Primary Sclerosing Cholangitis

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Sclerosing cholangitis is a clinical syndrome characterized by recurrent fever, pain, and jaundice resulting from fibrosing and inflammatory obstruction of the bile ducts caused by primary or secondary abnormalities of the biliary system.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic syndrome of unknown etiology characterized by diffuse fibrosing inflammation of the intra- and extrahepatic biliary ductal systems. The disease is usually progressive, albeit at an unpredictable rate, advancing to biliary cirrhosis, portal hypertension, and, unless intervention with liver transplantation is accomplished, premature death from liver failure. The diagnosis of PSC usually is based on a combination of clinical, biochemical, histologic and radiologic abnormalities. In the past, PSC often was diagnosed in its late stages after the patient became jaundiced and cachectic. More recently, increased physician awareness and accessibility of endoscopic retrograde cholangiography (ERCP) allow earlier recognition of the disease, in the asymptomatic stage. It often is seen in association with inflammatory bowel disease (IBD).

Primary sclerosing cholangitis must be distinguished from secondary sclerosing cholangitis, a syndrome with similar clinical characteristics but resulting from identifiable causes (Box 1). The term primary sclerosing cholangitis indicates that this form of sclerosing cholangitis is idiopathic but also associated with induration of the bile ducts that results from chronic inflammation and fibrous connective tissue as a result of inflammation of the bile ducts.
Epidemiology

PSC once was considered a medical curiosity; indeed fewer than 100 cases had been reported in the English-language literature between Delbert’s first description in 1924 and 1980. This situation has changed dramatically, and recent experience indicates that PSC and primary biliary cirrhosis (PBC) represent the two most common adult chronic cholestatic liver diseases. Moreover, PSC is now one of the most common indications for liver transplantation in adults [1]. Without question, the frequency of diagnosis of PSC has increased dramatically in the last 20 years. This increase likely reflects increased clinical awareness and use of ERCP rather than a true increase in the incidence of the disease.

There are no good data regarding the overall prevalence of PSC; thus, crude estimates are necessary. In the United States and Northern Europe, the estimated incidence of PSC is 0.9 to 1.3 cases per 100,000 population [2–5]. The prevalence in these areas ranges from 8 to 14 per 100,000 population but is far less in southern Europe and Asia. The frequency of PSC in United States minority populations is unknown. It appears to be rare among native Alaskans [6].

PSC is predominantly a disease of young and middle-aged men. Approximately 67% of patients are male, and the mean age at the time of diagnosis is 40 years. In Northern Europe and the United States, 70% to 80% of patients with PSC will have or develop IBD. Alternatively, in Western countries, 2.4% to 4% of patients with IBD will have primary sclerosing cholangitis [7–9].
Chronic ulcerative colitis (CUC) affects both sexes equally, and no major differences between male and female CUC patients with PSC have been identified.

**Diagnosis**

The diagnosis of PSC is based on selection and exclusion criteria. A persistent twofold or greater elevation of the serum alkaline phosphatase level is typical. Aminotransferase levels are often less than twice the upper limit of normal, and hyperbilirubinemia may be present. Although there are no unequivocally specific, biochemical markers for PSC, perinuclear antineutrophil cytoplasmic antibodies (pANCA) are present in the serum of 80% of patients who have PSC [10]. A positive pANCA is highly suggestive of the syndrome but not specific.

The radiologic inclusion criteria include the presence of multifocal, diffusely distributed strictures of the biliary system seen on cholangiography. Such strictures often are associated with tortuosity and irregularity of the extrahepatic or intrahepatic ductal systems (Fig. 1). Additionally, the cystic duct and pancreatic duct can be involved.

Hepatic histologic abnormalities seen in PSC can be categorized, as suggested by Ludwig [11], as follows: cholangitis or portal hepatitis (stage 1); periportal hepatitis or periportal fibrosis (stage 2); necrosis, septal fibrosis, or both extending beyond the limiting plate (stage 3); and biliary cirrhosis.

![Fig. 1. Cholangiogram with features typical of primary sclerosing cholangitis including intrahepatic stricturing with poststricture dilatation.](image)
(stage 4). Technically, a patient should not be considered as having PSC if he or she has had:

- Prior bile duct surgery other than simple cholecystectomy
- Documented choledocholithiasis before the development of symptoms
- The documentation of biochemical, radiologic, and histologic abnormalities

Additionally, sclerosing cholangitis should not be called primary if identifiable causes, such as those listed in Box 1, are apparent.

**Modes of presentation**

Until recently, the sine qua non for the diagnosis of PSC was an abnormal cholangiogram. Indeed, under most circumstances, this is still the case. Additionally, a small duct variety of PSC has been recognized in which cholangiographic abnormalities may not be present, but the liver histology most often shows the finding of pericholangitis with fibro-obliterative duct damage in a patient who has associated IBD or appropriate clinical symptoms (Table 1).

PSC usually begins insidiously, making it difficult to accurately determine the onset of the disease. Nevertheless, most patients with symptoms have had them for an average of 12 to 24 months before the diagnosis is made (Table 2). The gradual onset of progressive fatigue and pruritus followed by jaundice represents the most frequent symptom complex that leads to the diagnosis of PSC.

