bile acid receptor TGR-5.[31,32]

Biliary Epithelial Cells and Hepatobiliary Transporters

The biliary epithelial cell (BEC) is the primary target of immune injury in PSC. Normal BECs express only HLA class I, but HLA class II antigens (HLA-DR, DQ and DP) do express in BECs of patients with PSC. These antigens have potential to initiate immune response triggered by either auto- or exogenous antigens.[21] Autoantibodies against a cross-reactive peptide shared by colon and BECs were identified in up to two-thirds of patients with PSC.[33] Thus, anti-BEC antibodies can stimulate the production of

inflammatory cytokines and the expression of CD44 from BECs through TLR-4, TLR-9, and extracellular signal related kinase, and transcription factor.[34,35]

Genetic polymorphisms in hepatocellular transport system, particularly, the steroid and xenobiotic receptor appear to adversely modify disease course of PSC.[36] Further, knockout of multidrug resistance gene in mice, results in biliary changes resembling human PSC.[37]

Role of Microorganisms

Chronic inflammation of the gut promotes translocation of bacteria and their products, through a leaky gut wall into portal circulation and activate Kupffer cells, resulting in peribiliary cytokine/chemokine release, which in turn likely activates inflammation, ischemia and fibrosis of the biliary system.[21] More recent concepts suggest a role for microorganisms as a molecular mimic, triggering immune responses directed against biliary epithelium, especially in the immunogenetically susceptible host.[1,20,21] A potential bacterial antigen that may mimic autoantigen is the bacterial cell wall division protein FtsZ.[24] This bacterial protein shares high degree of structural homology with human TBB-5 and conserves across broad range of bacterial species in gut.[24,38]

Though there is data to support the model of immunobiology in PSC, significant peripheral and portal bacteremia has not been frequently noted in patients with severe UC who have undergone colectomy.[39]

Diagnosis and Clinical Features

The clinical presentation of PSC is variable. Majority of patients are asymptomatic at presentation and develop symptoms over time.[9] Symptomatic patients often present with right upper quadrant abdominal discomfort (30-40%), pruritus (20-40%), fever (11-35%), jaundice (27-30%) and weight loss (10-15%).[1,40-42] Jaundice typically occurs with the disease complications, i.e. dominant strictures, cholangitis, or in those with advanced cirrhosis. Fatigue is non-specific and does not correlate with liver disease severity.[43] Physical examination is often unremarkable, though hepatomegaly (44-55%) and splenomegaly (~30%) may be detected by abdominal ultrasound.[1,42] Liver function tests (LFT) typically show persistent elevation of alkaline phosphatase (ALP) (~3-10 times of the upper limit of normal) and majority of patients have mildly elevated serum alanine aminotransferase (ALT) and IgG, with normal bilirubin levels at the time of diagnosis.[2] However, normal LFT do not exclude the diagnosis of PSC.[2] Serum autoantibodies have neither acceptable sensitivity nor specificity for the diagnosis of PSC.[1,2]

