

## PRACTICE GUIDELINES

# Management of Primary Sclerosing Cholangitis

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### PREAMBLE

Guidelines for clinical practice are intended to indicate preferred approaches to medical problems as established by scientifically valid research. Double blind, placebo-controlled studies are preferable, but reports and expert review articles are also utilized in a thorough review of the literature conducted through the National Library of Medicine's MEDLINE. When only data that will not withstand objective scrutiny are available, a recommendation is identified as a consensus of experts. Guidelines are applicable to all physicians who address the subject, without regard to specialty training or interests, and are intended to indicate the preferable but not necessarily the only acceptable approach to a specific problem. Guidelines are intended to be flexible and must be distinguished from standards of care that are inflexible and rarely violated. Given the wide range of specifics in any health care problem, the physician must always choose the course best suited to the individual patient and the variables in existence at the moment of decision.

Guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee and approved by the Board of Trustees. Each has been intensely reviewed and revised by the Committee, other experts in the field, physicians who will use them, and specialists in the science of decision of analysis. The recommendations of each guideline are therefore considered valid at the time of their production based on the data available. New developments in medical research and practice pertinent to each guideline will be reviewed at an established time and indicated at publication to assure continued validity. (Am J Gastroenterol 2002;97:528-534. © 2002 by Am. Coll. of Gastroenterology)

### INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic progressive liver disorder that is characterized by ongoing inflammation, obliteration, and fibrosis of both intrahepatic and extrahepatic bile ducts. Diffuse strictures with short intervening segments of normal or dilated bile ducts produce the characteristic beaded appearance on cholangiography.

The pathogenesis of PSC is unknown, but available data suggest that both immunological and nonimmunological host defenses may be impaired (1). Hence, the normal intestinal flora or their metabolic products may play a pathogenic role (1). The disease is usually progressive and may lead to cirrhosis and portal hypertension. PSC is an uncommon disorder for which there are few extensive prevalence data. The estimated prevalence of PSC in the United States, based on studies of inflammatory bowel disease, is 6.3/100,000 (2). A true population-based study has only been done in Norway, where incidence and point prevalence were 1.3 and 8.5 per 100,000 inhabitants, respectively. This compares to incidence and point prevalence of 1.6 and 14.6 for primary biliary cirrhosis. These values seem to be higher than in the rest of Europe or the United States. The recognition of PSC as a distinct liver disease is relatively recent. Until 1970, fewer than 100 patients with PSC had been reported. However, the introduction of endoscopic retrograde cholangiography has changed our perception of this disease. It is now recognized more frequently and is the fourth leading indication for liver transplantation in adults (3). Here we will review the clinical features of PSC, and then propose recommendations regarding appropriate diagnostic and therapeutic strategies. There is no proven medical treatment short of liver transplantation. However, there is effective treatment of many of the symptoms associated with PSC.

### CLINICAL FEATURES

Approximately 70% of patients with PSC are men, with a mean age at diagnosis of 40 yr (4). There is a strong association between PSC and inflammatory bowel disease, particularly ulcerative colitis (2, 5). PSC may occur alone and, rarely, in association with retroperitoneal or mediastinal fibrosis. Patients with PSC and without inflammatory bowel disease were more likely to be female (6). Of the

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approximately 75–90% of patients who have inflammatory bowel disease, about 87% have ulcerative colitis, and 13% have Crohn's colitis. Approximately 4% of patients with inflammatory bowel disease will either have or develop PSC (7).

There are variations in the clinical course of patients with PSC. The majority of patients are initially asymptomatic but can usually be identified on the basis of a cholestatic pattern of liver tests—specifically, elevation of serum alkaline that is proportionately greater than elevations of the aminotransferases. Some asymptomatic patients may have surprisingly advanced disease. This can be demonstrated histologically and radiologically. Some patients may remain asymptomatic for many years. When symptoms of fatigue, pruritus, jaundice, and weight loss develop, these patients usually have advanced disease. Other patients with histologically and radiologically early disease may be symptomatic and have recurrent episodes of fever, chills, jaundice, right upper quadrant pain, or itching. Intermittent episodes of bacterial cholangitis may be present in 10–15% of patients with PSC. Complications of PSC include dominant strictures with pruritus and/or jaundice, cholelithiasis, cholangiocarcinoma, malabsorption of fat-soluble vitamins, bleeding from stomal varices, and osteopenia.

Although the majority of patients are asymptomatic at the time of diagnosis, most eventually develop fatigue, pruritus, and jaundice. Cirrhosis, portal hypertension, and liver failure usually follow. Patients who were symptomatic at diagnosis had shortened survival relative to those who were asymptomatic. The survival of asymptomatic patients is significantly shorter than that of a healthy control population. The estimated median survival time from diagnosis to liver transplantation or death is 10–15 yr (8, 9). There is no relationship between the course of PSC and that of the accompanying inflammatory bowel disease.

