Primary sclerosing cholangitis in adults: Management

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic progressive disorder of unknown etiology that is characterized by inflammation, fibrosis, and stricturing of medium and large-size ducts in the intrahepatic and extrahepatic biliary tree. The great majority of affected patients have underlying ulcerative colitis; the incidence may be as high as 90 percent when rectal and sigmoid biopsies are routinely obtained [1]. (See "Primary sclerosing cholangitis: Epidemiology and pathogenesis".)

PSC is associated with numerous complications, including cholestasis (with associated problems), dominant stricture formation, cholelithiasis and cholangitis, cholangiocarcinoma, and colon cancer (in patients with concurrent ulcerative colitis) [2,3]. In addition, PSC may follow a progressive course, resulting in portal hypertension and liver failure.

There are two major goals of treatment in PSC:

- Retardation and reversal of the disease process
- Management of progressive disease and its complications

The medical, endoscopic, and surgical therapies aimed at managing progressive PSC and cancer screening in patients with PSC will be reviewed here. As will be seen, there is **no** proven treatment that slows progression of the disease. However, excellent outcomes may be achieved after liver transplantation for advanced disease. The clinical manifestations and diagnosis of

PSC and the treatment of pruritus are discussed separately. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis" and "Pruritus associated with cholestasis".)

Our approach to patients with PSC is largely consistent with the British Society of Gastroenterology/UK-PSC Guidelines [4], a 2019 clinical practice guideline from the American Gastroenterological Association, a 2015 guideline from the American College of Gastroenterology, [5] and a 2010 guideline from the American Association for the Study of Liver Diseases [6].

DRUG THERAPY

A variety of immunosuppressive and anti-inflammatory agents have been studied in patients with primary sclerosing cholangitis (PSC) [3,7]. These include:

- Ursodeoxycholic acid
- Glucocorticoids
- Cyclosporine
- Methotrexate
- Vancomycin
- Azathioprine and 6-mercaptopurine
- Tacrolimus
- D-penicillamine
- Etanercept

Unfortunately, **none** has been conclusively proven to alter the natural history of this disorder, though there are some data that suggest patients who have a decrease in their alkaline phosphatase level during follow-up have improved survival [8]. Randomized trials of high-dose ursodeoxycholic acid (UDCA) are underway in an attempt to confirm encouraging results in pilot studies.

Ursodeoxycholic acid — UDCA, a hydrophilic bile acid, is the most extensively studied of all medical treatments for PSC. UDCA, at a dose up to 15 mg/kg per day, is thought to exert its effects in cholestatic conditions via protection of cholangiocytes against cytotoxic hydrophobic bile acids, stimulation of hepatobiliary secretion, protection of hepatocytes against bile acid-induced apoptosis, and induction of antioxidants [9].

UDCA, at a dose up to 15 mg/kg/day, has shown some efficacy in improving biochemical abnormalities and stabilizing hepatic inflammation but has not resulted in a survival benefit or a delay in the need for liver transplantation [10-18]. Three meta-analyses (all with eight

randomized controlled trials, though with minor differences in which studies were included) found that UDCA significantly improved liver biochemical tests [17-19]. None of the meta-analyses found a benefit on the risk of death or need for liver transplantation. One detected significant benefit in liver histology and a trend toward a reduction in histologic deterioration and improvement of cholangiographic abnormalities [17], whereas two found no benefit on histology [18,19]. In addition, there was no benefit from UDCA with regard to pruritus, fatigue, or cholangiocarcinoma development [19]. Thus, the available data do not demonstrate a consistent benefit on clinically important outcomes.

However, the majority of patients in the studies included in the meta-analyses already had significant hepatic fibrosis or cirrhosis. It is possible that use of UDCA in early stage PSC (eg, before onset of fibrosis) may be helpful, but the appropriate studies have been difficult to perform because of limited numbers of patients and significant heterogeneity in patient populations. Finally, UDCA has also been studied as an agent to prevent colorectal cancer in patients with PSC. This topic is discussed elsewhere. (See "Primary sclerosing cholangitis: Inflammatory bowel disease and colorectal cancer", section on 'Chemoprevention'.)

Complicating the issue is evidence that withdrawing UDCA may be associated with worsening biochemical test results and pruritus [20]. This was examined in a study with 26 patients with PSC who had been taking UDCA (10 to 15 mg/kg per day) and then had the medication stopped. Three months after stopping UDCA, there were increases in the patients' mean alkaline phosphatase (76 percent increase), gamma-glutamyl transpeptidase (118 percent increase), bilirubin (50 percent increase), alanine aminotransferase (64 percent increase), aspartate aminotransferase (45 percent increase), and Mayo Risk Score (0.5 point increase from baseline). In addition, there was a trend toward worsening pruritus compared with baseline. Limitations of the study included that most of the outcomes assessed were surrogate outcomes (eg, biochemical test results rather than clinically important outcomes, such as death or need for liver transplantation), it was unblinded (which could have influenced assessment of subjective outcomes, such as pruritus), it was of short duration (so a transient rebound effect could not be evaluated), and it was not known if the patients in the trial had initially responded to UDCA (introducing possible selection bias) [20,21].