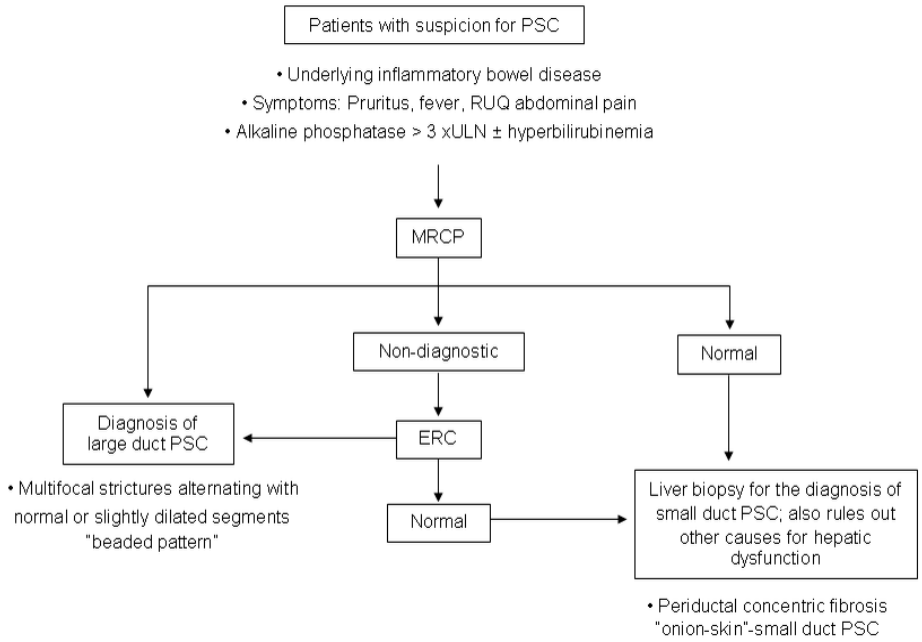

Figure 1. Algorithm for the diagnosis of primary sclerosing cholangitis (PSC) [Reprinted from Bunchorntavakul C, Reddy KR. Medical treatment of hepatobiliary diseases associated with ulcerative colitis. In: Lichtenstein GR, editor. Medical Therapy of Mucosal Ulcerative Colitis. New York, USA: Springer Publishing; 2012. In press]
Abbreviations: *MRCP, magnetic resonance cholangiopancreatography; ERC, endoscopic retrograde cholangiography*

A diagnosis of PSC is based on a constellation of an appropriate clinical and biochemical profile, and characteristic cholangiographic features (**Figure 1**).[2] Typical cholangiographic changes include multifocal, short, annular strictures with intervening segments of normal or dilated ducts involving the intrahepatic or extrahepatic biliary tree, or both, resulting in the characteristic "beads-on-a-string" or "beaded-like" appearance (**Figure 2**). Traditionally, endoscopic retrograde cholangiography (ERC) has been regarded as the gold standard for the diagnosis of PSC.

However, ERC is invasive and is associated with risk of complications requiring hospitalization (i.e. cholangitis, pancreatitis) in over 10% of PSC patients despite antibiotic prophylaxis.[44] Given its non-invasive nature, magnetic resonance cholangiography (MRC) has become a diagnostic procedure of choice for PSC, while ERC should be reserved for those patients who require endoscopic therapeutic intervention.[2] MRC has demonstrated a sensitivity of 80-91%, a specificity of 85-99%, and a diagnostic accuracy of 83-93%, and which is comparable or slightly inferior to ERC, for the diagnosis of PSC.[9] Nonetheless, early changes in PSC can be missed by MRC, and ERC may be helpful when MRC views are suboptimal.[2]

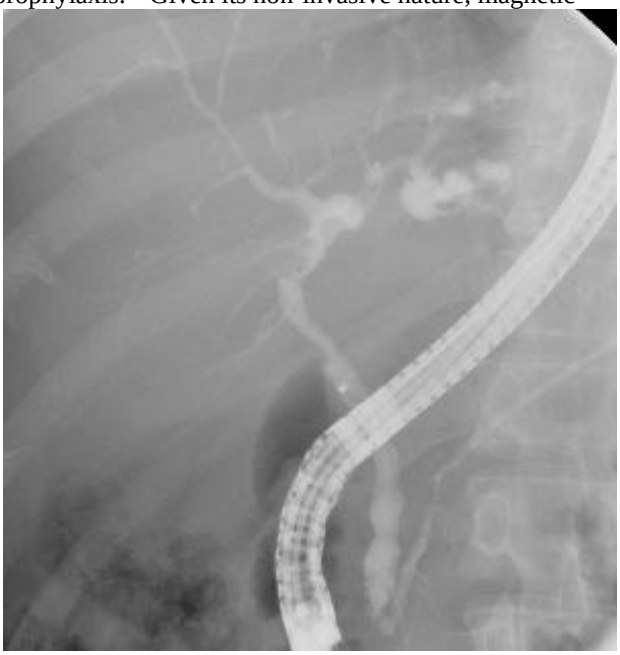

Figure 2. Typical endoscopic retrograde cholangiographic findings in primary sclerosing cholangitis.

Both intra- and extrahepatic ducts are often involved (60-70%), whereas localized intrahepatic duct (~25%) or extrahepatic duct disease alone (<5%) are less common.[2,42] Cystic duct, pancreatic duct, and gallbladder may be also involved. Severity of cholangiographic changes, scored by Amsterdam classification, is inversely correlated with transplant-free survival.[45]

It should be noted that several conditions (i.e. ischemia, malignancy, chronic infection, and inflammation) can cause sclerosing and multifocal stricturing process of the biliary tract. These conditions may have cholangiographic features similar to PSC, the so called secondary sclerosing cholangitis (**Table 1**).[2]

The findings on computer tomography and ultrasound are non-specific. Thickening and/or saccular dilatations of the bile ducts and evidence of portal hypertension (i.e. varices, splenomegaly, and ascites) may present. Contrast enhancement of thickened bile duct wall is suggestive of an inflammatory process. Interestingly, abdominal lymphadenopathy, particularly in perihepatic and celiac axis groups, is commonly detected in PSC (66-100%) and does not imply malignancy.[46,47]

In those with typical cholangiogram, a liver biopsy is not required for the diagnosis of PSC. The classic onion-skin fibrosis surrounding the bile duct may be seen in fewer than 10% of biopsy specimens in those with PSC, but when seen is almost pathognomonic. Nevertheless, liver biopsy may be needed to establish the diagnosis of small-duct PSC and PSC/autoimmune hepatitis (AIH) overlap as well as to exclude other causes of liver disease.