## DIAGNOSIS

The most accurate means to diagnose PSC is cholangiography. Serum liver tests usually show a cholestatic profile, particularly elevation of the serum ALP level. Although liver biopsy is usually consistent with PSC, it is rarely diagnostic. Liver biopsy is useful in staging and aids in prognosis. Neither liver histology nor cholangiography alone will reliably reflect the severity of the disease. They must be used together with symptoms, physical findings, blood tests, and imaging or upper endoscopy tests that indicate the presence and severity of portal hypertension.

### General

PSC must be distinguished from *secondary* sclerosing cholangitis due to other types of biliary disorders. These include chronic bacterial cholangitis in patients with bile duct stricture or choledocholithiasis, ischemic bile duct damage due to treatment with floxuridine, infectious cholan-

giopathy associated with AIDS, prior biliary surgery, congenital biliary tree abnormalities, and bile duct neoplasms.

### Blood Tests

Serum liver tests usually demonstrate a cholestatic pattern. The initial laboratory evaluation of cholestatic liver disease includes serum ALP, aminotransferases, bilirubin, albumin levels, and the antimitochondrial antibody test. The serum ALP level is usually elevated, although a small number of patients may have normal levels. Most patients have slight increases in serum aminotransferase levels. Serum albumin levels are normal early in the disease. In early stages of PSC, serum bilirubin values are usually normal, but they gradually increase as the disease progresses. Occasionally, striking fluctuations in bilirubin levels may occur, even at early stages.

Hypergammaglobulinemia is found in about 30% of patients, and increased IgM levels in 50% (10). Autoantibodies occur less frequently than in autoimmune chronic active hepatitis and primary biliary cirrhosis. Anti-smooth muscle antibodies and antinuclear antibodies are detectable in less than 10–20% of patients with PSC (11). Antimitochondrial antibodies are rarely, if ever, found in patients with PSC. About 30–80% of PSC patients have perinuclear antineutrophil cytoplasmic antibodies (12), and 52% have the human leukocyte antigen DRw52a (13). There is still no consensus as to whether specific alleles in the human leukocyte antigen loci, such as DRB1 0301 or DRB1 1301, are directly associated with PSC (14). As in primary biliary cirrhosis, levels of hepatic and urine copper levels are increased, as is the serum ceruloplasmin. Because copper is excreted primarily in bile, the amount of copper in the body increases as cholestasis worsens.

### Cholangiography

Cholangiography is the usual way to diagnose PSC. Endoscopic retrograde cholangiography is the test of choice. Transhepatic cholangiography is performed only if endoscopic retrograde cholangiography is unsuccessful. Magnetic resonance cholangiography is increasingly available but does not yet visualize the intrahepatic bile ducts sufficiently to replace direct cholangiography. The radiological findings of PSC are characteristic and include multifocal strictures and dilations, usually involving both the intrahepatic and the extrahepatic biliary trees. Diffuse strictures with short intervening segments of normal or dilated bile duct produce the classic beaded appearance. Some patients may have ulcerations in the larger bile ducts that resemble those seen in Crohn's disease. The gallbladder and cystic duct are involved in up to 15% of cases (15). Abnormalities of the pancreatic ducts resembling those of chronic pancreatitis have been reported (16, 17). Dominant strictures of the larger bile ducts were seen in only 7% of 1000 patients seen at the Mayo Clinic in the last 10 yr. Dilatation of these dominant strictures improved symptoms and blood tests (18).

There is one putative variant, called small duct PSC, in which the affected bile ducts are too small to be seen by cholangiography (19). The prevalence of small duct PSC is uncertain but was reported to be less than 5% of PSC patients at the Mayo Clinic (19). It is diagnosed in patients with inflammatory bowel disease who have cholestatic liver tests, and characteristic liver biopsies but normal endoscopic retrograde cholangiography and negative antimitochondrial antibody tests.

### **Histological Features**

PSC has been divided into four histological stages (20). Stage 1 represents the initial lesion, and the other stages presumably develop with time and the progression of disease. Stage 1 is characterized by the degeneration of bile duct epithelial cells and infiltration of the bile ducts by inflammatory cells, predominantly lymphocytes but occasionally neutrophils. There is inflammation, scarring and enlargement of portal triads, and, at times, portal edema. There may be proliferation of bile ducts in some portal triads, vacuolization of ductular epithelial cells, and concentric layers of connective tissue surrounding bile ducts (onionskin lesion). There is typically less inflammation in the portal triads than in primary biliary cirrhosis. In stage 2, the lesion is more widespread. The fibrosis and inflammation infiltrate the periportal parenchyma, and the periportal hepatocytes may be destroyed. Portal triads are often enlarged. Bile ductopenia is a prominent feature; concentric periductal fibrosis is less obvious. As the disease progresses to stage 3, there is formation of portal-to-portal bridging fibrous septa. Bile ducts are absent or have undergone severe degenerative changes. Cholestasis may be prominent, primarily in periportal and paraseptal hepatocytes. Stage 4, the end stage, is characterized by frank cirrhosis; the histological features are similar to those seen in other forms of that disease. In PSC, however, there may also be changes associated with large duct obstruction, the proliferation and dilation of interlobular bile ducts, and increased numbers of periportal neutrophils.