Patients who have PSC present clinically in a variety of ways:

- Asymptomatic, with abnormal liver tests;
- Pruritus, fatigue, jaundice;
- Recurrent cholangitis;
- Complications of chronic liver disease;
- Incidental discovery at laparotomy.

Most commonly, patients who have PSC will present without any symptoms or signs, but with a cholestatic biochemical profile identified during

<table>
<thead>
<tr>
<th>Diagnostic term</th>
<th>Cholangiopathy</th>
<th>Liver biopsy</th>
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<tbody>
<tr>
<td>Classic primary sclerosing cholangitis</td>
<td>Combined large and small duct</td>
<td>Typical</td>
</tr>
<tr>
<td>(PSC) Intrahepatic duct PSC</td>
<td>involvement</td>
<td></td>
</tr>
<tr>
<td>Intrahepatic duct PSC</td>
<td>Intrahepatic duct involvement only</td>
<td>Typical</td>
</tr>
<tr>
<td>Extrahepatic duct PSC</td>
<td>Large duct involvement only</td>
<td>Not diagnostic</td>
</tr>
<tr>
<td>Small duct PSC</td>
<td>Normal</td>
<td>Typical</td>
</tr>
</tbody>
</table>
routine examination. Often, these individuals have associated IBD for which they have been followed on a regular basis. A cholangiogram should be performed to confirm the suspected diagnosis. Alternatively, a patient may develop pruritus and fatigue, which may be associated with dark urine, light stools, and jaundice. This constellation of symptoms and signs, particularly in a young male who has IBD, often warrants cholangiography with or without liver biopsy.

Patients who have PSC also may present with episodes of fever and abdominal pain with or without associated jaundice. Such episodes of recurrent bacterial cholangitis occur more commonly in PSC patients who have had previous biliary tract surgical procedures, such as choledocho-enterostomy.

On occasion, the first symptoms of PSC may reflect complications of advanced liver disease, such as ascites or upper gastrointestinal bleeding from gastroesophageal varices.

Finally, a patient may undergo diagnostic laparotomy for other reasons such as exploration for malignancy or obesity surgery. The diagnosis of PSC may be suspected at laparotomy, because the common bile duct upon palpation is rope-like and hard. An operative cholangiogram then will show changes characteristic of PSC.

Several extremely uncommon modes of presentation of PSC deserve mention including:

A patient who has recurrent fever and septicemia of unknown etiology;
A patient who has a remote proctocolectomy and ileostomy and presents with peristomal variceal bleeding;
A patient who has steatorrhea and weight loss caused by either complicating pancreatic exocrine insufficiency or associated celiac sprue;
A patient who has IBD and a previous diagnosis of chronic idiopathic or autoimmune chronic active hepatitis that does not respond to standard immunosuppressive therapy.

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>75</td>
</tr>
<tr>
<td>Pruritus</td>
<td>70</td>
</tr>
<tr>
<td>Jaundice</td>
<td>65</td>
</tr>
<tr>
<td>Weight loss</td>
<td>40</td>
</tr>
<tr>
<td>Fever</td>
<td>35</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>55</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>30</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>25</td>
</tr>
<tr>
<td>Xanthomas</td>
<td>4</td>
</tr>
</tbody>
</table>
Associated diseases

Various diseases have been seen in association with PSC (Box 2). IBD is the most common and most important disease associated with PSC. The most common form of IBD associated with PSC is CUC; Crohn’s colitis or Crohn’s ileocolitis is associated much less often. Of interest are the observations that CUC associated with PSC most commonly involves a major portion of the colon, is frequently but associated with rectal sparing, and is more likely to be found in male than in female patients who have PSC. Additional features of this association include:

- No difference between patients who have PSC alone and PSC with associated IBD with respect to hepatobiliary symptoms and signs, standard biochemical tests, cholangiography, and hepatic histology;
- The diagnosis of IBD usually precedes the diagnosis of PSC, but diagnosis of PSC may precede that of IBD. PSC may develop after proctocolectomy for IBD, and PSC and IBD may be diagnosed simultaneously;
- The IBD associated with PSC is usually symptomatically quiescent or mild; however, some patients who have PSC and CUC require

<table>
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<tr>
<th>Box 2. Diseases associated with primary sclerosing cholangitis</th>
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<tr>
<td>IBD</td>
</tr>
<tr>
<td>Celiac sprue</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
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<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Retroperitoneal fibrosis</td>
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<tr>
<td>Thyroiditis</td>
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<tr>
<td>Sjogren’s syndrome</td>
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<tr>
<td>Autoimmune hepatitis</td>
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<tr>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
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<tr>
<td>Vasculitis</td>
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<tr>
<td>Peyronie’s disease</td>
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<tr>
<td>Membranous nephropathy</td>
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<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Histiocytosis X</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
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<tr>
<td>Eosinophilia</td>
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colectomy for colitic symptoms, premalignant changes, or malignant changes.

It should be mentioned that the association of celiac sprue with PSC is of importance, because it adds credence to the hypothesis of that, like IBD and celiac sprue, PSC is likely a disease of altered immunity. Other autoimmune diseases associated with PSC include rheumatoid arthritis, thyroiditis, Sjogren’s syndrome, autoimmune hepatitis, vasculitis, and eosinophilia.