Table 1. Causes of secondary sclerosing cholangitis.

Infections	• AIDS cholangiopathy (cryptosporidiosis, microsporidiosis) • Cytomegalovirus infection • Parasitic infection (liver flukes, biliary Ascariasis) • Recurrent pyogenic cholangitis (oriental cholangiopathy)
Chronic obstruction and/or external compression	• Choledocholithiasis • Cholagiocarcinoma • Diffuse intrahepatic metastasis • Portal hypertensive biliopathy • Biliary strictures (e.g. secondary to surgical trauma or chronic pancreatitis)
Immunologic	• IgG4-associated cholangitis with or without autoimmune pancreatitis • Mast cell cholangiopathy • Eosinophillic cholangitis • Histiocytosis X • Hepatic allograft rejection (acute and chronic)
Ischemic	• Intra-arterial chemotherapy • Systemic vasculitis • Radiation injury • Critically-ill patient, particularly with ARDS • Post-transplant setting (prolonged ischemia time, hepatic artery thrombosis)

NATURAL HISTORY OF PSC

The clinical course of PSC is variable. The median duration of survival from diagnosis to either death or LT is 12 years; the range extends to 21 years.[1,21,48] The overall survival is significantly decreased (~3-fold) compare to the general population, even when asymptomatic at diagnosis.[6,40] The clinical course is variable and is characterized by recurrent episodes of cholangitis, during which time the disease slowly progresses. Clinical features of pruritus and jaundice gradually develop overtime and finally end-stage liver disease (ESLD) and its complications (i.e. ascites, varices, encephalopathy) can appear.[1] In some patients, esophageal varices may present early in the course of their liver disease, which is possibly explained by localized vascular damage in the portal triad from bile duct inflammation causing presinusoidal portal hypertension.[9]

Serum bilirubin, albumin and age at the diagnosis of PSC were independent prognostic factors.[49] Although the traditional Child-Pugh classification system is informative with regard to outcomes, the Mayo PSC score model included age, bilirubin, AST, albumin, and history of variceal bleeding may provide more reproducible and more accurate prognostic information without the need for liver biopsy, especially in patients with early disease.[2,50] The addition of cholangiographic findings in the model may provide some additional prognostic value.[2,42,45] The limitations of prognostic models include the inability to account for the development of CHCA and impairment in health-related quality of life. The current AASLD guideline recommends against the use of prognostic models for predicting clinical outcomes in an individual PSC patient as no consensus exists regarding the optimal model.[2]

CHCA may complicate the course of PSC in 8-15% of patients, with annual incidence 0.6-1%.[1,3,9] Of interest is that the duration of PSC may not be a risk factor for CHCA and, in fact, in approximately 50% of patients with PSC plus CHCA, the malignancy is detected at the time of diagnosis or within the first year.[2,51] Compared to the general population, PSC patients are at higher risk for developing cancers (40-160 fold for colon cancer and 2-10 fold for any cancers).[3,6] Of note is that patients with advanced cirrhotic-stage PSC are at increased risk for hepatocellular carcinoma (reported in 2% of patients with PSC undergoing LT).[52]

The association between coexisting PSC and the disease extension and activity of UC remains controversial. UC patients with co-existing PSC tend to have higher incidence of pancolitis, backwash ileitis, and rectal sparing than UC patients without PSC.[9] However patients with PSC-UC may have lower grade of colonic inflammation and more often run a quiescent course of colitis than UC patients without PSC.[9,53] Colectomy with ileal pouch-anal anastomosis does not appear to alter the disease course of PSC.[9]

MEDICAL THERAPY FOR PSC

A number of medical treatments targeting to alleviate inflammation and cholestasis have extensively been investigated in PSC. However, the efficacy of these therapies is somewhat limited.