A 2010 guideline issued by the American Association for the Study of Liver Diseases recommends **against** use of UDCA in the treatment of primary sclerosing cholangitis [6], whereas a 2015 guideline from the American College of Gastroenterology does not make a recommendation about using UDCA other than to note that it should not be used in doses >28 mg/kg/day [5]. The guidelines note the lack of proven efficacy on hard endpoints such as death or liver transplantation for low- or intermediate-dose UDCA and the worse outcomes described

in a randomized controlled trial of high-dose UDCA (see below). A guideline from the British Society of Gastroenterology and UK-PSC recommended against use of UDCA for newly diagnosed patients [4]. Although standard-dose UDCA has not been associated with adverse outcomes, UDCA cannot be recommended routinely until further data on efficacy and safety are available.

Our approach is to not start UDCA in patients with PSC. In addition, we suggest stopping it in patients who are already taking it and offering to restart the drug at standard doses (13 to 15 mg/kg per day in divided doses) if any of the following occur:

- The patient's bilirubin or alkaline phosphatase increases [8,20,22].
- The patient has worsening pruritus.
- The patient is concerned about his or her liver tests worsening and prefers to resume the drug.

However, given the uncertainty regarding its benefits, an alternative approach is to start (or continue) UDCA in patients who want to take it despite the uncertain benefits [21]. After six months, if the alkaline phosphatase normalizes or is decreased by at least 40 percent, or if the patient experiences symptomatic improvement, UDCA can be continued. Otherwise, it is stopped.

A derivative of UDCA (24-norursodeoxycholic acid) has shown promise in an animal model of PSC [23]. In a randomized trial in which 161 patients with PSC were assigned to norursodeoxycholic acid (500 mg, 1000 mg, or 1,500 mg daily) or placebo, norursodeoxycholic acid was associated with a dose-related reduction in alkaline phosphatase [24].

High-dose UDCA — Pilot studies suggested that UDCA given in higher-than-standard doses (20 to 30 rather than 13 to 15 mg/kg per day) may increase the benefit [25-28]. However, a placebo-controlled trial involving 150 patients was stopped early because patients randomly assigned to UDCA at doses of 28 to 30 mg/kg per day were significantly **more likely** to reach the primary endpoint of death, need for liver transplant, or development of varices [29]. A follow-up study found that the increased risk of adverse events with high-dose UDCA was limited to patients with early histologic stage disease or with normal total bilirubin levels [30]. The reasons for the unexpected outcome are unclear, but based upon these data, high-dose UDCA should be avoided in patients with PSC.

Glucocorticoids — No studies have demonstrated a long-term benefit from glucocorticoid therapy, either alone or in combination with other agents [31-33]. In addition to lack of efficacy, patients with PSC tend to have bone loss that can lead to osteoporosis, which may be made worse by glucocorticoid therapy [34]. As an example, a pilot study of 21 patients treated with

oral budesonide found marginal improvement in the serum alkaline phosphatase and AST levels, but the Mayo Clinic Risk Score did not change significantly and significant femoral neck bone loss was observed [31]. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Metabolic bone disease'.)

Cyclosporine and tacrolimus — A single controlled clinical trial has assessed the efficacy of cyclosporine in the treatment of PSC [35]. Aside from a decrease in serum alkaline phosphatase in treated patients, there was no effect on symptoms or disease progression. A case report noted radiologic and biochemical improvement after treatment with cyclosporine followed by prednisolone; however, the patient was also given UDCA concomitantly, and follow-up was unavailable after eight months [36].

Tacrolimus (FK506), a macrolide antibiotic with immunosuppressive activity that is now widely used to prevent rejection in transplant recipients, has been studied in an open-label trial in patients with PSC [37]. After one year of therapy, serum bilirubin and alkaline phosphatase declined by over 50 percent and pruritus was improved. However, there was no significant change in endoscopic retrograde cholangiopancreatography (ERCP) findings or histology.

Methotrexate — There was initial enthusiasm for methotrexate as a therapeutic modality for PSC after two small studies suggested that the drug improved liver function tests and resulted in histologic improvement when used for up to 12 months [38,39]. However, subsequent randomized trials have had variable results:

- A trial of oral pulse methotrexate versus placebo resulted only in reduction in serum alkaline phosphatase in the methotrexate-treated patients [40]. There was no change in histology, degree of stricturing as demonstrated by ERCP, other liver function tests, or outcomes between treated and nontreated patients.

- Another report found that methotrexate in combination with UDCA was of no benefit compared with treatment with UDCA alone, and it was associated with toxicity such as pulmonary fibrosis and hair loss [41].