The most characteristic sign of PSC, the onionskin lesion, is rarely seen on a percutaneous liver biopsy (21). It is more common to see only a paucity of normal bile ducts with nonspecific fibrosis and inflammation in the portal triads. Therefore, a definite diagnosis must be established by cholangiography. Liver histology is used for confirmation and to determine the stage and the prognosis of disease. As sampling variation may occur with liver biopsy, histological staging requires the examination of a sufficiently large specimen that has at least 10 portal triads.

### **MANAGEMENT**

There is no proven medical therapy for PSC. The goal of management should be treatment of symptoms and complications of cholestasis, as well as attempts at treating the underlying disease process. In addition, efforts should be

made to recognize and treat or prevent the known complications of PSC such as fat-soluble vitamin deficiency, osteopenia, dominant biliary strictures, and cholangiocarcinoma. Liver transplantation is the only effective treatment and is recommended for patients with end-stage liver disease and symptomatic portal hypertension, liver failure, and recurrent or intractable bacterial cholangitis.

### **Management of Chronic Cholestasis and Its Complications**

Symptoms of chronic cholestasis in PSC are similar to those of primary biliary cirrhosis. They include fatigue, pruritus, steatorrhea, and metabolic bone disease. However, unique problems result from mechanical bile duct obstruction, including bacterial cholangitis, sepsis, and the formation of pigment stones within the obstructed bile ducts. In addition, patients with PSC are at risk of developing cholangiocarcinoma. Cholangiocarcinoma may be difficult to distinguish from the bile duct strictures typical of PSC.

**PRURITUS.** Pruritus is a common symptom of PSC and may be disabling. The precise cause of pruritus remains uncertain. Recent evidence suggests that pruritus may be mediated by an upregulation of central opioidergic receptors (22). It is not caused by the retention of bile acids in skin (23). A variety of agents have been evaluated in the management of pruritus. Cholestyramine, a nonabsorbed resin, is effective in most patients as long as there is adequate bile flow (24). The usual starting dose of cholestyramine is 4 g *t.i.d. p.o.* The dose must be adjusted in individual patients. There is usually a 2- to 4-day interval between the time that cholestyramine is begun and pruritus remits. Colestipol hydrochloride, another ammonium resin, is as effective as cholestyramine and may be used in those patients who cannot tolerate cholestyramine. Patients must be cautioned to take these resins 2.5 to 3 h before or after they take other medications. Many drugs will bind tightly to these resins in the intestinal tract, particularly ursodeoxycholic acid (UDCA), and will not be absorbed. Rifampin (150 mg *b.i.d.*) is effective in many patients whose pruritus does not respond to cholestyramine or colestipol (25). Phenobarbital (60–100 mg at bedtime) may also be helpful in this setting (26). Antihistamines are occasionally helpful in patients with mild pruritus if taken at bedtime. Naloxone (27) and naltrexone (28), opioid antagonists, may be helpful in patients who do not respond to any of the above. Large volume plasmapheresis is almost always effective if there is intractable pruritus that fails to respond to all of the above (29). However, it is expensive and time consuming and usually reserved for those awaiting liver transplantation. Methyltestosterone (30), ursodiol (31), *S*-adenosylmethionine (32), ondansetron (33), prednisone, and ultraviolet light (34) have been used to control pruritus in individual patients but are tried only if all else fails. Although ursodiol is commonly used for the management of pruritus, there are no controlled data supporting its use.

**STEATORRHEA AND VITAMIN DEFICIENCY.** Steatorrhea and malabsorption of fat-soluble vitamins may occur late in the course of PSC. Fat malabsorption in jaundiced patients is usually related to decreased secretion of conjugated bile acids into the small intestine. Other causes are pancreatic insufficiency and celiac disease, both of which may be associated with PSC (35, 36). Vitamin A deficiency has been reported in up to 82% of patients with advanced PSC (37). Vitamin D and E occur in approximately 40–50% of patients with advanced PSC (37). Clinically important vitamin K deficiency rarely occurs unless the patient is chronically jaundiced and takes cholestyramine regularly. In PSC patients with chronic jaundice, fat-soluble vitamin levels should be monitored, and deficiencies treated with supplements.