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) is a hydrophilic, tertiary bile acid which has been used for the treatment of a variety of chronic cholestatic conditions.[54] It has been shown to be effective therapy in primary biliary cirrhosis.[55] After oral administration, UDCA is absorbed mainly in the small intestine and then it has an entero-hepatic circulation. At a daily dose of 13-15 mg/kg, UDCA constitutes 40-50% of total bile acid pool, and results in a decrease in relative contribution of the more hepatotoxic endogenous hydrophobic bile acids.[54] The mechanisms underlying the potential beneficial effects of UDCA include protection of cholangiocytes against cytotoxicity of hydrophobic bile acids, stimulation of hepatobiliary secretion, and protection of hepatocytes from bile acid-induced apoptosis.[21,54]

Majority of the early studies of UDCA in PSC were small and/or uncontrolled. Many of these studies demonstrated LFT improvement by using doses of 10-15 mg/kg/day.[2,21,56] Lindor et al. conducted a randomized controlled trial (RCT) of UDCA 13-15 mg/kg/day for 2-5 years in 105 PSC patients. The results demonstrated improvement in LFT but not symptoms and the time to treatment failure defined by histologic progression by 2 stages, development of cirrhosis or esophageal varices, liver decompensation, LT, or death.[57] On the basis that higher doses of UDCA may be required to provide sufficient delivery of UDCA to the bile pool and also enhance immunomodulatory effects in the setting of cholestasis and bile duct injury in PSC, several studies using higher dose of UDCA were conducted and published in the early 2000s. A small RCT from Oxford using UDCA 20-25 mg/kg/day found significant improvement in LFT, histology, as well as cholangiographic features. However, no benefit in symptoms and survival was demonstrated.[58] Two studies comparing different doses of UDCA suggested that higher daily dose (25-30 mg/kg) was well-tolerated and provided benefits, which included survival benefit in one study, compared to a lower dose (10-20 mg/kg).[59,60]

Despite somewhat convincing data on benefits with higher doses, a large Scandinavian RCT evaluating UDCA 17-23 mg/kg/day in 219 PSC patients for 5 years found no significant favorable effect on survival, symptoms, and prevention of CHCA.[61] Recently, a multi-center RCT comparing high-dose UDCA (28-30 mg/kg/day) with placebo, in 150 PSC patients, was discontinued prematurely at 6 years due to a higher incidence of adverse outcomes (i.e. death, LT, esophageal varices) in the UDCA group.[62] The likelihood of developing adverse outcomes was not predicted by biochemical response.[62] A recent post-hoc analysis from this RCT reported that an increased risk of adverse events with high-dose UDCA treatment when compared with placebo was only apparent in patients with early histological stage disease or normal bilirubin.[63] Therefore, currently there is no established role for UDCA in slowing the progression of PSC. Further, high-dose UDCA may be harmful and is not recommended.[2,55]

Immunosuppressive Therapy

Unlike most of other immune-mediated diseases, treatment with corticosteroids and other immunosuppressive agents has not demonstrated consistent benefits in PSC. Corticosteroids demonstrated no benefit in PSC and was associated with worsening of osteoporosis.[64-66] Corticosteroids may be considered only in patients with PSC/AIH overlap and IgG4 associated cholangitis.[2] No controlled trial of azathioprine has been reported as monotherapy to date. A combination of azathioprine, prednisolone, and UDCA (500-750 mg/day) for PSC was reported in a small case series. All patients had ALP improvement (7 patients had been previously treated with UDCA, but ALP improved only after prednisolone and AZA were added) and 60% had histological improvement after 41 months.[67] Methotrexate may minimally improve ALP levels, but does not impact clinical outcomes of PSC.[68] Addition of methotrexate to UDCA was associated with toxicity and no improvement in LFT.[69] Mycophenolate mofetil was poorly tolerated and did not demonstrate clinical benefit in PSC.[70] Further, combination of mycophenolate mofetil and UDCA did not provide additional benefits.[69] Although tacrolimus[71] and cyclosporin[72] provided benefit in UC, they had no significant effects on liver disease outcomes and were poorly tolerated.[72] A pilot study involving 10 PSC patients failed to demonstrate clinical efficacy of infliximab (5 mg/kg) on the course of liver disease.[73]

Miscellaneous Treatment

D-penicillamine, a copper chelating agent, failed to demonstrate clinical benefits in a RCT of 70 PSC patients and it was associated with significant toxicity.[74] Colchicine, an anti-fibrogenic agent, using either alone or in combination with prednisone failed to show beneficial effects in two RCTs.[66,75] Silymarin, a milk thistle extract with several hepatoprotective properties was evaluated in a pilot study of 30 PSC patients for 1 year.[80] One-third of patients achieved substantial improvement in LFT, but no significant change in Mayo PSC risk score.[76] Recently, a pilot study of 23 PSC patients noted that docosahexaenoic acid supplementation was associated with a significant decline in ALP.[77] Etanercept, nicotine, bezafibrate, pirfenidone, minocycline, and probiotics, have been preliminarily evaluated in PSC and failed to demonstrate any benefits.[2,56,78,79]

