Sclerosing cholangitis represents an array of chronic, cholestatic diseases of the intrahepatic and extrahepatic bile duct systems. Clinically, this syndrome is characterized by progressive fatigue, pruritus, and in later stages, by abdominal pain, recurrent fever, and jaundice. These symptoms are resultant from inflammatory and fibrosing obstruction of the biliary system. The progressive medical course of sclerosing cholangitis can lead to destruction of the bile ducts and advancement to biliary cirrhosis, portal hypertension, cholangiocarcinoma, and liver failure. Premature death is frequently inevitable for patients without liver transplantation.

Sclerosing cholangitis can be due to primary or secondary disorders of the biliary tree. Primary sclerosing cholangitis (PSC) is idiopathic. PSC is typically a chronic, progressive disorder which is often refractory to medical therapy. This condition frequently occurs in association with inflammatory bowel disease (IBD), with only about 20% of patients not having any evidence of IBD. The majority of patients with PSC are found to have a concomitant diagnosis of ulcerative colitis (UC). Conversely, it has been estimated that PSC occurs in approximately 5%-10% of patients with UC, whereas the prevalence is lower in patients with Crohn’s disease.

Secondary sclerosing cholangitis (SSC) is clinically comparable to PSC, yet is caused by known disorders that afflict insult to the biliary tree. Examples of these processes include choledocholithiasis, bile duct malignancy, congenital bile duct abnormalities such as Caroli’s disease, biliary ischemia from hepatic arterial occlusion, chemotherapeutic agents (i.e., 5-fluorouracil) and acquired immunodeficiency syndrome (AIDS)-related cholangiopathy (Table 1).

Epidemiology

PSC was once a rarely made medical diagnosis. It was first reported in the medical literature by Delbert in 1924. In the last decade, especially with the use of advanced magnetic resonance imaging (MRI) and endoscopic retrograde cholangiopancreatography (ERCP) techniques, the frequency of diagnosis of PSC has increased dramatically. Today, PSC represents a common cause of adult cholestatic liver disease, and is one of the most common indications for liver transplantation in adults.
There are only a limited number of population-based studies of PSC. One study, which collected data from 1976 to 2000 and age- and/or sex-adjusted the population distribution to US whites in the year 2000 (because their population was >95% white during the study period), found that the age-adjusted incidence of PSC was 1.25 per 100,000 person-years in men (95% CI, 0.70 to 2.06) and 0.54 per 100,000 person-years (95% confidence interval [CI], 0.22 to 1.12) in women.2 The prevalence was 20.9 per 100,000 men (95% CI, 9.5 to 32.4) and only 6.3 per 100,000 women (95% CI, 0.1 to 12.5).2 The majority of cases (73%) were associated with IBD, mainly UC.2 Also, overall survival was significantly lower compared with an age- and healthy, gender-matched population with a mean time from diagnosis to death or liver transplantation ranging from 9.6 to 12 years.2,4

Although the explanation for this sex and age distribution is unclear, there seem to be no significant differences between gender and the frequency of associated IBD.5

The epidemiology of SSC is relatively ill-defined, likely due to its diverse causes as well as the lack of clinical studies. In one retrospective 10-year review (1992–2002) from the Mayo Clinic, there were 31 cases of SSC identified, as compared to over 1,000 cases of PSC.5 Fifty-eight percent of these patients were males, and the mean age at diagnosis was 57 years. In this case series, the most common causes of SSC were surgical trauma during cholecystectomy (42%) and choledocholithiasis (39%). Additional documented etiologies of SSC were recurrent pancreatitis and abdominal injury. The investigators of this study also reported data that postulated the life expectancy of SSC patients is shortened compared to matched PSC controls. In their SSC patient group, the median survival time without transplant was 72 months (95% CI, 40 to 102) compared with 89 months (95% CI, 74 to 117) in the PSC group (P < 0.03).5 Although this study suggests that patients with SSC may have a poorer outcome than patients with PSC, further studies are needed to confirm these data.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