**METABOLIC BONE DISEASE.** Osteoporosis is a more common complication of patients with chronic cholestasis than osteomalacia (38). The pathogenesis of osteoporosis in PSC or other chronic cholestatic liver diseases is unknown. Osteoporosis is not related to vitamin D deficiency. The serum concentrations of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, the physiologically active metabolites of vitamin D, are usually normal. The osteoporosis may be related to osteoblast inhibitors in cholestatic serum (39). There is no proven medical treatment for osteoporosis in PSC. Treatment with 25-hydroxyvitamin D with calcium, ursodiol, calcitonin, and bisphosphonates has been suggested, but there are no controlled data that demonstrate efficacy (40). Alendronate is more effective than etidronate in osteopenic patients with PBC (41). However, there have been no published controlled trials of bisphosphonates in the osteoporosis associated with PSC.

**BACTERIAL CHOLANGITIS.** Bacterial cholangitis may occur after endoscopic procedures or in patients with bile duct stones or tight strictures. Antibiotics are effective in treating recurrent episodes of ascending cholangitis but have not been shown to slow the progression of PSC. Anecdotal reports suggest that such drugs reduce the frequency and severity of attacks of recurrent bacterial cholangitis. Ciprofloxacin has been recommended for treatment and prophylaxis of bacterial cholangitis because of its high biliary tract penetration. Alternative agents are amoxicillin or trimethoprim-sulfamethoxazole. Tetracycline was ineffective in one small study in PSC (42). However, there have been no randomized prospective trials that have critically evaluated antibiotics in PSC. Additional controlled trials are needed to evaluate the efficacy of antibiotics.

**DOMINANT BILIARY STRICTURES.** Dominant strictures of the extrahepatic bile duct occur in 7–20% of patients with PSC (18, 43). Several studies reported successful management with endoscopic balloon dilation or biliary stenting of the dominant strictures (44–47). Endoscopic dilation was associated with fewer episodes of cholangitis and improvement of cholangiographic appearance and biochemical tests.

There are no randomized controlled trials that have evaluated the efficacy of endoscopic therapy. There appears to be little risk and some potential benefit in this approach. In one uncontrolled trial, endoscopic dilation plus ursodiol appeared to prolong survival without liver transplantation when compared to the expected survival in untreated patients (47). Another approach to the dominant stricture is surgical dilation or choledochojejunostomy. Surgical resection of hilar and extrahepatic strictures in noncirrhotic patients may postpone the need for transplantation and the development of cholangiocarcinoma in carefully selected patients (48). However, surgical resection carries the risk of postoperative infection and increases scarring in the portahepatis, potentially complicating future liver transplantation.

**CHOLANGIOCARCINOMA.** There is an increased incidence of cholangiocarcinoma in patients with PSC. The reported frequencies of cholangiocarcinomas associated with PSC range from 6% to 30% (49). Patients with longstanding chronic ulcerative colitis and cirrhosis are at highest risk. Most cholangiocarcinomas occur at or near the junction of the right and left hepatic bile ducts. The lack of sensitive and specific serological tumor markers as well as the insensitivity of biliary brush cytology have hampered early diagnosis of cholangiocarcinoma. The serological tumor markers, such as carcinoembryonic antigen and cancer antigen 19-9, have not been useful in diagnosing early, potentially treatable cholangiocarcinomas (50). In addition, it is difficult to distinguish PSC from PSC complicated by cholangiocarcinoma. Often an unsuspected cholangiocarcinoma is found after liver transplantation when the resected liver is examined in the pathology laboratory. Treatment of clinically apparent cholangiocarcinoma by resection, chemotherapy, and radiation has been discouraging, as have been the results with liver transplantation (51). Some experts have suggested surgical extirpation of the biliary tree or liver transplantation before the development of cholangiocarcinoma. The value of screening for cholangiocarcinoma has not been proven.

#### *Specific Therapy of PSC*

A variety of choleric, immunosuppressive, and antifibrotic agents have been used to treat PSC. However, no drug has been shown to alter its natural history.

The evaluation of treatment of PSC has been limited by the uncertainty about its cause and the unpredictable course of the disease. The course of PSC is indolent in most patients but may be rapidly progressive in some and associated with spontaneous exacerbations and remissions in others. Hence, even if a drug is effective, it will probably be years before its efficacy can be proven.

**UDCA.** UDCA, a hydrophilic bile acid, has been widely used to treat PSC. Therapy with the drug leads to a 2- to 3-fold increase in serum bile acid concentration. There is an increase in the biliary and urinary excretion of bile acids and

**Table 1.** Controlled Trials of UDCA in PSC\*

Reference	No. of Patients	UDCA Dose	Treatment Duration	Symptoms	Liver Function Tests	Histology
Beuers (54)	14	13–15 mg/kg/day	12 mo	Unchanged	Improved	Improved
Stiehl (47, 52)	20	750 mg/day	Mean = 45 mo	Unchanged	Improved, except bilirubin	Improved
Lindor (56)	105	13–15 mg/kg/day	Mean = 0.5–72 mo	Unchanged	Improved	Unchanged
Mitchell (57)	24	20 mg/kg/day	24 mo	Unchanged	Improved	Improved

\* No study has shown improvement in the natural history of PSC.

an increase in bile flow. *In vitro*, UDCA stabilizes liver cell membranes exposed to toxic concentrations of the naturally occurring bile acid chenodeoxycholic acid.