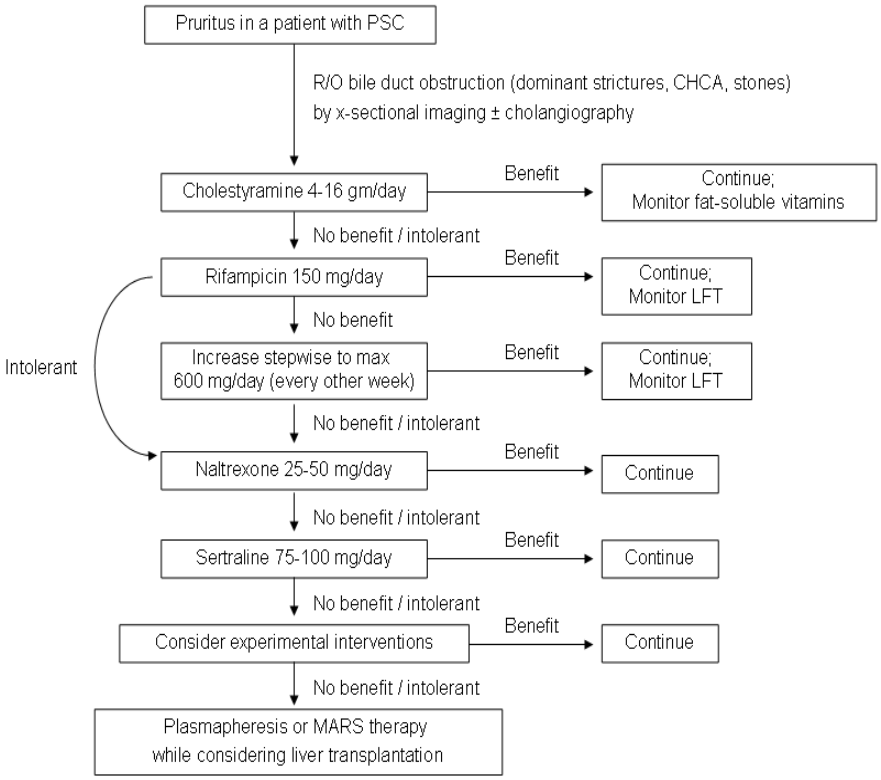

Figure 3. Algorithm for the management of pruritus in primary sclerosing cholangitis (PSC). [Adapted from EASL guideline 2009, with permission]
Abbreviations: *CHCA, cholangiocarcinoma; LFT, liver function test*

MEDICAL MANAGEMENT FOR COMPLICATIONS OF PSC

Pruritus

Pruritus is a presenting symptom in 20-40% of PSC and the frequency tends to increase over the course of the disease.[41,42] It can significantly negatively impact on patient's quality of life, resulting in sleep deprivation, emotional/psychological disturbance, and even suicidal ideation. Dominant bile duct strictures and concomitant dermatological conditions must be sorted out, since the management in those cases may be completely different. As in pruritus associated with other chronic cholestatic conditions, the current guidelines recommend cholestyramine as first line therapy. and rifampicin, naltrexone, and sertraline respectively as second, third, and fourth line treatments.[55,80] LT is reserved for patients with intractable pruritus and individuals who fail all options. Extracorporeal albumin dialysis, as well as a trial of experimental agents, such as propofol, dronabinol, ondansetron, gabapentin, or stanozolol, can be pursued for those who have a poor quality of life, and while awaiting LT (**Figure 3**).[55,80]

Cholangiocarcinoma

CHCA occurs in up to one third of patients with PSC in highly selected series if they are followed long enough.[1,3,9] The development of cholangiocarcinoma is unpredictable and unrelated to the duration of disease, symptoms, and severity of PSC. Risk factors include the duration of UC, colonic dysplasia, variceal bleeding, proctocolectomy, alcohol consumption, and polymorphisms in the NKG2D gene.[2,81] The diagnosis of CHCA in the setting of PSC is often problematic, particularly for the periductal infiltrative type. The presence of mass-like lesion or a long biliary stricture, especially in the hilar area, strongly raises the possibility of CHCA. In PSC patients with suspicion for CHCA, CA 19-9 at a cut-off of 129 U/mL has value in determining the likelihood for CHCA; positive predictive value was 57% and negative predictive value 99%.[82] However, caution must be exercised since CA 19-9 is undetectable in person with Lewis-negative blood type and can be elevated in other conditions, such as cholangitis, and non-biliary cancers.[83] A combination of cross-sectional liver imaging studies, tumor biomarkers, and cholangiography with tissue sampling is often required, and is recommended, to make the accurate diagnosis of CHCA in PSC (**Figure 4**).[2,51,83]