Complications

As itemized in Box 3, the complications of PSC can be categorized under two major headings: general complications (ie, those that are common to other forms of chronic liver disease) and specific complications (ie, those that are to be more specific to PSC). Liver failure and portal hypertension occur in PSC as they do in other forms of chronic liver disease. Hepatic osteodystrophy, specifically osteoporosis, is common in PSC. Approximately 50% of patients with PSC have bone mineral density levels below the fracture threshold [12]. Vitamin levels, hormone levels, and severity of PSC and CUC do not correlate with the severity of bone disease. Despite active investigation, the pathogenesis remains unclear. Finally, malabsorption of fat and fat-soluble vitamins occurs in PSC usually on the basis of intraluminal bile acid deficiency caused by cholestasis, or less commonly caused by associated celiac sprue or chronic pancreatitis. The management of these complications is similar to their management in other forms of chronic liver disease.

In contrast, the complications that appear to be peculiar to PSC pose unique and challenging management problems. Although PSC most

<table>
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<tr>
<th>Box 3. Complications of primary sclerosing cholangitis</th>
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<tr>
<td><strong>General complications</strong></td>
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<tr>
<td>Liver failure</td>
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<tr>
<td>Portal hypertension</td>
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<tr>
<td>Hepatic osteodystrophy</td>
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<tr>
<td>Steatorrhea</td>
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<tr>
<td>Fat-soluble vitamin deficiency</td>
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</table>

| **Specific complications**                            |
| Dominant stricture                                    |
| Cholelithiasis/choledocholithiasis                     |
| Adenocarcinoma of the bile duct                       |
| Peristomal varices                                    |
commonly involves the entire biliary system, the presence of a dominant stricture (ie, a high-grade, localized area of narrowing) (Fig. 2) may result in the rapid worsening of jaundice and in recurrent clinical episodes of bacterial cholangitis. Moreover, benign dominant strictures may be difficult to distinguish from a high-grade stricture because of adenocarcinoma of the bile duct. Cholelithiasis appears to occur more commonly in patients who have PSC than in the general population; indeed, using ultrasound screening, approximately 25% of patients with PSC have gallstones [13]. Because most of these patients are young men, among whom gallstones are uncommon, this likely represents an increased frequency of cholelithiasis. Choledocholithiasis related to pigment stones also may complicate PSC.

Finally, patients with PSC who have undergone proctocolectomy for associated CUC with traditional or continent ileostomy frequently develop varices around the stoma as a manifestation of portal hypertension. These varices are painful, frequently bleed such that transfusions are necessary, and can be reversed only by alleviating the portal hypertension, ideally by orthotopic liver transplantation or transjugular intrahepatic portosystemic shunt [14].

Cholangiocarcinoma

Currently adenocarcinoma of the bile duct represents the most lethal and devastating complication of PSC. Clinical observations have established unequivocally that cholangiocarcinoma arises in the biliary system of patients who have pre-existing primary sclerosing cholangitis. In fact, most consider PSC to be a premalignant lesion much the same as CUC is considered to be a premalignant lesion of the colon. The frequency of cholangiocarcinoma is acknowledged to be increased relative to the general population; however, absolute numbers vary. Autopsy studies suggest a frequency of somewhere
between 20% and 43%, whereas clinical reviews, including experience with PSC patients undergoing orthotopic liver transplantation, suggesting a frequency closer to 10% [15]. The risk factors for the development of adenocarcinoma of the bile ducts in patients who have PSC include IBD, alcohol use, smoking, and diabetes [16,17]. Patients who have both PSC and adenocarcinoma of the bile ducts usually, but not always, have cirrhosis, portal hypertension, and long-standing CUC; they generally will be older at the time of diagnosis of PSC and may show progressive changes on cholangiography. Nevertheless, young patients with early PSC also have been identified with this devastating complication. Cholangiocarcinoma should be a primary consideration in any PSC patient who experiences a sudden, rapid decline in clinical or biochemical status. The diagnostic use of the tumor marker CA19-9 was evaluated in PSC patients. Using a lower cutoff value of 100 U/mL, the sensitivity and specificity of CA19-9 in detecting cholangiocarcinoma were 75% and 80%, respectively [18]. Significant elevations in CA19-9 can be seen in patients before the clinical diagnosis of cholangiocarcinoma. This observation implies that the tumor may be identified while it is at an occult and potentially treatable stage. A normal CA19-9 level in a patient who has PSC does not exclude the diagnosis of cholangiocarcinoma, however.

Patients with PSC have an increased risk of developing cholangiocarcinoma. Approximately 0.6% to 1.5% of patients per year will develop superimposed adenocarcinoma of the bile duct, resulting in a 20% lifetime risk [19,20]. The management of a suspected or established cholangiocarcinoma superimposed on PSC is complicated and largely ineffective. Diagnosis may be established by ERCP, although cytologic brushings are often inconclusive. If the lesion is surgically resectable, and the patient is not a candidate for transplantation, an attempt at surgical resection is warranted, although surgical margins are often positive, and cure is rare. Five-year survival rates range from 9% to 28% [21]. Survival after liver transplantation for cholangiocarcinoma is extremely poor, with 3-year survival rates ranging from 0% to 39% [22–24]. Recurrence of the malignancy is nearly universal. Even cholangiocarcinoma discovered incidentally on explanted liver from PSC patients receiving transplantation have shown a propensity to recur.