There have been several small studies and one large controlled trial that reported improvements in symptoms and liver tests with UDCA (52–55) (Table 1). The long term beneficial effects of UDCA on the natural history were unclear because these trials were of relatively short duration and included few patients. A prospective randomized double-blind placebo-controlled trial of 105 patients continued for 2 yr confirmed earlier reports that UDCA (13–15 mg/kg of body weight/day) significantly improved liver tests (56). However, UDCA had no beneficial effect on time to treatment failure or liver transplantation. Furthermore, UDCA did not improve symptoms, cholangiographic appearance, and liver histology.

A nonrandomized study of UDCA with endoscopic dilation of dominant stricture indicates that this combination may be more effective than UDCA alone (47).

Higher dose UDCA in a pilot study appears to be promising. A double-blind placebo-controlled pilot study of higher dose (20 mg/kg) UDCA in patients observed for 2 yr showed that UDCA was associated with improvement of ALP and liver histology (57). The higher dose UDCA was well tolerated and had no significant side effects. In addition, there is a trial that employs a still higher dose of UDCA, 25–30 mg/kg/day (58). It is as well tolerated as lower doses of UDCA. Because there are no long term data on higher doses of UDCA, their ability to improve the natural history of PSC is still unproven.

**IMMUNOSUPPRESSIVE AND ANTIFIBROTIC AGENTS.** Despite anecdotal reports of improvement with glucocorticoids and azathioprine in patients with PSC, there is little enthusiasm for their use (59). In addition, glucocorticoids may accelerate the onset and progression of osteoporosis and increase the likelihood of spontaneous bone fractures. Colchicine was not effective in a double blind study of 85 patients with PSC (60), and neither was the combination of colchicine and prednisone (61). In a randomized trial of 34 patients, cyclosporine had no beneficial effect on pruritus, fatigue, liver tests, or survival free of liver transplantation (62). Tacrolimus (FK 506) appeared to improve liver tests in a small, uncontrolled pilot study of 1 yr duration. However, its short duration and lack of histological and cholangiographic data limited its value (63). Methotrexate improved

liver tests and liver histology in an uncontrolled trial of 10 patients (64). However, in a double blind, controlled trial of 24 patients, methotrexate was not effective in prolonging survival free of liver transplantation when compared to a placebo (65). Pentoxifylline prevents the production of tumor necrosis factor, which has been postulated to have a role in hepatic injury in PSC. In a pilot study of 20 patients, pentoxifylline was not beneficial in improvement of symptoms or liver tests (66). D-Penicillamine, a cupruritic and antifibrotic agent, was evaluated in a double-blind prospective trial in 70 patients observed during 36 months (67). D-Penicillamine produced the expected cupriuresis, but had no beneficial effect on symptoms, liver tests, liver histology, or survival.

**OTHER AGENTS.** Several other agents have been used to treat PSC, including cholestyramine and nicotine (68). The rationale for nicotine is based on the observation that PSC is less common in smokers and nicotine has a beneficial effect in some patients with ulcerative colitis. However, neither agent was effective.

## INDICATIONS FOR LIVER TRANSPLANTATION

For patients with advanced PSC, liver transplantation is the only effective therapeutic option.

Indications for liver transplantation include bleeding from varices or portal gastropathy, intractable ascites with or without spontaneous bacterial peritonitis, recurrent episodes of bacterial cholangitis, progressive muscle wasting, and hepatic encephalopathy. A number of transplant centers now report a 3-yr survival rate of 85–90% for patients with PSC (69). However, stricturing of the transplanted bile ducts is a post-liver transplantation problem that is more common in PSC patients than in other diseases that lead to liver transplantation. The pattern of the strictures is similar to that seen in PSC. Possible causes include recurrence of PSC, ischemia, chronic rejection, or infectious cholangitis related to the Roux-en-Y biliary anastomosis and immunosuppression. How often and when PSC recurs after liver transplantation is uncertain. Data from one center suggest that PSC recurs in 10–20% of PSC patients (70), whereas others report lower rates of recurrence (71).

In PSC patients with inflammatory bowel disease who undergo liver transplantation, inflammatory bowel syndrome symptoms are generally improved. On the other

hand, there is a continuing and perhaps increased risk of colon cancer in inflammatory bowel disease patients. Thus, it is important to continue annual surveillance colonoscopies in PSC patients who have chronic ulcerative colitis.