The prognosis of CHCA in PSC is dismal with 3-year survival less than 20% even in surgically resected patients.[2] Innovative approaches using a combination of neoadjuvant chemoradiotherapy and LT provide excellent outcomes with 5-year survival of up to 82% in carefully selected patients with PSC.[84] The survival benefit of other palliative modalities including external beam radiation, endoscopic ablative therapy, and systemic chemotherapy has not been clearly demonstrated.[2]

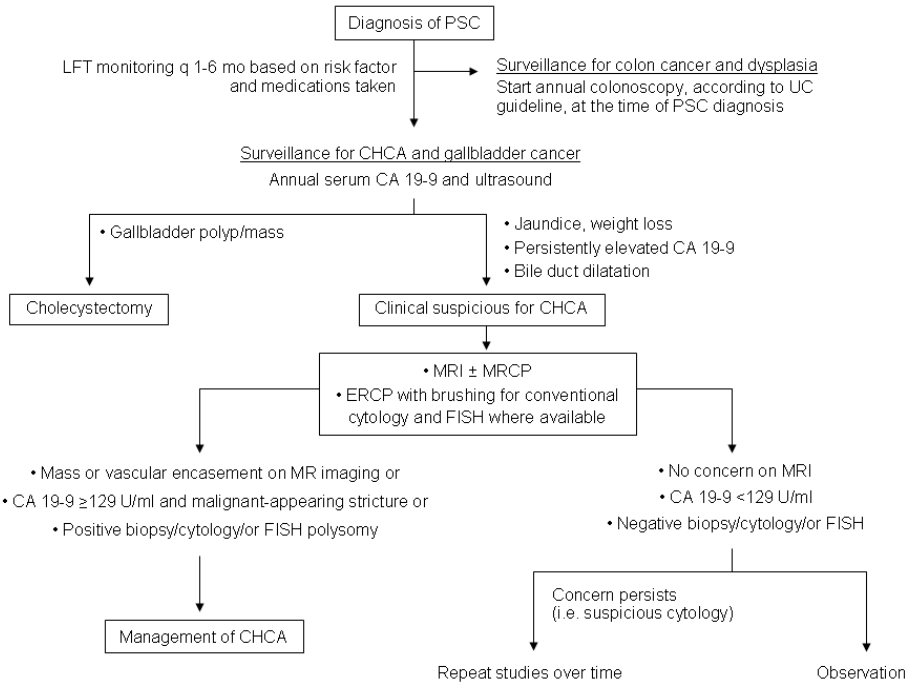

Figure 4. Algorithm for the surveillance and the diagnosis of malignancy in primary sclerosing cholangitis (PSC) [Reprinted from Bunchorntavakul C, Reddy KR. Medical treatment of hepatobiliary diseases associated with ulcerative colitis. In: Lichtenstein GR, editor. Medical Therapy of Mucosal Ulcerative Colitis. New York, USA: Springer Publishing; 2012. In press]

Abbreviations: *CHCA, cholangiocarcinoma; LFT, liver function test; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography*

Colorectal Neoplasia

PSC has been shown to be an independent risk factor for the development of colorectal neoplasia in patients with UC.[85] This risk appears to persist even after LT.[9,13] Patients with IBD and PSC have a risk of developing colonic neoplasms soon after the coexistence of the two diseases is discovered.[82] The colonic neoplasms that developed in this population were spread throughout the colon.[82] Therefore colonoscopy surveillance for colonic neoplasia is recommended to begin at the time of the diagnosis of PSC.[2] There are controversial data suggesting the use of UDCA in preventing the development of colorectal neoplasia in PSC-UC.[2,55] Two recent large cohorts found that long-term high-dose UDCA does not prevent but may actually increase rate of colorectal cancer or dysplasia in patients with PSC.[86,87] Concordantly, the current US guideline recommends against the use of UDCA as chemoprevention in patients with PSC-UC.[2]

Gallbladder Disease

Gallbladder abnormalities are commonly observed in PSC patients and these include gall stones (26%), PSC involving the gallbladder (15%), and gallbladder neoplasms (4-14%).[2,88] Interestingly, 40-60% of gallbladder polyps detected in patients with PSC are malignant.[89,90] Therefore, surveillance by ultrasound should be done annually.[2] According to the current guideline, cholecystectomy is recommended in PSC patients with a gallbladder mass lesion regardless of size since the 1-cm rule may not reliably predict malignant potential of the gallbladder polyp in the setting of PSC.[2,91] Nevertheless, a recent retrospective data suggested that cholecystectomy in PSC patients, particularly with high Child-Pugh score, is associated with considerable morbidity (~40%). Observation may be considered in those PSC patients with gallbladder polyps < 0.8 cm, which are unlikely to be malignant.[92]