Diagnosis

Biochemical tests

Virtually all patients who have PSC will have an elevated serum alkaline phosphatase level, usually greater than three times the upper limit of normal (Table 3). Rarely, the serum alkaline phosphatase level may be normal. Similarly, most patients will have an increase in serum aspartate or alanine aminotransferase levels, usually only to a mild-to-moderate degree. At the time of diagnosis, one half to two thirds of patients who have PSC will have an
increase in their total serum bilirubin. Bilirubin levels may fluctuate considerably, with high levels suggesting disease progression or the development of complications such as a benign dominant stricture or superimposed adenocarcinoma of the bile duct. Abnormalities in serum albumin and prothrombin levels at the time of diagnosis are uncommon; however, with advanced disease, these values become abnormal in most patients. Serum copper and serum ceruloplasmin levels are increased commonly, and urine copper excretion is accelerated. Moreover, hepatic copper levels may be increased in most patients who have PSC, frequently in the range seen in Wilson’s disease. The abnormalities in copper metabolism reflect the cholestatic nature of the syndrome. Until recently, there were no serologic markers in the serum that strongly suggested the syndrome of PSC. For example, tests for antimitochondrial antibody usually are negative; if positive, the antibody is present in only low titer. Similarly, smooth muscle antibodies and antinuclear antibodies (50%) are occasionally positive [10]. Although the serum IgM levels may be increased in PSC, they rarely reach the levels seen in PBC. Recently, it has been demonstrated that perinuclear antineutrophil cytoplasmic antibodies (pANCA) occur in 80% of patients who have PSC [10]. Disease activity does not correlate with pANCA positivity or titer, although one study has reported a worse prognosis among pANCA-positive PSC patients as compared with pANCA-negative patients. Although the sensitivity of pANCA is high, the specificity is much lower, as it has been found in patients who have CUC, Crohn’s disease, autoimmune chronic active hepatitis, and several other hepatobiliary conditions. After liver transplantation, pANCA often persists. Other laboratory abnormalities occasionally are noted in PSC. For example, eosinophilia of a mild-to-moderate degree rarely may be observed.

Cholangiography

The increased frequency of diagnosis of PSC is because of the availability of endoscopic and transhepatic cholangiographic techniques. Indeed, in most cases, the diagnosis of PSC requires a characteristic

### Table 3
Biochemical tests in primary sclerosing cholangitis at diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Percent of patients with abnormal results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum alkaline phosphatase</td>
<td>99</td>
</tr>
<tr>
<td>Serum transaminases</td>
<td>95</td>
</tr>
<tr>
<td>Serum bilirubin</td>
<td>65</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>20</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>10</td>
</tr>
<tr>
<td>Serum copper</td>
<td>50</td>
</tr>
<tr>
<td>Serum ceruloplasmin</td>
<td>75</td>
</tr>
<tr>
<td>Urinary copper</td>
<td>65</td>
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</tbody>
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cholangiogram. The radiologic features most commonly seen in the syndrome include:

- Diffusely distributed, multifocal annular strictures with intervening segments of normal or slightly ectatic ducts (see Fig. 1);
- Short band-like strictures;
- Diverticulum-like outpouchings.

Cholangiographic abnormalities may be limited to the intrahepatic and proximal extrahepatic ducts. Other diffuse diseases—metastases, advanced cirrhosis, polycystic liver disease, and lymphoma—also may produce narrowing and deformity of bile duct cholangiographically. These abnormalities, however, rarely are difficult to distinguish from the characteristic constellation of radiographic abnormalities present in PSC. Additionally, the pancreatic main pancreatic duct and cystic duct may be involved.

In the past few years, magnetic resonance technology has improved significantly, and magnetic resonance cholangiopancreatography (MRCP) offers the potential for a noninvasive diagnostic test [25,26]. MRCP allows not only the visualization of the intra-and extrahepatic biliary tree, but also ducts proximal to tight strictures, which may not be visualized adequately during ERCP. Additional advantages of MRCP include the avoidance of radiation, the risk of pancreatitis, conscious sedation, and invasive diagnostic testing. MRCP, however, does not permit intervention such as bile duct brushing, balloon dilatation, or stenting. Therefore, it is reasonable to perform MRCP initially and then proceed to ERCP if necessary.

Liver biopsy

The main features on liver biopsy specimens include concentric periductal fibrosis (onion skinning) and inflammation, bile duct proliferation alternating with ductal obliteration, and ductopenia (Fig. 3). A staging system

![Liver biopsy](image)
developed by Ludwig is shown in Table 4. Most if not all patients with PSC have a fibrooliterative cholangitis (chronic nonsuppurative obliterative cholangitis) on biopsy. This near diagnostic lesion is, unfortunately, often not seen on liver biopsy specimens in patients who have PSC. Nevertheless, accumulating experience with liver biopsies in patients who have PSC suggests that the other histologic findings noted in Table 4 can be strongly suggestive of the syndrome.