## CONTROVERSIAL ISSUES

There are many unresolved questions regarding practice guidelines for PSC because of insufficient data. Some of the unresolved issues are:

1. What is the role of UDCA in PSC? Are larger doses truly efficacious? Should standard doses (13–15 mg/kg of body weight/day) be offered given the lack of proven efficacy?
2. What is the optimal endoscopic method for treating dominant strictures, balloon dilation or stenting? If dilation is effective, how often should it be done? Should dilation be done in the asymptomatic nonjaundiced patient?
3. What can be done to detect cholangiocarcinoma early? Despite the relatively high incidence of cholangiocarcinoma in PSC, surveillance guidelines have yet to be defined.
4. What is the appropriate treatment for osteoporosis associated with PSC? Is there any short of liver transplantation?
5. What is the role of immunosuppressive therapy and antibiotics in PSC? Should combination therapy be tried? If so, what drugs should be used?
6. Is there any way to diagnose PSC before there are characteristic cholangiographic abnormalities? Because these are caused by scarring that could be irreversible, it is possible that all patients with PSC have medically untreatable disease at the time of diagnosis.
7. Is PSC one disease or is it a syndrome, similar to chronic hepatitis?

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## REFERENCES

1. Lee Y-M, Kaplan MM. Primary sclerosing cholangitis. *N Engl J Med* 1995;332:924–33.
2. Olsson R, Danielsson A, Järnerot G, et al. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. *Gastroenterology* 1991;11:56–63.
3. Primary liver disease of liver transplant recipients, 1991 and 1992. *UNOS Update* 1993;9(8):27–9.
4. Lindor K, Wiesner R, LaRusso N. Recent advances in the management of primary sclerosing cholangitis. *Semin Liver Dis* 1987;7:322–7.
5. Fausa O, Schrupf E, Elgjo K. Relationship of inflammatory bowel disease and primary sclerosing cholangitis. *Semin Liver Dis* 1991;11:31–9.
6. Rabinovitz M, Gavalier JS, Schade RR, et al. Does primary sclerosing cholangitis occurring in association with inflammatory bowel disease differ from that occurring in the absence of inflammatory bowel disease? A study of 66 subjects. *Hepatology* 1990;11:7–11.
7. Schrupf E, Elgjo K, Fausa O. Sclerosing cholangitis in ulcerative colitis. *Scand J Gastroenterol* 1980;15:689–97.
8. Farrant JM, Hayllar KM, Wilkinson M, et al. Natural history and prognostic variables in primary sclerosing cholangitis. *Gastroenterology* 1991;100:1710–7.
9. Broome U, Olsson R, Loof L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut* 1996;38:610–5.
10. Van Milligen de Wit AW, van Deventer SJ, Tytgat GN. Immunogenetic aspects of primary sclerosing cholangitis: Implications for therapeutic strategies. *Am J Gastroenterol* 1995;90:893–900.
11. Wiesner RH, LaRusso NF, Ludwig J, et al. Comparison of the clinicopathological features of primary sclerosing cholangitis and primary biliary cirrhosis. *Gastroenterology* 1995;88:108–114.
12. Duerr RH, Targan SR, Landers CJ, et al. Anti-neutrophil cytoplasmic antibodies: A link between primary sclerosing cholangitis and ulcerative colitis. *Gastroenterology* 1991;100:1385–91.
13. Zetterquist H, Broomé U, Einarsson K, et al. HLA class II genes in primary sclerosing cholangitis and chronic inflammatory bowel disease: No HLA-DRw52a association in Swedish patients with sclerosing cholangitis. *Gut* 1992;33:942–6.
14. Moloney MM, Thomson LJ, Strettell MJ, et al. HLA-C genes and susceptibility to primary sclerosing cholangitis. *Hepatology* 1998;28:660–2.
15. Jeffrey GP, Reed WD, Carrello S, et al. Histological and immunohistochemical study of the gallbladder lesion in primary sclerosing cholangitis. *Gut* 1991;32:424–9.
16. MacCarty RL, LaRusso NF, Wiesner RH, et al. Primary sclerosing cholangitis: Findings on cholangiography and pancreatography. *Radiology* 1983;149:39–44.
17. Epstein O, Chapman RWG, Lake-Bakaar G, et al. The pancreas in primary biliary cirrhosis and primary sclerosing cholangitis. *Gastroenterology* 1982;83:1177–82.
18. Kaya M, Petersen BT, Angulo P, Lindor KD. Balloon dilatation compared to stenting of dominant strictures in primary sclerosing cholangitis. *Gastroenterology* 2000;111:34A.
19. Wee A, Ludwig J. Pericholangitis in chronic ulcerative colitis: Primary sclerosing cholangitis of the small bile ducts. *Ann Intern Med* 1985;102:581–7.
20. Ludwig J, Barham SS, LaRusso NF, et al. Morphologic features of chronic hepatitis associated with primary sclerosing cholangitis and chronic ulcerative colitis. *Hepatology* 1981;1:632–40.
21. Wiesner RH. Current concepts in primary sclerosing cholangitis. *Mayo Clin Proc* 1994;69:969–82.
22. Jones EA, Bergasa NV. The pruritus of cholestasis and the opioid system. *JAMA* 1992;268:3359–62.
23. Ghent CN. Pruritus of cholestasis is related to effects of bile salts on liver, not the skin. *Am J Gastroenterol* 1987;82:117–8.
24. Datta D, Sherlock S. Treatment of pruritus of obstructive jaundice with cholestyramine. *Br Med J* 1963;1:216–9.
25. Bachs L, Pares A, Elena M, et al. Effects of long-term rifampicin administration in primary biliary cirrhosis. *Gastroenterology* 1992;102:2077–80.
26. Bloomer JR, Boyer JL. Phenobarbital effects in cholestatic liver diseases. *Ann Intern Med* 1975;82:310–7.
27. Bergasa NV, Talbot TL, Alling DW, et al. Effects of naloxone infusions in patients with the pruritus of cholestasis. A double-blind, randomized, controlled trial. *Ann Intern Med* 1995;123:161–7.
28. Wolfhagen FH, Sternieri E, Hop WC, et al. Oral naltrexone