Azathioprine and 6-mercaptopurine — There have been no controlled trials of azathioprine (or its analogue 6-mercaptopurine) for the treatment of PSC. Anecdotal reports of azathioprine have shown varying results [42,43]. However, many centers have used these agents for the treatment of concurrent inflammatory bowel disease and have noted no improvement in PSC [44]. A population-based study from Sweden of patients with PSC and IBD found that use of azathioprine was also associated with reduced mortality (HR 0.66; 95% CI 0.52-0.84) and risk of death or liver transplantation (HR 0.65; 95% CI 0.50-0.83). It is unclear whether this benefit may extend to patients without IBD [45].

Penicillamine — The discovery of increased serum, urinary, and hepatic copper concentrations in patients with PSC provided the rationale for the use of penicillamine in this disorder [46]. However, a randomized trial suggested no benefit on disease progression and more frequent side effects [47]. Subsequent studies have shown that the hepatic copper concentration is normal in early PSC and then increases with advancing stages of the disease, an effect that was positively correlated with the serum bilirubin [48]. These findings suggest that increased hepatic copper stores in PSC are secondary to cholestasis rather than a primary event, perhaps explaining the lack of efficacy of penicillamine.

Anti-TNF agents — Tumor necrosis factor (TNF), released by activated Kupffer cells in the liver, has been postulated to have a role in the hepatic injury seen in PSC. Among the anti-TNF drugs, etanercept was of no benefit in a pilot study of 10 patients [49], and infliximab was ineffective in a placebo-controlled, double-blind study in 24 patients [50].

Pentoxifylline blocks the production of TNF. Although pentoxifylline-inhibited hepatic fibrosis in an experimental model [51], it was not helpful in a pilot study in humans [52].

Combination therapy — The value of combining one or more of the drugs discussed above is uncertain. In a series of 15 patients, combined therapy with azathioprine, prednisolone, and UDCA was associated with improvement in liver biochemical tests and liver histology [53]. Significant radiographic deterioration was seen in only 1 of 10 patients who underwent cholangiography after a median follow-up of 41 months. Adverse drug reactions led to withdrawal of study medications in two patients.

Other pilot trials found no benefit from combining budesonide with UDCA and only a minor short-term effect from combining prednisone with UDCA [54]. Combination therapy with UDCA plus metronidazole has been associated with histologic improvement in the preliminary report of a small randomized controlled trial [55].

Antibiotics — The rationale for antibiotic therapy in PSC is based upon studies in rodents, which have shown that hepatobiliary disease resembling PSC can be seen in animals with intestinal overgrowth, perhaps due to an unspecified toxin released by enteric bacteria [56]. A controlled trial involving 80 patients found that the combination of metronidazole plus UDCA improved serum alkaline phosphatase levels and the Mayo Risk Score significantly more than UDCA plus placebo [57]. However, no significant effect on disease progression was observed on liver histology or ERCP. Our approach is to give long-term antibiotics for patients with recurrent cholangitis despite attempted treatment of dominant strictures.

- An observational study involving 14 children with PSC found that oral vancomycin improved liver biochemical tests and symptoms, particularly in those without cirrhosis

[58]. Improvement in liver histology was observed in one patient who had a repeat liver biopsy two months after beginning treatment. Improvement in serum alkaline phosphatase and the Mayo Risk Score was also observed with minocycline in a one-year pilot study involving 16 patients [59]. There was no effect on serum bilirubin or albumin, and liver histology was not assessed.

- A randomized trial with 35 patients with PSC assigned patients to receive vancomycin (125 or 250 mg four times daily) or metronidazole (250 or 500 mg three times daily) for 12 weeks [60]. A decrease in alkaline phosphatase at the end of treatment was seen in patients who received vancomycin, and the Mayo Risk Score decreased in those who received low-dose vancomycin or low-dose metronidazole.

- An open-label study of oral vancomycin therapy that enrolled both children and adults with PSC (n = 59) reported that 81 percent showed reduction in ALP and 22 percent normalized ALP after a median treatment duration of 2.7 years [61]. However, a retrospective review from the Pediatric PSC Consortium showed no evidence of clinical benefit in children with PSC [62].

Additional randomized, placebo-controlled studies with long-term follow-up are needed to understand the efficacy and safety of oral vancomycin therapy in adult and pediatric PSC.

Probiotics — Probiotics were studied in a randomized, placebo-controlled, crossover study of 14 patients with PSC [63]. There was no effect on symptoms (fatigue, pruritus, or stool frequency) or in laboratory parameters.

Antifibrotics — Simtuzumab, an antibody directed against lysyl oxidase like-2 (LOXL2), was studied as an antifibrotic therapy for PSC [64]. However, this therapy was ineffective in a Phase 2 study.