From a histologic viewpoint, abnormalities seen in liver biopsy from patients who have PSC must be differentiated from those seen in specimens from patients who have PBC, prolonged extrahepatic obstruction, and autoimmune hepatitis. Indeed, PBC has many histologic features on biopsy specimens that overlap with those seen in PSC, including periportal cholestasis, copper deposition, and granulomas. Nevertheless, the classic florid duct lesion is not seen in PSC and is nearly pathognomonic of PBC. Conversely, fibrous obliterative cholangitis, the hallmark of PSC, is not observed in PBC.

Changes showing pleomorphic or fibrous cholangitis also may be present in biopsy specimens from patients who have idiopathic or autoimmune hepatitis, and cholangiography may be necessary to help with biopsy interpretation.

**Etiology**

The cause of PSC is unknown; genetic factors, acquired factors, or both may be involved. Factors include:

- Portal bacteremia;
- Absorbed colonic toxins;
- Toxic bile acids;
- Copper toxicity;
- Viral infection;
- Genetic predisposition;
- Immunologic mechanisms;
- Ischemic arteriolar injury.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Hepatic histology in primary sclerosing cholangitis Ludwig staging system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal stage (stage 1)</td>
<td>Portal hepatitis, bile duct abnormalities, or both; fibrosis or edema may be present; abnormalities do not exist beyond the limiting plate</td>
</tr>
<tr>
<td>Periportal stage (stage 2)</td>
<td>Periportal fibrosis with or without inflammation extending beyond the limiting plate; piecemeal macroabscesses may be present</td>
</tr>
<tr>
<td>Septal stage (stage 3)</td>
<td>Septal fibrosis, bridging necrosis, or both</td>
</tr>
<tr>
<td>Cirrhotic stage (stage 4)</td>
<td>Biliary cirrhosis</td>
</tr>
</tbody>
</table>
Currently, the pathogenesis of PSC is linked most closely with alterations in immune mechanisms. For example, PSC is associated with CUC and, to a lesser extent, with celiac sprue, two diseases thought to result from alterations in the immune system. Moreover, HLA B8 frequently is noted to be present in autoimmune diseases, occur with greater frequency in PSC than in the general population. Other more direct lines of evidence supporting immunologic basis for the disease include the inhibition of leukocyte migration by biliary antigens, elevated IgM levels, the presence of circulating immune complexes, decreased clearance of immune complexes, and increased complement catabolism. Additionally, cells involved in the destruction of bile ducts in PSC have been shown recently to be T lymphocytes. Enhanced autoreactivity of suppressor/cytotoxic T lymphocytes from the peripheral blood of patients who have PSC also has been reported [27].

The most likely scenario for the etiopathogenesis of PSC involves the exposure of a genetically predisposed individual to an acute insult to the biliary system, perhaps a transient viral infection. It is proposed that an alteration in the bile ducts that marks them as foreign then results and leads to their destruction by autoimmune mechanisms.

The diagnosis of PSC is usually not difficult, assuming the clinician is aware of the syndrome. PSC should be the major working diagnosis in a male with chronic cholestatic liver test abnormalities and IBD. In such a patient, the first major diagnostic study should be a cholangiogram (either MRCP or ERCP). Generally, a suitable cholangiogram in the appropriate clinical setting is all that is required for diagnosis. A liver biopsy also may be useful to provide diagnostic confirmation; however, its primary value is for accurate histologic staging and prognosis.

Natural history

Information regarding the natural history of PSC is currently in evolution. Given the lack of knowledge of the pathogenesis of PSC and the sometimes variable and often unpredictable nature of the syndrome, defining the natural history and prognosis of PSC is difficult. Nevertheless, based on various recent studies, most would agree that PSC is usually a progressive syndrome leading to significant complications related to chronic cholestasis. The largest of several studies addressing this issue analyzed data on 174 patients who had PSC. During the study, 34% died as a result of underlying liver disease or the development of cholangiocarcinoma; an additional 10% were referred for liver transplantation. Median survival from the time of diagnosis was 12 years [28]. A subgroup of 45 patients with asymptomatic PSC has been followed for over 6 years. During this period, 66% had histologic progression of disease; 29% developed portal hypertension, and 31% had liver failure resulting in death or need for liver transplantation. Both symptomatic and asymptomatic patients had reduced survival when compared with age-, sex-, and race-matched
United States population [29]. Another report on over 100 patients who had PSC and followed retrospectively for a mean of 6 years indicated that 16% of patients died secondary to liver failure, and an additional 21% underwent transplantation for advanced liver disease. The estimated median survival in the group was 12 years [30]. These and other studies strongly suggest that PSC is a progressive disease that frequently leads to death from liver failure.

Other studies have suggested that PSC may follow a more benign course. In one retrospective study based on historical data from 42 patients who had PSC and followed for a mean of 56 months, the investigators estimated 75% 9-year survival [31]. In several studies from Scandinavia, authors estimated a mean survival time of 17 years for patients who had PSC [32]. Thus, a body of data suggests that PSC has a relatively good prognosis.

Recently, a group of 83 patients who had well-characterized small duct PSC were compared with a game-matched cohort of patients who had large duct PSC. Twenty-three percent of the patients who had small duct PSC progressed to large duct PSC in a median of 7.4 years. One (1.2%) small duct PSC patient who progressed to large duct PSC developed cholangiocarcinoma. This compares favorably with 12% of large duct PSC patients who developed cholangiocarcinoma. In addition, patients with small duct PSC had a significantly longer transplant-free survival period compared with their large duct PSC counterparts (13 years versus 10 years) [33].