- treatment for cholestatic pruritus: A double-blind, placebo-controlled study. *Gastroenterology* 1997;113:1264-9.
29. Cohen LB, Ambinder EP, Wolke AM, et al. Role of plasmapheresis in primary biliary cirrhosis. *Gut* 1985;26:291-4.
  30. Lloyd-Thomas H, Sherlock S. Testosterone therapy for the pruritus of obstructive jaundice. *Br Med J* 1952;2:1289-91.
  31. Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. *N Engl J Med* 1994;330:1342-7.
  32. Almasio P, Bortolini M, Pagliaro L, Coltorti M. Role of S-adenosyl-L-methionine in the treatment of intrahepatic cholestasis. *Drugs* 1990;40(3):111-23.
  33. Raderer M, Muller C, Scheithauer W. Ondansetron for pruritus due to cholestasis. *N Engl J Med* 1994;330:1540.
  34. Hanid MA, Levi AJ. Phototherapy for pruritus in primary biliary cirrhosis. *Lancet* 1980;2:530.
  35. Borkje B, Vetvik K, Odegaard S, et al. Chronic pancreatitis in patients with sclerosing cholangitis and ulcerative colitis. *Scand J Gastroenterol* 1985;3:539-42.
  36. Hay JE, Wiesner RH, Shorter RG, et al. Primary sclerosing cholangitis and celiac disease: A novel association. *Ann Intern Med* 1988;109:713-7.
  37. Jorgensen RA, Lindor KD, Sartin JS, et al. Serum lipid and fat-soluble vitamin levels in primary sclerosing cholangitis. *J Clin Gastroenterol* 1995;20:215-9.
  38. Hay JE, Lindor KD, Wiesner RH, et al. Metabolic bone disease in primary sclerosing cholangitis. *Hepatology* 1991;14:257-61.
  39. Janes CH, Dickson ER, Okazaki R, et al. Role of hyperbilirubinemia in the impairment of osteoblast proliferation association with cholestatic jaundice. *J Clin Invest* 1995;95:2581-6.
  40. Crippin JS, Jorgensen RA, Dickson ER, et al. Hepatic osteodystrophy in primary biliary cirrhosis: Effects of medical treatment. *Am J Gastroenterol* 1994;89:47-50.
  41. Pares A, Guanabens N, Inmaculada R, et al. Aledronate is more effective than etidronate for increasing bone mass in osteopenic patients with primary biliary cirrhosis. *Hepatology* 1999;30:1245A.
  42. Mistilis SP, Skyring AP, Goulston SJ. Effect of long-term tetracycline therapy, steroid therapy and colectomy in pericholangitis associated with ulcerative colitis. *Australas Ann Med* 1965;14:286-94.
  43. May GR, Bender CE, LaRusso NF, Wiesner RH. Non-operative dilation of dominant strictures in primary sclerosing cholangitis. *AJR* 1985;145:1061-4.
  44. Johnson GK, Geenen JE, Venu RP, et al. Endoscopic treatment of biliary duct strictures in sclerosing cholangitis: A larger series and recommendations for treatment. *Gastrointest Endosc* 1991;37:38-43.
  45. Lee JG, Schutz SM, England RE, et al. Endoscopic therapy of primary sclerosing cholangitis. *Hepatology* 1995;21:661-7.
  46. Van Milligen de Wit AW, van Brancht J, Rauws EA, et al. Endoscopic stent therapy for dominant extrahepatic bile duct strictures in primary sclerosing cholangitis. *Gastrointest Endosc* 1996;44:293-9.
  47. Stiehl A, Rudolph G, Sauer P, et al. Efficacy of ursodeoxycholic acid treatment and endoscopic dilation of major duct stenoses in primary sclerosing cholangitis. An 8-year prospective study. *J Hepatol* 1997;26:560-6.
  48. Ahrendt SA, Pitt HA. Surgical treatment for PSC. *J Hepatobiliary Pancreat Surg* 1999;6:366-72.
  49. Rosen CB, Nagorney DM, Wiesner RH, et al. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Ann Surg* 1991;213:21-5.
  50. Nichols JC, Gores GJ, LaRusso NF, et al. Diagnostic role of serum CA19-9 for cholangiocarcinoma in patients with primary sclerosing cholangitis. *Mayo Clin Proc* 1993;68:874-9.