Other agents — Several other agents have been used to treat PSC, including colchicine, cholestyramine, mycophenolate mofetil, and docosahexaenoic acid [33,65-67]. None of these therapies has been shown to halt disease progression. Vedolizumab does not appear to have a role in the treatment of PSC [68,69]. In a retrospective study of 102 patients with PSC and IBD who had received at least three doses of vedolizumab, vedolizumab appeared to improve IBD disease activity but was not associated with a biochemical response [68]. Vedolizumab therapy for concomitant IBD did not improve liver biochemical tests in pediatric PSC-IBD [70]. A population-based study of PSC-IBD from Sweden found use of statins was associated with a reduced risk of all-cause mortality (hazard ratio [HR] 0.68; 95% CI 0.54-0.88) and death or liver transplantation (HR 0.50; 95% CI 0.28-0.66).

ENDOSCOPIC THERAPY

A subset of patients with primary sclerosing cholangitis (PSC) has a dominant extrahepatic biliary stricture that is potentially amenable to endoscopic therapy. The proportion of patients that fall into this category at diagnosis is not well defined [71-73]. One of the largest series included 125 patients and found a dominant stricture in the common bile duct and/or right or left hepatic duct in 56 patients (45 percent) [74]. Furthermore, patients who do not have a stricture at baseline may develop a stricture over time. In one report, for example, 43 of 106 patients (40 percent) without a stricture developed a dominant stricture during five years of follow-up [73]. Our approach to patients with a dominant stricture is to perform endoscopic therapy to dilate and/or stent the stricture if the patient has pruritus and/or cholangitis. Dominant strictures should also be evaluated for possible malignancy during endoscopic retrograde cholangiopancreatography (ERCP) with brushings for cytology, biopsies, and fluorescence in-situ hybridization. An international PSC study group consensus statement proposed criteria for definition of a dominant stricture in PSC requiring imaging findings along with symptoms and biochemical test abnormalities [75].

Whether treatment of a dominant stricture improves outcomes has not been evaluated in controlled trials. Casting doubt on the efficacy of such interventions was a report involving 125 patients, 56 of whom had a dominant stricture, none of which were treated [74]. All patients were followed for up to one year with serial evaluation of measures of cholestasis. Changes in serum alkaline phosphatase and bilirubin were not significantly different in patients with and without a dominant stricture, suggesting that the dominant strictures did not contribute significantly to cholestasis. The authors concluded that endoscopic therapy of dominant strictures should **not** be undertaken routinely until benefit is demonstrated in controlled trials.

Although this study did not determine whether patients with a dominant stricture improved biochemically or clinically following endoscopic measures aimed at relieving the obstruction, a number of other reports have documented clinical and radiographic improvement in such patients following endoscopic dilation with or without placement of a biliary stent [71,72,76-80]. An illustrative report included 32 patients, the majority of whom were treated with short-term placement of a 10 Fr polyethylene stent, which was removed after a mean of 11 days [80]. Cholestatic complaints improved in 83 percent of patients after a mean of two months, and the serum bilirubin concentration returned to normal in 12 of 14 patients who were initially jaundiced. Only 40 percent of patients required additional endoscopic intervention after three years of follow-up.

In a randomized controlled trial of short-term endoscopic stenting, short-term stents were not superior to balloon dilatation and were associated with a significantly higher occurrence of treatment-related complications [81].

- Therapeutic ERCP should only be performed at centers with highly experienced endoscopists.

- Efforts should be made to exclude cholangiocarcinoma, which may appear as a dominant stricture. Serum CA 19-9, brush cytology of the biliary tree, endobiliary biopsy and FISH as all used in the assessment of a dominant biliary stricture [82]. One review from 2008 reported that when the cutoff value is set at 20 U/ml, sensitivity and specificity are 78 and 67 percent, respectively. When combined with the use of abdominal sonography, the values are 91 and 62 percent, respectively; the addition of CT scan as the modality was associated with increased sensitivity but lower specificity (100 and 38 percent, respectively) [83]. A "cut-off" value of 100 has low sensitivity but high specificity [84]. Therefore, all modalities should be used in attempting to differentiate benign from malignant strictures in PSC, including ERCP with brush cytology, endobiliary biopsies, FISH and cross-sectional imaging. Single-operator cholangioscopy with targeted biopsies has been proposed as the most accurate and cost-effective modality for diagnosis of cholangiocarcinoma in PSC by one group [85].

  Percutaneous or EUS-guided needle biopsies should not be performed among potential liver transplant candidates; patients with hilar cholangiocarcinoma are excluded from consideration for liver transplantation because of concerns for tumor seeding if the peritoneum has been breached by a percutaneous or EUS-guided biopsy [86,87].

- Antibiotic prophylaxis should be given, since patients with PSC are at increased risk for the development of cholangitis following biliary tract manipulation. However, these patients remain at some risk of cholangitis even if prophylaxis is given. In a series of 168 patients with PSC and 981 who had at least one ERCP in the prior year, the incidence of cholangitis was significantly higher in the PSC group despite routine use of antibiotics before the procedure (4 versus 0.2 percent) [88].

SURGICAL THERAPY

Surgical options for primary sclerosing cholangitis (PSC) include biliary reconstructive procedures, proctocolectomy (in patients with ulcerative colitis), and liver transplantation [89].