Several possibilities for these differences regarding the natural history of PSC are apparent, including inherent disease variability, small patient numbers, clinically silent progression, short follow-up, incomplete data, retrospective analysis, and design deficiencies (eg, lead time bias, backdating of diagnosis, variable referral patterns, and length bias). Nevertheless, even if these differences are taken into account, the weight of current evidence indicates that PSC is a progressive disease. Assuming that PSC evolves into a ductopenic syndrome affecting large and small bile ducts, the overall result is that interlobular and septal bile ducts become obliterated and nonfunctional. When a critical number of ducts is lost, cholestasis and ultimately portal fibrosis and biliary cirrhosis occur.

One of the main purposes of analyzing the natural history of PSC is to more accurately determine its rate of progression and to be able to estimate survival for the individual patient at any particular point in the course of the patient’s disease. Predicting survival based on clinical, biochemical, and histologic features of PSC is also very important for the timing of liver transplantation. Five major worldwide centers interested in PSC combined data to develop a prognosis model based on four independent variables from which risk scores could be calculated and translated into a survival curve for the individual patient at any time during the course of his or her disease. The variables identified include age, serum bilirubin, hepatic histologic stage, and the presence or absence of splenomegaly [34]. This and other models (Table 5) provide some objective evidence with regard to disease
progression and estimation of survival, but require cross-validation and application assessment before their true utility can be ascertained.

Management

The management of PSC provides a challenge to the clinician given the array of symptoms and complications that can develop in the absence of effective, specific therapy for the underlying hepatobiliary disease. The first decision for the physician regarding management is whether any therapeutic intervention is needed in a patient who has newly diagnosed PSC. In the asymptomatic patient who has minimal liver test abnormalities and an early histologic lesion by liver biopsy, observation is a reasonable approach. Alternatively, experimental therapy might be considered in the context of a randomized, controlled trial. Such an approach may be modified in the future with additional progress in the understanding of the natural history of the syndrome. If a decision is made to intervene therapeutically, one needs to clearly identify the goals of treatment. Specifically, therapy can be directed toward relief of symptoms, the correction of complications, or the underlying hepatobiliary disease. For example, pruritus and fat-soluble vitamin deficiencies are common problems in patients who have PSC, and conventional approaches to their management are reasonable. Similarly, when complications such as variceal bleeding develop, appropriate interventions (eg, use of beta blockers, endoscopic variceal obliteration, or transjugular intrahepatic portosystemic shunt) should be considered.

Assuming intervention is contemplated; three categories of therapeutic options are available to the clinician for treating patients who have PSC, including medical treatment, mechanical manipulation, and surgical intervention. As mentioned earlier, complications of PSC include those that are relatively specific for this chronic cholestatic syndrome. Therapeutic approaches for the major specific complications are available, although their effectiveness is quite variable.

<table>
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<th>Multicenter</th>
<th>Kings College</th>
<th>Mayo model</th>
<th>Swedish</th>
<th>Revised Mayo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<tr>
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<td>Hepatomegaly</td>
<td>Bilirubin</td>
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<tr>
<td>Histologic stage</td>
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<td>Histologic stage</td>
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<td>Albumin</td>
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<tr>
<td>Hemoglobin</td>
<td>Splenomegaly</td>
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<td>—</td>
<td>AST</td>
</tr>
<tr>
<td>IBD</td>
<td>Alkaline phosphatase</td>
<td>—</td>
<td>—</td>
<td>Variceal bleed</td>
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</tbody>
</table>

Abbreviations: AST, Aspartate aminotransferase; IBD, inflammatory bowel disease.
Medical

Medical approaches for treating the underlying hepatobiliary disease in PSC have focused principally on the use of choleretic, immunosuppressive, and antifibrogenic agents (Box 4).

Considerable recent interest has focused on the use of ursodeoxycholic acid (UDCA), the 7β epimer of chenodeoxycholic acid, for treating PSC. Although this agent is known to be choleretic and to dissolve cholesterol gallstones, its mechanism of action in PSC is unknown. Three potential mechanisms of action have been suggested:

- Direct protection against hepatotoxicity endogenous bile salts;
- Competitive inhibition of the absorption of hepatotoxic endogenous bile salts at the terminal ileum;
- Suppression of the expression of abnormal HLA class I antigens on hepatocyte membranes.

UDCA has been shown to improve several biochemical parameters, including the serum bilirubin, alkaline phosphatase, and ALT, but not slow the course of illness or prolong survival [37]. A large, prospective, randomized–controlled trial from the United States demonstrated that UDCA at doses of 12 to 15 mg/kg/d had no effect on liver histology or transplant free survival [38]. A Scandinavian randomized–controlled trial using 17 to

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**Box 4. Therapeutic options in primary sclerosing cholangitis**

**Medical**
- Supportive
- Possible definitive treatment
  - Choleretic
    - Ursodeoxycholic acid
  - Immunosuppressive
    - Prednisone
    - Azathioprine
    - Cyclosporine
    - Methotrexate
  - Antifibrogenic
    - Colchicine
- Mechanical
  - Cholangioplasty
- Surgical
  - Reconstructive biliary tract procedures
  - Proctocolectomy
  - Liver transplantation
22 mg/kg/d of UDCA similarly showed no effect on quality of life or transplant-free survival, although this study may have been underpowered [39]. Small pilot studies have suggested that higher doses of UDCA (25 to 30 mg/kg/d) may be more effective than previously applied doses [40,41]. A large National Institutes of Health (NIH)-sponsored trial of high-dose UDCA therapy in PSC is underway [42]. At this time, UDCA cannot be recommended for treating primary sclerosing cholangitis outside of a controlled trial.