The majority of patients with sclerosing cholangitis are asymptomatic in the early stages of disease, though their disease may be advanced by the time a diagnosis is made. Two-thirds of patients have noted progressive fatigue, pruritus, or even jaundice at the time of diagnosis. As the disease progresses, patients may develop right upper quadrant pain, fever, weight loss, or cholangiocarcinoma. These features may lead to concern for bacterial cholangitis from biliary obstruction rather than advanced disease. Signs of advanced liver disease such as skin telangiectasias, peripheral edema, palmar erythema, muscle wasting, testicular atrophy, and asterixis may also be seen.

Specific selection and exclusion criteria form the basis for making the diagnosis, and these include results of clinical, biochemical, radiologic, and histologic data. Liver function tests show a cholestatic pattern with two-fold or greater alkaline phosphatase elevation. Additionally, aminotransferase elevation is usually present, though levels typically will be <300 IU/L. Large fluctuation in serum bilirubin levels can occur, potentially as a result of transient bile duct obstruction or concomitant bacterial cholangitis. Although there are no specific biochemical markers for PSC, approximately 80% of patients with PSC have serum antibodies against perinuclear antigen in neutrophil cytoplasm (p-ANCA).6 A positive p-ANCA is sensitive for this syndrome but is not specific, as p-ANCA positivity can also be found in other disorders, such as autoimmune hepatitis, primary biliary cirrhosis, or UC.4

ERCP and Magnetic Resonance cholangiopancreatography (MRCP) are commonly performed to visu-
alize the intra- and extrahepatic ductal systems. Diagnostic radiologic criteria include the presence of multifocal strictures and dilations of both the intrahepatic and extrahepatic biliary systems seen on cholangiography. These strictures and dilations usually create tortuosity and irregularity of the biliary ductal systems, which are typically characterized as having a “beaded” appearance.7

Liver biopsy is rarely diagnostic. It can be used primarily to exclude other co-existing diseases or to support the diagnosis in challenging cases. Also, liver biopsy can be useful in determining if the patient has disease progression to cirrhosis. Unfortunately, sclerosing cholangitis is a disease with a high degree of sampling variability on liver biopsy.7 For these reasons, histology is no longer included in current survival models for sclerosing cholangitis.7 The most characteristic finding in sclerosing cholangitis on liver biopsy is concentric layers of fibrous tissue causing obliteration of the small interlobular bile ducts. Concentric replacement by connective tissue is typically seen in an “onion skin” pattern, which is rarely seen due to a lack of uniform distribution. Granulomas may be seen, but are a rare finding. The liver histology staging system for PSC is similar to that used in primary biliary cirrhosis, where Stage 1 is mild chronic portal hepatitis or cholangitis confined to the portal tracts; Stage 2 is periportal hepatitis or fibrosis extending into surrounding parenchyma; Stage 3 is septal fibrosis, necrosis, or both extending beyond the limiting plate and bridging fibrosis is usual, as is loss of interlobular bile ducts and cholestasis; and Stage 4 is biliary cirrhosis.4

Sclerosing cholangitis should not be identified or evaluated as PSC if other causes can be identified, such as those listed in Table 1.

### COMPLICATIONS OF SCLEROSING CHOLANGITIS

Complications common to chronic cholestatic liver diseases such as sclerosing cholangitis include pruritus, fatigue, steatorrhea, fat soluble vitamin deficiencies (vitamins A, D, E, K), and hepatic osteodystrophy (Table 2).3