Biliary reconstruction — Studies using various methods of biliary-enteric drainage, with or without intraoperative stent insertion, have reported excellent outcomes (free of jaundice and cholangitis) for several years after the procedure [90-92]. However, there may be significant morbidity and mortality, particularly in patients with cirrhosis. In addition, surgery carries a risk of postoperative infection and increases scarring in the porta hepatis, potentially complicating future liver transplantation [90].

The enthusiasm for biliary surgery declined further after a retrospective study found liver transplantation to be superior to biliary surgical procedures [93]. The actuarial symptom-free survival rate in 23 patients treated by nontransplantation biliary surgery was 35 percent at 10 years; the actuarial survival rate from the onset of PSC (56 percent at 10 years) was identical to that expected from the prognostic model. In comparison, the actuarial patient survival rate five years after transplantation in 28 patients was greater than that expected from prognostic models (89 versus 31 percent).

Thus, surgical therapies other than transplantation should generally be **avoided** in patients with PSC. The only exception may be in patients with isolated focal extrahepatic strictures and early histologic stage disease [94].

Proctocolectomy — A retrospective study found that, in patients with both PSC and chronic ulcerative colitis, proctocolectomy did not result in improvement of biochemical test results, cholangiography, hepatic histology, or survival [95]. Thus, this procedure should be performed only if it is indicated because of the colitis.

Liver transplantation — Liver transplantation is the treatment of choice for patients with advanced liver disease due to PSC, and patients should generally be referred for liver transplantation once their Model for End-stage Liver Disease (MELD) score is ≥15 [5]. Outcomes for liver transplantation in PSC compare favorably to transplants for other indications, with five-year survival rates as high as 85 percent [96-98]. As an example, in a series of 150 patients, the actuarial 1-, 2-, 5-, and 10-year survival was 94, 92, 86, and 70 percent, respectively [99].

The average life expectancy of PSC patients is estimated to be 15 to 20 years after diagnosis without liver transplantation [100]. It is difficult to estimate the proportion of patients who will ultimately need to liver transplantation due to variability in access to liver transplantation and regional differences in policies regarding transplant for cholangiocarcinoma. PSC has excellent outcomes after liver transplantation although recurrent disease may occur in up to one-third of patients; living-donor liver transplantation is associated with higher rates of recurrence than deceased-donor liver transplantation [100]. IBD with an intact colon, prolonged ischemic time, history of acute cellular rejection, cytomegalovirus infection, and lymphocytotoxic cross match

are risk factors for recurrent PSC. Risk factors for recurrent PSC include IBD with intact colon, prolonged ischemic time, acute cellular rejection, cytomegalovirus infection, and lymphocytotoxic cross match.

Evaluation of PSC patients for liver transplantation is inherently difficult due to the unpredictability of the disease course and the high risk of biliary tract malignancy. Several prognostic models have been developed to assist clinicians in predicting the natural history of PSC; one of the best known is the Mayo Risk Score (table 1). (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Prognosis'.) A calculator for the model is available online. A PSC Risk Estimate Tool (PREsTO) has been developed to assess risk in PSC using 9 variables: bilirubin, albumin, serum alkaline phosphatase (SAP) times the upper limit of normal (ULN), platelets, AST, hemoglobin, sodium, patient age and the number of years since PSC was diagnosed [101]. The PREsTO scoring system predicts liver decompensation in PSC. The enhanced liver fibrosis test (ELF) which utilizes a panel of circulating fibrosis markers is used in Europe and has been shown to predict transplant-free survival in PSC [102]. The Amsterdam-Oxford model has also been proposed as a validated model for risk prediction in PSC; this model incorporates PSC subtype, age at PSC diagnosis, AST, ALP, total bilirubin, albumin and platelet count [103]. Plasma bile acid profiles may predict future liver decompensation in patients with PSC [104].

However, the MELD score has become the primary tool for predicting prognosis in patients with PSC and other causes of end-stage liver disease. The United Network for Organ Sharing version of the MELD score is used to allocate prioritization for liver transplantation in the United States. A complete discussion of the MELD score and its use in liver transplantation is covered elsewhere. (See "Model for End-stage Liver Disease (MELD)".)

Most of the indications for liver transplant in PSC patients are similar to those in other forms of end-stage liver disease [105]. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation".)

Jaundice alone, in the absence of other signs of liver failure, is not an absolute indication for transplant. There are special circumstances in which liver transplantation may be indicated despite a low priority MELD score. These may include:

- Recurrent or refractory cholangitis
- Intractable pruritus
- Peripheral or hilar cholangiocarcinoma <3 cm in diameter (in the context of a clinical trial)

In these and other situations, individual transplant centers may submit a petition to a regional review board for additional MELD points to assign an appropriate level of prioritization. The

merits of these cases are decided on an individual basis.

