

PRIMARY SCLEROSING CHOLANGITIS AND PRIMARY BILIARY CIRRHOSIS

By Marvin Jose Lopez, M.D. and Young-Mee Lee, M.D.
Division of Gastroenterology,
New England Medical Center, Boston, MA

PRIMARY SCLEROSING CHOLANGITIS (PSC)

What is PSC?

Primary sclerosing cholangitis (PSC) is an uncommon, chronic disorder that involves scarring and inflammation of the large bile ducts of the liver. The disease leads to progressive destruction and blockage of the bile ducts and inability of the liver to secrete bile into the intestines. Bile is a substance that is produced by the liver and helps with digestion of dietary fat. Bile ducts function as the liver's plumbing system and allow bile to flow out of the liver. When bile backs up in the liver, a progressive scarring of the liver occurs which leads to cirrhosis.

What causes PSC?

The cause of PSC is unknown. Studies suggest impairment of the immune system or chronic infections as likely causes. It is not known if heredity plays a role, that is, if a person can inherit PSC if other members in the family are affected.

How common is PSC?

PSC is rare. Seventy percent of patients with PSC are men. The average age at diagnosis is forty years. Up to ninety percent of patients with PSC have some form of inflammatory bowel disease. Ulcerative colitis is the more common of the two forms of inflammatory bowel disease and occurs in approximately eighty-seven percent of PSC patients. Crohn's disease is seen in the remaining thirteen percent. Alternatively, only four percent of all patients with inflammatory bowel disease have PSC.

What are the symptoms of PSC?

The majority of patients with PSC have no symptoms. However, some patients complain of tiredness, itching or diarrhea. Fevers, chills, jaundice (yellow discoloration of the eyes and skin) and abdominal pain may occur in some patients. Some patients have a slow progressive course where the disease does not cause symptoms or complications for many years. Other patients may have a rapidly progressive course with the early development of bile duct obstruction, cirrhosis and liver failure.



What tests are needed to evaluate PSC?

Blood tests

The first step to screen patients for PSC is to do blood tests. In PSC, the blood test called alkaline phosphatase is often abnormal, though a small percent of patients with PSC may have normal levels. Other liver enzymes including the aminotransferases (ALT and AST) may also be abnormal. Bilirubin levels are normal early in the disease, then begin to increase in a fluctuating manner depending on the degree of blockage or stricturing of the bile ducts. A significant rise in the alkaline phosphatase and bilirubin can indicate a stricture in the main bile duct. The albumin and prothrombin time are proteins made only in the liver and are secreted into blood. When these blood tests are abnormal, they signify worsening liver function.

Cholangiogram

A cholangiogram is a useful test for diagnosing PSC. Cholangiography can be performed several ways. Cholangiography is an X-ray test that involves injection of dye into the bile ducts. A cholangiogram is usually performed using an endoscopic retrograde cholangiopancreatographic (ERCP) scope, which is a special upper endoscopy instrument useful for examining the bile, liver and pancreatic ducts. ERCP is a test that involves the insertion of a small flexible tube through the mouth into the esophagus, stomach then into the first part of the small intestine called the duodenum. In the duodenum there is a tiny opening called the ampulla, which is connected to the main bile duct. Bile flows from the liver through this opening into the small intestine. A small plastic catheter can be passed through the scope, into the ampulla and advanced into the bile duct where dye can be injected and any strictures viewed using X-ray pictures. If a patient cannot undergo an ERCP, a transhepatic cholangiogram may be performed instead. The transhepatic cholangiogram involves taking x-ray pictures of the bile ducts following insertion of a needle through the skin directly into the liver and the dye being injected into the bile ducts. In PSC, the bile ducts both within and outside of the liver may have areas of narrowing (strictures) and dilatations producing a beaded appearance that is characteristic of this disease. Both tests are done using sedation (medication to improve patient comfort during the procedure).

Magnetic Resonance Imaging

Magnetic resonance cholangiopancreatography (MRCP) is an alternative diagnostic test to ERCP and transhepatic cholangiogram for making the diagnosis of PSC. MRCP is a safe and non-invasive test that takes images of the bile pancreatic ducts and has replaced ERCP as the first imaging test in patients suspected of having PSC. Published data has demonstrated that the predictive positive and predictive negative values for MRI in diagnosis of PSC are both 80%.



Liver Biopsy

A liver biopsy is a test used to obtain liver tissue that is examined under a microscope. It involves the insertion of a needle, typically between the ribs on the right side of the abdomen, into the liver for the purpose of obtaining a tiny sample. Local anesthesia is used before inserting the needle. The tissue specimen is then examined under a microscope. A liver biopsy can be helpful in making the diagnosis of PSC and in assessing the severity of scarring and extent of liver damage. Hence, a biopsy may be helpful in determining prognosis.

What are the complications of PSC?