Metabolic bone disease, specifically osteoporosis, is quite common in sclerosing cholangitis.8 The mechanism and pathogenesis of this phenomenon is unknown, but vitamin and hormone levels as well as severity of sclerosing cholangitis do not seem to correlate with the severity of bone disease. Patients with PSC can also be prone to developing fractures after liver transplantation due to immobilization and dual therapy with corticosteroids. Although treatment of metabolic bone disease has not been studied at length in this setting, management and treatment principles are similar to current therapy for osteopenia and osteoporosis. Regular screening with radiologic techniques, such as dual photon absorptiometry, is recommended. Calcium supplementation with measurement of Vitamin D levels is also recommended, and institution of bisphosphonate therapy should be considered in the setting of osteoporosis.8

Pruritus is a frequently debilitating complication which can be treated with antihistamines, bile acid-binding resins such as cholestyramine, opioid antagonists, rifampin, phenobarbital, and activated charcoal. Deficiencies in fat-soluble vitamins are treated with supplementation of vitamins A, D, E, and K.3

Peculiar to sclerosing cholangitis are dominant biliary strictures (high-grade, local area of narrowing) and cholangiocarcinoma (CC). A dominant biliary stricture will be present in approximately 20% of patients with sclerosing cholangitis.9 Strictures can occur anywhere in the intrahepatic or extrahepatic biliary tree. These patients usually present with symptoms typical of mechanical biliary obstruction such as

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**Table 2. Complications of Sclerosing Cholangitis**

- Progression to cirrhosis with liver failure
- Portal hypertension
- Metabolic bone disease
- Steatorrhea
- Fat-soluble vitamin deficiency
- Dominant biliary strictures
- Cholelithiasis/cholangitis
- Cholangiocarcinoma
- Colon cancer
- Pruritus
- Chronic fatigue
- Recurrent bacteremia
pruritus, worsening jaundice, and/or cholangitis. Dominant strictures may be of benign or malignant origin, and this distinction may be difficult to make. This reinforces the need to perform cytologic brushings of the stricture during ERCP to exclude malignancy.

The most challenging and lethal complication of PSC is CC, a ductal carcinoma within the biliary tree. The presence of CC lends a poor prognosis in patients with PSC, and is currently the leading cause of death in this patient population. It has been estimated that the incidence of CC in PSC patients is approximately 1%-1.5% per year, resulting in a 20% lifetime risk. The development of CC is unpredictable on the basis of the duration, symptom complexity, or severity of PSC. In patients with sclerosing cholangitis, 15% of CC presents with an intrahepatic location, 20% in the distal common bile duct, and 65% in the hilar region. The risk factors for carcinogenesis in sclerosing cholangitis patients are not well defined. Alcohol consumption, diabetes, and smoking have been suggested to be risk factors, while duration of PSC or presence of IBD do not appear to have an association for CC in PSC patients.

The diagnosis and management of CC associated with PSC is complicated and challenging. Biliary brush cytology, endobiliary biopsy, and computed tomography (CT) or MRI scanning are all tests used to make the diagnosis of CC. The diagnostic use of the tumor marker CA 19-9 has been studied, and appears to be an additional useful strategy for screening/surveillance of CC in combination with cross-sectional liver imaging. Significant elevations in this tumor marker can occasionally be seen before the clinical or radiologic diagnosis of CC is made. In a study by Charatcharoenwitthaya et al., which compared operative performance of individual diagnostic tests for CC, serum CA 19-9 testing (optimal cutoff value was 20 U/mL) yielded a sensitivity of 78% and specificity of 67%. Cross-sectional liver imaging (ultrasound, CT, and MRI) for detecting CC in PSC had a low sensitivity (10%–32%) considering only a definite finding positive for malignancy. Among the three imaging methods studied, ultrasound examination had the best accuracy (90%) and positive predictive value for detecting CC in patients with sclerosing cholangitis.

Surgical resection and evaluation for liver transplantation are treatment options in patients with CC. Unfortunately, survival after liver transplantation is extremely poor. The estimated 3-year survival rates post-liver transplantation range from 0%-39%, due mostly to recurrent disease. For this reason, many transplant centers do not transplant these patients outside of specific experimental study protocols.