  51. Marsh JW Jr, Shunzaburo I, Makowka L, et al. Orthotopic liver transplantation for primary sclerosing cholangitis. *Ann Surg* 1988;207:21-5.
  52. Stiehl A, Walker S, Stiehl L, et al. Effect of ursodeoxycholic acid on liver and bile duct disease in primary sclerosing cholangitis. A 3-year pilot study with a placebo controlled study period. *J Hepatol* 1994;20:57-64.
  53. Chazouilleres O, Poupon R, Capron JP, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis. *J Hepatol* 1990;11:120-3.
  54. Beuers U, Spengler U, Kruis W, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: A placebo-controlled trial. *Hepatology* 1992;16:707-14.
  55. O'Brien CB, Senior JR, Arora-Mirchandani R, et al. Ursodeoxycholic acid for the treatment of primary sclerosing cholangitis: A 30 month pilot study. *Hepatology* 1991;14:838-47.
  56. Lindor KD, The Mayo PSC-UDCA Study Group. Ursodiol for primary sclerosing cholangitis. *N Engl J Med* 1997;336:691-5.
  57. Mitchell SA, Bansi D, Hunt N, et al. High dose ursodeoxycholic acid (UDCA) in primary sclerosing cholangitis (PSC): Results after two years of a randomised double-blind placebo-controlled trial. *Gastroenterology* 1997;112:1335A.
  58. Harnois DM, Angulo P, Jorgensen RA. High dose ursodeoxycholic acid as a therapy for patients with primary sclerosing cholangitis. *Gastroenterology* 2000;118:902A.
  59. Wagner A. Azathioprine treatment in primary sclerosing cholangitis. *Lancet* 1971;2:663-4.
  60. Olsson R, Broome U, Danielsson A, et al. Colchicine treatment of primary sclerosing cholangitis. *Gastroenterology* 1995;108:1199-203.
  61. Lindor KD, Wiesner RH, Colwell LJ, et al. The combination of prednisone and colchicine in patients with primary sclerosing cholangitis. *Am J Gastroenterol* 1991;86:57-61.
  62. Wiesner R, Steiner B, LaRusso N, et al. A controlled clinical trial evaluating cyclosporine in the treatment of primary sclerosing cholangitis. *Hepatology* 1991;14:63A.
  63. Van Thiel DH, Carroll P, Abu-Elmagd K, et al. Tacrolimus (FK 506), a treatment for primary sclerosing cholangitis: Results of an open-label preliminary trial. *Am J Gastroenterol* 1995;90:455-9.
  64. Knox TA, Kaplan MM. Treatment of primary sclerosing cholangitis with oral methotrexate. *Am J Gastroenterol* 1991;86:546-52.
  65. Knox TA, Kaplan MM. A double-blind controlled trial of oral-pulse methotrexate therapy in the treatment of primary sclerosing cholangitis. *Gastroenterology* 1994;106:494-9.
  66. Bharucha AE, Jorgensen RA, Lichtman SN, et al. A pilot study of pentoxifylline for the treatment of primary sclerosing cholangitis. *Am J Gastroenterol* 2000;95:2338-42.
  67. LaRusso NF, Wiesner RH, Ludwig J, et al. Prospective trial of penicillamine in primary sclerosing cholangitis. *Gastroenterology* 1988;95:1036-42.
  68. Angulo P, Bharucha A, Jorgensen R, et al. Oral nicotine in treatment of primary sclerosing cholangitis: A pilot study. *Dig Dis Sci* 1999;44:602-7.
  69. Langnas AN, Grazi GL, Stratta RJ, et al. Primary sclerosing cholangitis: The emerging role for liver transplantation. *Am J Gastroenterol* 1990;85:1136-41.
  70. Graziadei IW, Wiesner RH, Marota PJ, et al. Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. *Hepatology* 1999;30:1121-7.
  71. Harrison RF, Davis MH, Neuberger J, et al. Fibrous and obliterative cholangitis in liver allografts: Evidence of recurring primary sclerosing cholangitis? *Hepatology* 1994;20:356-61.