Patients with PSC are at risk for developing other associated problems.

Dominant Stricture

A dominant stricture is a blockage in one of the large bile ducts that serve to drain bile from the smaller bile ducts of the liver and deliver it into the small intestine. A dominant stricture occurs in seven to twenty percent of patients with PSC. When a dominant stricture is present, bile is blocked from flowing through the bile duct and, therefore, may back up in the liver. Substances that are normally excreted into bile accumulate in the bloodstream and body tissues. This can lead to jaundice (yellowish discoloration of the eyes and skin), stone formation in the bile ducts and infection in the bile ducts known as cholangitis. At ERCP a piece of plastic tubing called a “stent” can be placed across a dominant stricture in an effort to relieve the blockage.

Fat Soluble Vitamin Deficiencies

Vitamins A, D, E and K, are known as fat-soluble vitamins because they dissolve in oils rather than water. One function of bile is that it improves the intestine’s ability to dissolve and absorb these vitamins. If bile from the liver does not get into the intestines in adequate amounts, fat-soluble vitamins may not get absorbed and deficiencies can occur. Blockage of bile ducts may also cause diarrhea because fat in the diet will be poorly absorbed.

Osteoporosis

Osteoporosis or bone thinning is another complication of PSC. The cause of osteoporosis in PSC is unclear.

Cholangiocarcinoma

The risk of developing cancer involving the bile ducts (known as cholangiocarcinoma) is higher in patients with PSC than in a healthy population. Cholangiocarcinoma may occur in 7 to 15% of patients with PSC. Patients with a long history of inflammatory bowel



disease and smokers are at the highest risk. As there are no early symptoms of cholangiocarcinoma that make it easy to distinguish from symptoms of PSC, it is difficult to diagnose early. Researchers and physicians continue to work on ways of making early diagnosis of cholangiocarcinoma.

Cirrhosis

Cirrhosis is a process of advanced scarring of the liver.. The fibrosis or scarring of the liver seen in cirrhosis leads to obstruction of blood flow through the liver. This prevents the liver from performing its critical functions of purifying the blood and nutrients absorbed from the intestines. The end result is liver failure.

Cirrhosis is the seventh leading cause of death in the United States and can be caused by genetic disorders, such as hemochromatosis, viral infections, such as hepatitis or by alcoholism. To learn more about cirrhosis and its potential complications, please click [here](#) to access a patient brochure published by the ACG on cirrhosis.

In all patients with PSC problems can develop that result in irreversible liver failure. These problems include bleeding from swollen veins (varices) most commonly in the esophagus, collection of fluid in the abdomen (ascites) and legs, and episodes of confusion (hepatic encephalopathy) due to the inability of the scarred liver to remove toxins from the blood stream.

Colon Cancer

There is an increased risk of colon cancer in patients with PSC and inflammatory bowel disease. Colonoscopy with biopsies throughout the colon once a year is recommended.

What are the treatments for PSC?

Many medications have been studied but none have proven to alter the course of PSC. This is primarily due to uncertainty regarding its cause. Medications such as ursodeoxycholic acid (UDCA), colchicine, steroids and methotrexate have been used to treat PSC. Studies evaluating higher doses of UDCA than had been used previously are ongoing.

Therapy is directed towards treating symptoms, preventing and managing complications of PSC. Patients with PSC should avoid alcohol, which may cause or worsen liver damage. Vaccinations for hepatitis A and B should be administered. Vitamin supplements should be prescribed for patients with advanced disease at risk for deficiencies. Medications such as diphenhydramine, cholestyramine, rifampin and phenobarbital have been helpful in relieving itching. Osteoporosis is managed with supplemental calcium and vitamin D. Treatment of itching and osteoporosis in PSC is similar to that used for treating Primary Biliary Cirrhosis (see below). Alendronate is a medication often used to decrease further bone loss that may help in PSC. ERCP can be



used to open the bile duct blockage with balloons inserted into the area of narrowing. This can lead to improved bile flow. Antibiotics are given when infections occur.

When should liver transplantation be considered?

Patients who develop complications of cirrhosis and those with recurrent cholangitis are candidates for liver transplantation. Liver transplantation is the only effective treatment for patients who have developed late stage PSC (cirrhosis). Studies have shown that approximately eighty to ninety percent of patients who undergo liver transplantation for late stage PSC are alive one to three years later. After transplantation, many patients report having a good quality of life.

PRIMARY BILIARY CIRRHOSIS (PBC)

What is PBC?