Various agents that may affect the immune system have been evaluated in uncontrolled trials. Corticosteroids have been used, both topically and systemically, in several small studies. A small controlled trial of biliary lavage with corticosteroids versus placebo showed no difference between drug and placebo [43]. Uncontrolled observations in a small number of patients who had a marked inflammatory component to their PSC showed impressive responses to orally administered corticosteroids; other uncontrolled trials have shown no beneficial effect. The risks of systemic corticosteroids in patients who have PSC are significant and include osteoporosis and an increased risk of infection. Other in-human modulating agents such as methotrexate, azathioprine, cyclosporine, tacrolimus, and pentoxifylline have failed to show efficacy in controlled trials [37,44]. A small double-blind, placebo-controlled, randomized study of 24 patients who had PSC and were treated with infliximab also showed no benefit [45].

The antifibrogenic agent, colchicine, has been evaluated for treating PSC. A randomized study of 84 patients treated with either colchicine or placebo showed no improvement in biochemical, clinical, or histologic parameters after 35 months of follow-up [46]. It is, therefore, unlikely that colchicine, alone or in combination with prednisone, will be an effective option for treating PSC.

Patients who have recurrent episodes of cholangitis without dominant stricture formation should be treated with broad-spectrum antibiotics [37]. Prophylactic antibiotics are favored by some in patients who have frequent episodes of cholangitis; this approach is reasonable, but its efficacy has not been established by randomized trials and carries the risk of the development of resistant organisms. In the 10% to 15% [9] of patients who develop dominant strictures in the biliary tract that lead to cholestatic symptoms, antibiotics are ineffective and can lead to a delay in diagnosis. Dilatation of critical biliary strictures (cholangioplasty) in an asymptomatic patient presents a dilemma; early intervention may prevent future episodes of cholangitis. Manipulation of the biliary tree, however, also can cause cholangitis. Indeed, a growing experience with stricture dilation in symptomatic patients who have PSC strongly suggests that balloon dilatation is effective in alleviating pruritus and in diminishing the frequency of cholangitis episodes caused by dominant strictures. Retrospective model analysis has shown that cholangioplasty improves survival [47]. The most prudent approach may be to perform cholangioplasty when jaundice or bacterial cholangitis develop or there is significant concern for cholangiocarcinoma.
Complications caused by cholestasis associated with PSC include pruritus, steatorrhea, fat-soluble vitamin deficiency, and osteoporosis. Pruritus can be particularly debilitating and does not correlate with disease progression. In fact, pruritus tends to diminish in later stages of disease. Various options for treating cholestatic pruritus are available, including cholestyramine, activated charcoal, phenobarbital, rifampin, plasmapheresis, opiate antagonists, and ondansetron. Controlled trials have demonstrated that UDCA is not effective for treating pruritus associated with PSC [38,39]. Steatorrhea and fat-soluble vitamin deficiency often coexist. Causes other than PSC, including pancreatitis and celiac sprue, should be considered. Supplementation of vitamins A, D, E, and K may be required. Finally, osteoporosis and subsequent compression fracture are common in PSC. Unfortunately, effect of therapy, apart from liver transplantation, has not been found.

Surgical

There are three surgical procedures considered of potential benefit for treating PSC: (1) biliary tract reconstructive procedures, (2) proctocolectomy in a patient who has PSC and CUC, and (3) orthotopic liver transplantation. The author considers biliary tract reconstructive procedures in the same category as balloon dilatation of a dominant structure; that is, it represents a palliative procedure whose objective is to alleviate symptoms rather than to affect the natural history of the underlying hepatobiliary disease. It must be mentioned, however, that some surgeons have encouraged an aggressive surgical approach to treating PSC itself, using various imaginative procedures for internal or external biliary drainage; to the author’s knowledge, however, no controlled trials have been performed. Although such procedures might provide transient symptomatic benefit in the occasional patient who has jaundice and pruritus caused by a dominant structure, the same result almost always can be accomplished via a nonsurgical mechanical approach as described earlier. Thus, the author reserves hepatobiliary surgical drainage procedures for the very rare PSC patient who has severe pruritus and jaundice or recurrent bacterial cholangitis with a dominant extrahepatic narrowing and in whom balloon dilatation by means of percutaneous or endoscopic route is not feasible or has been tried unsuccessfully. In such cases, a choledochoduodenostomy may be appropriate.