In addition to the nearly 160-fold increased risk for hepatobiliary cancer, sclerosing cholangitis patients also carry a 10-fold risk for colon and rectal cancer. Patients with the combination of both PSC and UC carry an additional risk of developing colon and rectal cancer. Some consider PSC to be a pre-malignant lesion, much the same as UC is considered to be a pre-malignant lesion of the colon. Broome et al. reported a 5-fold increase in the absolute cumulative risks of developing colonic dysplasia and/or colorectal cancer for UC patients with PSC after 20 years of active colitis. Based upon these data, it is important to place this patient population in detailed colonoscopic surveillance programs for adequate screening for dysplasia. Surveillance colonoscopy should begin once a diagnosis of UC is made in a patient with PSC.

**TREATMENT OF SCLEROSING CHOLANGITIS**

The major goals of treatment in sclerosing cholangitis are aimed at slowing and reversing the disease process as well as managing progressive disease and its complications. Current medical therapy does not have a significant impact on slowing the progression of sclerosing cholangitis, but has a greater role in the treatment of its complications.

**Medical Therapy**

Extensive interest has focused on the use of ursodeoxycholic acid (UDCA), a hydrophilic bile acid, for treating PSC. Standard dose UDCA, at a dose of 15 mg/kg/day, has been shown to provide symptomatic relief (fatigue, pruritus) and also suggested stabilization of hepatic inflammation. It has not resulted in slowing the course of illness or delaying liver transplantation. There have been some pilot studies using high-dose UDCA (20 to 30 mg/kg/day) in patients with PSC. However, a recent placebo-controlled trial of 150
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(continued from page 22)

Table 3.  
Previously Investigated Medical Therapies¹⁸

- Ursodeoxycholic acid
- Corticosteroids
- Cyclosporine
- Methotrexate
- Azathioprine and 6-mercaptopurine
- Tacrolimus (FK506)
- Penicillamine
- Colchicine
- Antibiotics

Options for surgical therapy for sclerosing cholangitis include biliary tract reconstructive procedures, proctocolectomy (in patients with concomitant UC), and liver transplantation. Biliary reconstruction carries a significant rate of morbidity and mortality, especially in patients with cirrhosis.¹ Also, post-operative infection and scarring may potentially complicate future liver transplantation for patients. Therefore, surgical biliary tree procedures other than liver transplantation should be avoided in patients with sclerosing cholangitis. Exceptions to this include patients with focal extrahepatic strictures or acute cholangitis not amenable to endoscopic treatment.¹

Proctocolectomy is only indicated for reasons dependent on the disease course of UC. In patients with both UC and sclerosing cholangitis, proctocolectomy has not been found to improve serum biochemical markers, hepatic histology, or mortality.²⁰

Orthotopic liver transplantation remains the treatment of choice for patients with advanced PSC. It has been demonstrated that liver transplantation prolongs survival in patients with end-stage PSC.³ Recent results reveal that outcomes for liver transplantation in PSC patients are no different than outcomes for patients with other forms of advanced liver disease.³ Five-year survival rates have been documented to be between 75% to 85%.²¹ The Model of End-stage Liver Disease (MELD) scoring system and Child-Pugh score have been recognized as valid tools for predicting prognosis of patients with consequences of end stage liver disease with sclerosing cholangitis.³ However, these prognostic scores for cirrhotic diseases do not estimate survival of PSC patients well. The well known Mayo survival model, which includes more reproducible variables (age, bilirubin, albumin, aspartate aminotransferase, and history of variceal bleeding) has an accuracy to comparable models and shows correlation between estimated and actual survival of patients undergoing liver transplantation.²²

Indications for transplant in PSC patients are similar to guidelines for other forms of chronic liver disease. Unfortunately, the presence of CC is currently seen as a contraindication to liver transplantation because of poor outcomes related to recurrent disease. At this time, liver transplantation is only recommended for PSC patients with CC within experimental protocols.²¹
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