Primary Biliary Cirrhosis (PBC) is a chronic liver disease that is characterized by inflammation and destruction of the bile ducts. PBC is usually diagnosed in patients between the ages of 35 to 60 years. About 90 to 95 percent of patients are women. Liver inflammation over a long period of time may cause scarring which leads to cirrhosis. The cause of PBC is unknown, but it is most likely an autoimmune disease. In autoimmune diseases, the immune system attacks a specific tissue in the body. In PBC, it is thought that the immune system attacks and destroys small bile duct cells in the liver. In addition, there are environmental factors such as infections, which may trigger the disease. Due to widespread laboratory screening, the number of patients being diagnosed at the early, asymptomatic stage has risen dramatically over the past decade. More than 60 percent of newly diagnosed PBC patients now are asymptomatic.

What are the signs and symptoms of PBC?

Many patients may not have symptoms for years, and some may never have complaints relating to their disease. Because of the varying and sometimes subtle symptoms, doctors may have difficulty making the diagnosis. Signs and symptoms may include the following:

- Hypercholesterolemia
- Intense itching of the skin (pruritus)
- Dry eyes and mouth (sicca syndrome)



What type of tests are needed to evaluate PBC?

Many patients are now diagnosed before symptoms are present. Typically, the blood tests show a higher than normal alkaline phosphatase level with a normal bilirubin. Usually, the bilirubin does not increase until a late stage of the disease. Your doctor may decide to conduct one or more of the following tests.

- *Anti-mitochondrial antibody (AMA) blood test* - Up to 95% of patients with PBC will have a positive AMA test. This test is used to help confirm a diagnosis of PBC.
- *Liver function tests* - Blood tests that are specific for liver disease are total bilirubin, alkaline phosphatase, aminotransferase levels (ALT, AST), albumin and prothrombin time.
- *Cholesterol and triglyceride levels* - These blood tests are often increased.
- *Ultrasound exam of the liver* - Images of the liver and bile ducts are taken to assess for liver abnormalities.
- *Liver biopsy* - A small sample of liver tissue helps to confirm the diagnosis and determines the severity of the liver damage.

Treatment of complications of PBC

Some patients have complications of PBC that require therapy. In many cases, doctors find that symptoms can be controlled by lifestyle modifications and medications.

Itching

Itching can be a troublesome symptom of PBC. Itching may range from mild to severe, where a patient's lifestyle may be impaired. Itching may be worse with fatty meals or at night, interfering with sleep. The first medications that are used by doctors include diphenhydramine, cholestyramine and colestipol. Rifampin is used in patients who fail or are intolerant to cholestyramine and colestipol. In resistant cases, opioid antagonists such as nalmefene, naloxone and naltrexone are used. Plasmapheresis and ultraviolet light have been utilized in extreme cases. Liver transplantation is indicated for patients with uncontrolled itching.

Osteoporosis

When the diagnosis of PBC is made, bone mineral density should be assessed to determine if a patient has osteoporosis or bone thinning. In many cases, doctors may suggest that their patients start exercise if possible, stop smoking and take calcium 1500 mg/day with vitamin D 1,000 IU/day. Hormone replacement therapy (estrogen) is safe in PBC and is recommended where appropriate. When osteoporosis is evident, therapy with medications such as Fosamax® (alendronate) and Actonel® may be helpful in PBC.



Fat-soluble vitamin deficiencies

As PBC progresses, some patients lose the ability to absorb fat-soluble vitamins A, D, E and K. Measurement and replacement of these vitamins is recommended.

Treatment of underlying disease

Ursodiol

Ursodiol is currently the only drug approved by the FDA for the treatment of PBC. It is often the initial therapy for patients. The drug is a “gentler” bile acid than those normally made by the body and is well tolerated. Studies have shown that ursodiol, given in a dose of 13 to 15 mg/kg daily up to four years, delays the time to liver transplantation. In addition to improving blood tests, there are some patients with PBC whose disease appears to become inactive (remission) on ursodiol.

Colchicine

Colchicine is associated with improvement of liver tests in some patients with PBC and improved itching in two recent studies. However, there was no improvement in liver biopsy findings.

Methotrexate

In early studies, methotrexate had appeared to be associated with improvement in symptoms, liver function tests and liver biopsies. However, an 8-year multicenter NIH trial has clearly documented that the use of Methotrexate is not associated with improvements in liver disease and the development of complications of cirrhosis.

Liver Transplantation

Many people with PBC may never develop cirrhosis or liver failure. However, as can be seen in PSC, a late stage of PBC can be liver failure. For those people who reach the late stages of PBC, liver transplantation may be considered. The signs and symptoms of liver failure, which may or (depending on the specific aspects of the symptoms / disease) may not prompt consideration of any potential role for liver transplant, are the following:

- Persistent jaundice
- Fluid retention with swelling of hands, feet and abdomen
- Variceal bleeding (internal bleeding from swollen intestinal blood vessels, commonly in upper stomach and esophagus)
- Bone thinning and/or fractures
- Hepatic coma or encephalopathy



The survival for PBC patients after liver transplantation is excellent. With better understanding of the nature of PBC and its complications, many patients will have improved outcomes.