Recurrent disease — Several reports have described recurrent PSC following liver transplantation in 14 to 20 percent of patients [98,106-116]. As an example, in one series with 130 patients, the cumulative incidence of recurrence at 1, 5, and 10 years post-transplantation was 2, 12, and 20 percent [112]. In a second study that included 565 patients who underwent successful liver transplantation for PSC, recurrence was seen in 14 percent of patients after a median follow-up of nine years [115]. The diagnosis of recurrence is based upon consistent findings of liver biopsy and cholangiography in the absence of other conditions that could account for the findings, such as an ABO blood group-incompatible liver allograft, dominant anastomotic stricture, or hepatic artery thrombosis [108].

The natural history of recurrent disease is variable, similar to the nontransplant setting. Only approximately one-third of patients with recurrence develop progressive disease leading to retransplantation or death. Risk factors for recurrence, particularly the influence of the immunosuppressive regimen, remain incompletely understood, although a variety of risk factors have been reported in various series including age, sex mismatch, male sex, coexistent IBD, presence of an intact colon after transplantation, cytomegalovirus (CMV) infection, recurrent acute cellular rejection, steroid-resistant cellular rejection, use of OKT3, presence of cholangiocarcinoma before transplantation, use of extended donor criteria, and prolonged use of glucocorticoids [113,115,117]. One report found that colectomy before and during initial liver transplantation for PSC was protective against recurrence [117].

Inflammatory bowel disease — The natural history of inflammatory bowel disease (most often ulcerative colitis) following liver transplantation is variable [118-124]. Although the disease may remain quiescent in some patients, it may become aggressive in others despite the immunosuppression used for the transplant.

One of the largest series to evaluate this issue included 303 patients with inflammatory bowel disease (IBD) who underwent liver transplantation between 1981 and 1997 at the University of Pittsburgh [121]. Progression of IBD was assessed based upon the need for colectomy and clinical features of disease activity. The influence of transplantation on the disease course was determined using multivariate statistical models that adjusted for the duration of follow-up and other covariates that might influence the course of IBD. The authors found that the only two independent risk factors for IBD progression were older age at the time of transplant (age >30 years, hazard ratio [HR] 1.5) and liver transplantation itself (HR 3.1). The incidence rates for colectomy rose from 0.007 per year before liver transplantation to 0.025 per year after transplantation.

A limitation of this analysis was that it did not include some potentially relevant covariates in the model, such as pretransplant IBD disease activity and the extent of the disease. Furthermore, IBD disease activity was assessed retrospectively, raising the potential for misclassification, since other causes of bowel disturbance may occur in the transplant setting (eg, CMV, lymphoma, post-transplant lymphoproliferative disorder). Thus, this study confirms that IBD activity may progress after transplantation in some patients, but it does not provide a profile of patient characteristics or immunosuppressive regimens associated with increased risk.

Some of these issues were addressed in a series that included 353 patients with IBD who underwent liver transplantation between 1984 and 2006 [125]. The patients were followed for a median of five years. Among the 218 patients with an intact colon and colonoscopies performed both before and after transplantation, 124 patients (57 percent) had macroscopic colonic inflammation prior to transplantation (75 percent mild, 22 percent moderate, and 3 percent severe). Following transplantation, 153 patients (70 percent) had macroscopic inflammation (60 percent mild, 23 percent moderate, and 17 percent severe; $p<0.001$). Overall, IBD activity decreased in 17 percent of patients, remained unchanged in 43 percent, and increased in 40 percent. Age less than 20 years at the time of IBD diagnosis and the use of tacrolimus plus mycophenolate mofetil were associated with an increased risk of worsening inflammation (HRs of 1.8 and 3.9, respectively), whereas the use of cyclosporin and azathioprine was associated with a decreased risk (HR 0.4).

Another retrospective study compared patients with PSC and IBD who underwent liver transplantation with those who did not undergo transplantation and found a decreased risk of colectomy among those who underwent liver transplantation [124]. The study included 167 patients with PSC and ulcerative colitis who were followed between 1985 and 2011 [124]. A liver transplantation was performed in 86 patients, whereas 81 patients were not listed for liver transplantation (patients who were listed for liver transplantation but did not receive a transplant were excluded). The median follow-up was 11 years among those who received a liver transplantation and 14 years for those who were not listed for transplantation. Patients who underwent liver transplantation had a significantly lower colectomy rate during follow-up than those who were not listed (27 versus 75 percent; adjusted HR 0.43; 95% CI 0.25-0.75). Other risk factors for undergoing colectomy included a high revised PSC Mayo risk score (table 1) at diagnosis (HR 0.52; 95% CI 0.37-0.72) and the development of colon cancer or dysplasia (HR 2.47; 95% CI 1.63-3.75).

CANCER SCREENING

In addition to age-appropriate cancer screening, patients with primary sclerosing cholangitis (PSC) typically undergo screening for gallbladder carcinoma, cholangiocarcinoma, colon cancer, and hepatocellular carcinoma [87].