DOMINANT STRICTURES

A dominant stricture, defined as a stenosis ≤ 1.5 mm in diameter of the common bile duct and/or ≤ 1 mm of right or left hepatic duct, has been encountered in 45-58% of PSC patients during follow up.[2,92] Although stenotic lesions in PSC are more often benign than malignant in nature,[93] suspicious for CHCA should always be raised and excluded (see above). Signs and symptoms of dominant strictures (cholangitis, jaundice, pruritus, right upper quadrant pain or worsening LFT) should be treated with balloon dilatation to relieve biliary obstruction. Although, there is no RCT to date, biliary stenting has not been shown to provide additional benefit over balloon dilatation alone and ,further, may be prone to early occlusion and infections.[21,77] As a result, balloon dilatation has become the preferred option and stenting is reserved for strictures that are refractory to dilatation.[2] The percutaneous approach is associated with similar efficacy, but has increased morbidity and, therefore, should be reserved for patients who fail endoscopic approach.[2] Endoscopic and percutaneous dilatations achieve 1- and 3-year palliation in 80% and 60% of patients, respectively.[94] Carefully selected non-cirrhotic patients with dominant strictures may benefit from a surgical bilioenteric bypass. In a series of 127 PSC patients who underwent extra-hepatic biliary resection (N=77) or LT (N=49), extra-hepatic biliary resection for non-cirrhotic patients was associated with low perioperative morbidity, few readmissions, no new events of CHCA, and 10-year survival of >60%.[95] It should be noted that there is no data that supports surgical management of a dominant stricture influencing favorably the natural history of PSC.

Bacterial Cholangitis

Patients with PSC are susceptible to repeated episodes of bacterial cholangitis, especially following biliary tract manipulation.[96] If cholangitis occurs without biliary intervention, the presence of dominant strictures, stones, or CHCA should be considered. Common causative organisms are gram-negative enteric bacteria and enterococci.[96] The majority of patients respond to broad-spectrum intravenous antibiotic plus biliary drainage. Patients with recurrent bacterial cholangitis may benefit from long term antibiotic prophylaxis.[2]

Portal Hypertension and End-Stage Liver Disease

Management of portal hypertension and its complications in patients with PSC does not differ from other etiologies. The ultimate treatment for ESLD associated with PSC is LT with 5-year survival rates of ~85%.[2] Resection of the extrahepatic biliary tree along with a Roux-en-Y choledochojejunostomy is widely accepted as a method of choice for biliary reconstruction in LT for PSC.[55] As in non-PSC, the Model for End-Stage Liver Disease (MELD) score is most widely utilized for organ allocation for PSC patients, although the presence of dominant strictures may affect MELD score by increasing bilirubin levels. Other unique indications for LT in PSC patients include intractable pruritus, recurrent bacterial cholangitis, and CHCA.[2] Recurrence of PSC occurs in 20-25% of the liver grafts after 5-10 years following LT,[91,92] but this is sometimes difficult to assess due to the similarities in biliary changes seen with ischemia and preservation injury, infections, and chronic rejection. Potential risk factors associated with disease recurrence included recipient age, male gender, gender mismatch, coexistent IBD, presence of intact colon after LT, cytomegalovirus infection, recurrent acute cellular rejection, and presence of HLA-DRB1*08.[93]

The activity of UC following LT is heterogeneous. Contrary to general wisdom, while on LT-related immunosuppression, 30-61% of PSC-IBD patients experience a deterioration of their IBD.[94,97] Further, the increased risk of developing colorectal neoplasia persists after LT.[98]

Metabolic Bone Disease

PSC patients with longstanding IBD, and particularly with the prolonged use of corticosteroid therapy frequently have decreased bone mass density (BMD).[99] The presence of PSC, with or without cirrhosis, further adversely impacts BMD by several mechanisms including vitamin D malabsorption, altered bone turnover rate, and hypogonadism.[100] A recent study of 237 PSC patients with 10 years of follow-up showed that patients lost 1% of their BMD per year. Osteoporosis was detected in 15% of PSC patients and risk factors included older age, low body mass index, and long duration

of IBD.[101] The surveillance and management of osteoporosis in PSC does not substantially differ from other situations, and there is particular emphasis on calcium and vitamin D supplementation.[2,99] Oral bisphosphonates may induce esophageal ulcerations which could precipitate variceal hemorrhage. Therefore parenteral bisphosphonates may be a reasonable approach for patients with esophageal varices.[2]