Until the mid-1990s, the role of proctocolectomy for treating patients who had PSC with associated CUC was uncertain. The rationale for this procedure was that, by removing the colon, one may affect the progress of the underlying hepatobiliary disease beneficially in a patient with both PSC and CUC. This issue is an important one, not only because beneficial treatment for PSC is needed, but also because proctocolectomy in patients who have PSC and CUC may be associated with considerable morbidity. Proctocolectomy with a continent or conventional ileostomy results in development of varices around the ostomy stoma in at least 25% to 50% of
patients who have PSC. In many of these patients, serious and often life-threatening bleeding can occur from these abdominal wall varices. This complication can be avoided by performing an ileal pouch–anal anastomosis rather than a conventional Brooke ileostomy. The Mayo Clinic group prospectively studied the effects of proctocolectomy on the progression of clinical, biochemical, cholangiographic, and hepatic histologic features in 53 patients who had PSC and CUC. Patients with both diseases who had undergone proctocolectomy (n = 23) were compared with those who had not (n = 30) over 4 years. New onset of complications, serial changes in biochemical tests, histologic progression of liver biopsy, and survival were not different in the two groups [48]. Based on these data, it appears that proctocolectomy for CUC is not beneficial for PSC in patients who have both diseases. Proctocolectomy is appropriate in a patient who has PSC and CUC for traditional colitis indications (eg, medical intractability, development of persistent high-grade dysplasia).

Liver transplantation

Orthotopic liver transplantation is a realistic consideration for patients who have any form of advanced liver disease, including PSC. Indeed, it remains the only life-saving therapeutic alternative and, in the judgment of most, the treatment of choice for patients who have advanced disease. Recent results suggest that the outcome of liver transplantation in patients who have PSC is no different and perhaps better than the outcome in patients who have other forms of noninfectious, nonmalignant chronic liver disease, with 5-year survival rates of 75% to 85% [49]. Using the PSC survival models in Table 5, it has been demonstrated that liver transplantation significantly prolongs survival in patients who have end-stage PSC. The Model of End-stage Liver Disease (MELD) scoring system has been validated in patients who have PSC [50].

Cholangiocarcinoma generally has been considered a contraindication to liver transplantation because of poor outcomes caused by recurrent disease. Recently, the Mayo Clinic group reported its experience in a highly selected population of patients who had cholangiocarcinoma measuring less than 3 cm in maximal diameter without evidence of extra hepatic spread. These patients received external beam radiation plus 5-fluorouracil intravenously followed by endoscopic brachytherapy and exploratory laparotomy. Patients who remain eligible for continuation within the protocol then received further chemotherapy and rapid liver transplantation. Five-year survival rates have been approximately 70%. These results have not been duplicated [51]. At this time, liver transplantation for cholangiocarcinoma can be recommended only within experimental protocols.

Despite excellent survival, special problems may occur after liver transplantation for patients who have PSC. For example, early postliver transplant surgical complications may be increased in patients who have PSC.
Moreover, diffuse biliary stricture occurs more frequently in PSC patients who undergo liver transplantation than it does in other liver diseases. Although biliary stricture after liver transplantation for PSC raises the question of recurrence of disease, other factors (eg, reflux of intestinal contents with associated chemical or bacterial cholangitis related to the Roux-en-Y biliary anastomosis; ductopenic rejection, which occurs more frequently in PSC patients) represent alternative etiologies for biliary stricture in PSC after transplantation. Finally, symptoms related to IBD usually improve or remain quiescent after liver transplantation in the patients who have PSC and IBD possibly because of the immunomodulatory and anti-inflammatory effects of the immunosuppressive agents. This effect is not universal, however. The incidence of colon cancer may be increased following liver transplantation in patients who have PSC and associated CUC, emphasizing the importance of continued annual colon cancer surveillance in these patients.

Summary

PSC is a generally progressive, sometimes fatal chronic hepatobiliary disorder for which no effective medical therapy now exists. The syndrome, which occurs mostly in young men, is characterized by frequent association with IBD, usually CUC, chronic cholestasis, a relative paucity of serologic markers, and characteristic abnormalities in some liver biopsy specimens and in virtually all cholangiograms. Although a definitive conclusion regarding natural history of the syndrome requires additional studies, the weight of evidence suggests that the disease progresses slowly and relentlessly over 5 to 15 years from an asymptomatic stage to a condition characterized by cholestasis and complicated by cirrhosis, portal hypertension, and, in perhaps 10% to 15% of patients, carcinoma of the bile ducts. Management first should involve a thoughtful decision to observe (which may be reasonable in some asymptomatic patients with early disease) or to intervene, particularly in patients who have symptoms, in the context of a randomized, controlled clinical trial. Before intervention is undertaken, however, therapeutic goals need to be defined and should focus on either alleviating symptoms dealing effectively with complications, or attempting to affect the underlying hepatobiliary disease. Symptomatic treatment and therapy for complications are similar to those employed in other chronic liver diseases. Additionally, balloon dilatation of dominant strictures is appropriate in selected, symptomatic patients. Current medical therapy directed at arresting the progression of the underlying hepatobiliary disease remains experimental and includes choleretic, antifibrogenic, and immunosuppressive agents. Although biliary tract reconstructive surgery may alleviate symptoms in a small number of selected patients who have PSC, its effect on the natural history of the syndrome has not yet been determined and may
be deleterious. In contrast, orthotopic liver transplantation may prolong life for patients who have advanced disease and should be considered before potentially life-threatening complications occur.

References