Gallbladder carcinoma and cholangiocarcinoma — PSC is associated with an increased risk of cholangiocarcinoma and gallbladder carcinoma.

Surveillance for cholangiocarcinoma and gallbladder cancer should be performed in all adult patients ≥20 years with PSC regardless of disease stage [87]. Surveillance is particularly important in the first year after diagnosis, and in patients with ulcerative colitis, and those diagnosed at an older age.

Surveillance is not recommended in PSC patients with small-duct PSCs or those younger than age 20 years due to the low risk of hepatobiliary cancers [87]. Guidelines for cancer surveillance in patients with PSC are available from several groups, however, there is no consensus on the best approach, and institutional practice is variable [5,6,87,126,127]. Our approach is largely consistent with these guidelines and consists of the following:

- Ultrasound, abdominal computed tomography (CT) scan, or magnetic resonance imaging (MRI)/MRCP with or without serum levels of the tumor marker cancer antigen (CA) 19-9 every 6 to 12 months. MRI/MRCP is our imaging modality of choice because of the superior sensitivity of MRI compared with US for detection of cholangiocarcinoma.

- Cholecystectomy in patients found to have gallbladder mass lesions regardless of size based on the patient's surgical candidacy from a liver disease perspective (ie, presence and degree of portal hypertension) [4,6,128].

- Endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology should not be used routinely for surveillance of cholangiocarcinomas in PSC [87]. Brush cytology has limited sensitivity for diagnosing cholangiocarcinoma [129,130]. However, PSC patients with worsening clinical symptoms, worsening cholestasis, or a dominant stricture or increasing CA19-9 should be evaluated by ERCP with brush cytology with or without fluorescence in situ hybridization analysis and/or cholangioscopy.

The efficacy of tumor markers for early diagnosis of cholangiocarcinoma in patients with PSC has not been established. In a three-year prospective study of 75 patients with PSC without clinical signs of cholangiocarcinoma, elevated serum levels of CA 19-9 (>37 units/mL), carcinoembryonic antigen (CEA; >5 ng/mL), and two other markers (CA-50 and CA-242) were not useful in diagnosing cholangiocarcinoma because of limited specificity [131]. Specificity can be increased by using higher cutoff values but at the cost of lower levels of sensitivity.

In a study of 208 patients found a sensitivity, specificity, positive predictive value, and negative predictive value of 78, 98, 56 and 99 percent, respectively, using an absolute CA 19-9 level of 129 units/mL as a cutoff value [132]. An important caveat is that in another study, more than one-third of patients with this cutoff level of CA 19-9 did not have cholangiocarcinoma after an average of 30 months of follow-up [133]. Another issue is that CA 19-9 requires the presence of the Lewis blood group antigen (a glycosyl transferase) to be expressed. Individuals with a Lewis-negative phenotype (an estimated 5 to 10 percent of the population) do not make CA 19-9 and therefore will not benefit from CA 19-9 testing.

Colon cancer — The prevalence of ulcerative colitis in patients with PSC approaches 90 percent and is associated with a high risk of colonic dysplasia [134,135]. As a result, patients with PSC and inflammatory bowel disease (IBD) should undergo surveillance colonoscopy every one to two years from the time of diagnosis of PSC [5,6], and patients with PSC without IBD should undergo surveillance colonoscopy every three to five years, including biopsies to look for previously undiagnosed colitis [5,136]. (See "Primary sclerosing cholangitis: Inflammatory bowel disease and colorectal cancer", section on 'Management'.)

Several reports have suggested that the incidence of colon cancer is high in patients with ulcerative colitis and PSC who undergo liver transplantation [122,137-141]. The mechanism by which this might occur is unclear but may be related to the presence of longstanding ulcerative colitis or to the use of immunosuppressive drugs. An exception to these reports is a study with 303 patients in which the only identified risk factor for colon cancer following transplantation was the duration of IBD [121]. Considering the available data, we suggest that patients who have had a liver transplant for PSC who also have inflammatory bowel disease undergo routine yearly surveillance colonoscopy. Among those with worsening inflammation who are receiving tacrolimus and mycophenolate mofetil, it may be reasonable to consider switching their immunosuppression to cyclosporin and azathioprine, after first discussing the change with the transplantation center. (See "Primary sclerosing cholangitis: Inflammatory bowel disease and colorectal cancer" and "Liver transplantation in adults: Initial and maintenance immunosuppression".)

Hepatocellular carcinoma — Patients with cirrhosis require screening for hepatocellular carcinoma. Screening recommendations for patients at risk for hepatocellular carcinoma are discussed elsewhere. (See "Surveillance for hepatocellular carcinoma in adults".)

Health maintenance

- Patients with PSC have high rates of osteoporosis and non-vertebral fracture. Patients with PSC should be screened at the time of diagnosis and then at regular intervals (every one to

five years per the European Association for the Study of the Liver and every two to three years per the American Association for the Study of Liver Diseases [AASLD]) [6,126].