PSC VARIANTS

Small-duct PSC

Small-duct PSC, previously termed as pericholangitis, refers to a subgroup of patients who have biochemical and histological features compatible with PSC, but have normal cholangiography. Small-duct PSC represents approximately 6-11% of PSC patients and often co-exists with IBD (~80%). It is potentially progressive but is associated with a better long-term prognosis as compared with large-duct PSC (LT-free survival 13 years vs. 10 years, respectively).[102] CHCA is rarely seen in patients with small-duct PSC. Approximately 25% of patients eventually progressed to large-duct PSC over a median of 7.4 years, and some patients progressed to ESLD requiring LT without developing large-duct disease.[102] Given a relatively small number of patients, the management of small-duct PSC is not well-defined. In a longitudinal cohort of 42 patients from Mayo Clinic followed up to 25 years, UDCA 13-15 mg/kg/day improved LFT, but did not significantly delay disease progression.[103]

PSC/Autoimmune Hepatitis (AIH) Overlap PSC/AIH

overlap is an ill-defined immune-mediated disorder, which is predominantly encountered in children and young adults.[104] A diagnosis of PSC/AIH overlap is made when both typical cholangiographic features of PSC and the definitive diagnosis of AIH based on modified AIH score are present.[104,105] The prevalence of PSC/AIH overlap in PSC patients has varied from 7-14% based on the revised AIH criteria, and 50-88% of these patients have co-existing IBD.[104] The presentation of PSC-AIH overlap may be either simultaneous or sequential. Particularly in the setting of IBD, patients with PSC with an elevation of ALT should prompt a search for AIH. On the other hand, PSC should be considered in AIH patients with cholestasis, histological bile duct injury, and in those who show a poor response to therapy.[104] Patients with PSC/AIH overlap seem to benefit from UDCA and immunosuppressive agents, and survival is apparently better than in classical PSC, but with a poorer outcome than AIH.[106,107] In a prospective Italian study, a combination of UDCA, prednisolone, and azathioprine reported a good biochemical response (ALT, but not ALP) in 7 patients with PSC/AIH overlap.[107]

PSC AND IGG4-ASSOCIATED DISEASE

IgG4-associated disease manifests most commonly as autoimmune pancreatitis, which is characterized by stricturing of the pancreatic duct, pancreatic enlargement, a raised serum IgG4 level, and a lymphoplasmacytic infiltrate on biopsy. Further, with or without pancreatic involvement, it can affect other organ systems, especially the biliary tree causing cholangiographic changes mimicking PSC.[108] Distinguishing between classical PSC and IgG4-associated cholangitis is important since the latter generally responds to corticosteroid therapy. Therefore, changes in the magnetic resonance imaging of the pancreas should be looked for, and the current AASLD guideline recommends measuring serum IgG4 levels in all patients with possible PSC to exclude IgG4-associated cholangitis.[2] In North America and Scandinavian cohorts, an elevated serum IgG4 level (>104-140 mg/dl) was observed in 9-22% of clinically typical patents with PSC.[109-111] In these patients, frequency of IBD was lower, parameters of liver disease severity (serum bilirubin, ALP, and PSC Mayo risk score) were more pronounced at diagnosis and time to LT was shorter.[109-111] Types of biliary involvement (intrahepatic, extrahepatic, or both) were similar in both groups.[109-111] Limited data indicates that majority of PSC patients with elevated IgG4 over the short-term responded to corticosteroid therapy[109] ,however whether this group of patients will respond in the same way as those with autoimmune pancreatitis is yet to be determined.[21]

SUMMARY

PSC is a chronic cholestatic liver disease characterized by progressive inflammatory destruction of intrahepatic and extrahepatic bile ducts. It is strongly associated with IBD, particularly UC. The pathogenesis of PSC remains unclear, however the pathogenesis is thought to involve immunological mechanisms. A diagnosis of PSC is based on a constellation of clinical, biochemical, and typical cholangiographic features, and usually without the need for liver histopathology. Complications specific to PSC include bacterial cholangitis, dominant biliary strictures, and CHCA. CHCA is the most dreaded complication among these patients. A variety of immunosuppressive, antiinflammatory, and antifibrotic agents have been studied in this disease but none has shown a consistent benefit on overall or transplant-free survival. LT remains the only effective therapeutic option for patients with advanced PSC. Cancer surveillance, management of portal hypertension and its complications, and treatment of manifestations of cholestasis in those with PSC are clinically relevant. Further understanding into PSC pathogenesis is desperately required in order to effectively improve our current approaches to the management of this disease.

CONFLICT OF INTEREST
None.

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