- Patients with advanced liver disease should also be screened for fat-soluble vitamin deficiency [5].

- Patients with advanced liver disease (evidence of cirrhosis, platelet count <150,000) should undergo screening for esophageal varices. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'Variceal hemorrhage'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Primary sclerosing cholangitis".)

SUMMARY AND RECOMMENDATIONS

- There are two major goals of treatment in primary sclerosing cholangitis (PSC):
  - Retardation and reversal of the disease process
  - Management of progressive disease and its complications

- A variety of immunosuppressive and anti-inflammatory agents have been studied in patients with PSC, but none has shown a consistent benefit on overall or transplant-free survival. Thus, a role for any medical therapy is unproven. (See 'Ursodeoxycholic acid' above.)

- In patients who are already taking UDCA, we suggest stopping UDCA but reinstituting it at standard doses (13 to 15 mg/kg per day in divided doses) if they develop worsening pruritus or jaundice (**Grade 2C**). However, given the uncertainty regarding its benefits, an alternative approach is to start (or continue) UDCA in patients who want to take it despite the uncertain benefits. After six months, if the alkaline phosphatase normalizes or is decreased by at least 40 percent, or if the patient experiences symptomatic improvement, UDCA can be continued. Otherwise, it is stopped. (See 'Ursodeoxycholic acid' above.)

- We suggest that patients with a dominant stricture and pruritus and/or cholangitis undergo endoscopic therapy to dilate and/or stent the stricture, provided that the patient has access to a center with considerable expertise in therapeutic biliary endoscopy (**Grade**

2C). An important potential clinical benefit is relief of jaundice and pruritus, although a benefit on disease progression has not been clearly established. (See 'Endoscopic therapy' above.)

- Balloon dilation is preferred to short-term stenting for management of symptomatic dominant strictures.

  Dominant strictures should be evaluated for possible malignancy during endoscopic retrograde cholangiopancreatography (ERCP) with brushings for cytology, biopsies, and fluorescence in-situ hybridization. Findings that should increase the clinical suspicion for cholangiocarcinoma include an elevated serum cancer antigen (CA) 19-9 or carcinoembryonic antigen measurement in conjunction with an imaging study (abdominal CT scan, ultrasonography, magnetic resonance imaging [MRI], or magnetic resonance cholangiopancreatography [MRCP]) showing a mass lesion, interval change in bile duct dilation, a new "dominant" stricture with upstream biliary dilation, or clinical features such as weight loss. (See "Clinical manifestations and diagnosis of cholangiocarcinoma".)

  Transperitoneal biopsies (percutaneous, EUS-guided) should be avoided in patients with hilar cholangiocarcinoma who are potential liver transplant candidates, as such interventions could be a contraindication for liver transplantation. Consultation with a liver transplant center is advisable in such patients prior to obtaining a transperitoneal biopsy and endobiliary methods should be attempted for tissue diagnosis of suspected cholangiocarcinoma.

- Long-term prophylactic antibiotics are indicated for patients with recurrent cholangitis despite efforts to treat a dominant stricture. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis".)

- Given the high incidence of cholangiocarcinoma and gall bladder cancer, we suggest screening adult patients (≥20 years) with large duct PSC for hepatobiliary cancers (**Grade 2C**). Screening consists of either ultrasound, abdominal CT or MRI with MRCP, with or without measurement of a serum CA 19-9 every 6 to 12 months. (See 'Gallbladder carcinoma and cholangiocarcinoma' above.)

  Other screening examinations include bone density examination at diagnosis and every two to three years thereafter. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Metabolic bone disease'.)

- In addition to screening for gallbladder carcinoma and cholangiocarcinoma, patients should also undergo screening for colorectal cancer and, if they have cirrhosis,

hepatocellular carcinoma. (See 'Cancer screening' above.)

- Treatment of pruritus is discussed separately. (See "Pruritus associated with cholestasis".)
- Liver transplantation is now the treatment of choice for patients with advanced liver disease secondary to PSC.

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GRAPHICS

Mayo model for predicted survival in primary sclerosing cholangitis

R = 0.03 (age [yrs]) + 0.54$_e$(bilirubin [mg/dL]) + 0.54 log$_e$(AST [IU/L]) + 1.24 (variceal bleeding [0=no/1=yes]) - 0.84 (albumin [g/dL]).]
Survival function coefficient [$S_0(t)$]
1 year = 0.963
2 years = 0.919
3 years = 0.873
4 years = 0.833
Calculated patient survival
Probability of survival at time t years is calculated as $S(t) = S_0(t)^{exp(R-1.00)}$

Adapted from: Kim WR, Therneau TM, Wiesner RH, et al. A revised natural history model for primary sclerosing cholangitis. Mayo Clin Proc 2000; 75:688. Calculator for this model available at: http://www.mayoclinic.org/gi-rst/mayomodel3.html (Accessed on September 11, 2007).

Graphic 54210 Version 2.0

Contributor Disclosures

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