Primary biliary cirrhosis (PBC)
Primary sclerosing cholangitis (PSC)
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Primary biliary cirrhosis (PBC)

What is primary biliary cirrhosis?

Primary biliary cirrhosis (PBC) is a chronic, progressive disease of the liver that is initially focal, i.e. it affects only certain regions of the liver, but over time progresses to affect the entire organ. It starts in the small bile ducts, which are destroyed by an inflammation. This results in retention of the bile produced in the liver and the deposition of toxic bile acids and other toxic compounds.

Because the inflammation is not caused by white blood cells and no pus is produced, the disease is also known as non-suppurative destructive bile duct inflammation. Its more common name, primary biliary cirrhosis, is due to the fact that the disease was formerly identified only in its terminal stage, which is characterized by cirrhosis. Today, early diagnosis is possible. The old name primary biliary cirrhosis, however, has been retained because of its established place in clinical practise. Because the blood or serum of patients with PBC contains so-called immune markers, which point to the presence of certain immunological reactions, and corresponding cells are found in the liver (see below), scientists speak of an autoimmune disease in which the cells of the immune system attack the body’s own tissues.

Frequency of the disease and its duration

In 80–90% of cases, primary biliary cirrhosis affects women, males only in 10–20%. The disease very rarely strikes children but its frequency is higher than thought even a few years ago.

Untreated, patients with PBC have an average survival of 12 years, with a maximum of 20 years. The
medications currently available have resulted in a significant prolongation of the clinical course and the option of liver transplantation, which may ultimately be required, can result in a large proportion of patients being cured.

**Staging**

Current practice divides PBC into four stages (stages I–IV), although the exact length of the individual stages is unclear.

**Stage I:** In this stage, the inflammatory changes are restricted to the bile ducts (figure 1) and the immediately surrounding connective tissue (non-suppurative destruction of the bile ducts). The inflammatory cells involved at this stage are so-called immunocompetent cells, which, as mentioned above, attack the person’s own liver. Cells of this type are also found in other immune diseases of the liver, for example in autoimmune hepatitis.

**Stage II:** This stage is characterized by increased formation of bile ducts (bile duct proliferation). These new bile ducts try to replace the destroyed ones. The inflammatory changes in the surrounding connective tissue consolidate and may spread to neighboring liver tissue (figure 2).

**Stage III:** More and more bile ducts are now destroyed (bile duct rarefication). Adjacent hepatic tissue is increasingly affected by inflammatory change and an increase in connective tissue heralds the onset of cirrhosis (figure 3).

**Stage IV:** Connective tissue has increased further and has separated the remaining liver tissue into fields of different size. Because of the tendency of liver tissue to regenerate, regeneration nodes of varying size appear (figure 4). This makes the surface of the liver
Primary biliary cirrhosis (PBC)

Inflammatory cells which destroy the bile ducts

Connective tissue

Liver cells (Liver lobule)

Figure 1: PBC stage I

Inflammation invades the liver tissue

The number of bile ducts has increased (bile duct proliferation) and bile ducts are destroyed

Figure 2: PBC stage II
The number of bile ducts is reduced (bile duct rarefication)

Connective tissue and the inflammation further invade the liver tissue which is divided in areas of different size

Figure 3: PBC stage III

Reduction of the number of inflammatory cells

Intense augmentation of the connective tissue, which completely divides the liver tissue (liver cirrhosis)

Figure 4: PBC stage IV
bumpy. The bile ducts continue to disappear and inflammatory cells in the surrounding connective tissue have become fewer. We have now reached complete cirrhosis (PBC). Since in complete liver cirrhosis not only bile ducts have changed their course in the liver but also blood and lymph vessels, blood and lymph can be accumulated and esophageal varices and ascites will develop.
How does one recognize primary biliary cirrhosis?

The first symptom of PBC is often pruritus (itching), which can be mild but may be moderate or even severe, and which is most noticeable at night. Most often affected are the arms, back and legs. Pruritus can increase in the warmth (for example in the bed) or in dry air (heating period). Patients may also experience significant fatigue or reduction in performance as a first sign of the disease (table 1). More rarely, there may be yellowish gray subcutaneous deposits of fat, called xanthelasmata in the nasal region of the eyelids, though these more commonly do not appear until later in the course of the disease.

PBC may manifest itself for the first time following pregnancy. In these cases, patients may have experienced gestational cholestasis (reduced outflow of bile) during the last three months prior to delivery, which, however, resolves after the birth. Not longer afterwards, however, the same symptoms (especially pruritus) recur. These cases of recurrent symptoms following delivery are mostly due to PBC, as is easily demonstrated using laboratory data (see below).

Table 1

**Characteristics of PBC**

- Females are most commonly affected, less often males
- First disease manifestation following pregnancy
- Pruritus (itching of arms, legs, back)
- Tiredness, fatigue, reduced performance
- Sometimes xanthelasmata (subcutaneous fat deposits in the eyelids)
How does your physician diagnose PBC?

In the past, PBC was difficult to diagnose. Because it was typically first diagnosed in an advanced stage, it received the name “primary biliary cirrhosis”. Today, simple blood tests can confirm the diagnosis in earlier stages (stage I and II), when patients have not yet developed cirrhosis.

Physical examination

In early disease stages, the physician typically finds no changes on physical examination. There is no jaundice (yellow discoloration of the skin and eyes caused by increase in serum bilirubin) and the liver and spleen are not enlarged. Ultrasound of the liver returns normal findings or, if abnormal, are of the type associated with fatty degeneration (steatosis). In a more advanced stage, the liver may be enlarged, followed later by signs of cirrhosis (see table 4). At ultrasound, the liver surface is wavy or bumpy, due to scar tissue the liver itself shrinks and decreases in size over time, and because a reverse blood flow exists spleen size increases. Since similar alterations can be found in patients in whom liver cirrhosis developed of different reasons all findings are not typical for PBC alone.

Laboratory tests, ultrasound tomography

Even at an early stage there are typical changes on laboratory examinations of the blood. Almost 100% of patients show elevation of so-called antimitochondrial antibodies (AMA) in the blood. AMAs are antibodies that circulate in the blood and are directed at the mitochondria, cell organelles in which the energy metabolism of liver and bile duct epithelial cells is located. AMAs, although they are not the cause of
PBC, nor are they responsible for the severity of the disease, are strong evidence for the diagnosis (table 2). In addition, there are increased blood levels of enzymes such as alkaline phosphatase (AP) and \( \gamma \)-glutamyltranspeptidase (GGT or \( \gamma \)GT), which indicate inflammatory changes of the bile ducts and cholestasis. Also characteristic for the disease is an increase in blood levels of a protein called immunoglobulin M (IgM). If these parameters in the blood are increased and if repeated examinations document the presence of AMAs, the diagnosis of PBC can be considered confirmed, even when the patient has no symptoms. Levels of other liver enzymes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and glutamate-dehydrogenase (GLDH), which indicate inflammatory changes in the liver, may be slightly elevated. This is due to the fact that the inflammation primarily affects the bile ducts, not the liver tissue itself.

In more advanced disease stages (stages III and IV), there is hardly any further change in laboratory parameters. Thus, laboratory values by themselves say little about the stage of the disease. In late stages, liver function gradually declines, resulting in a drop in the protein (albumin) concentration of the blood and in

**Table 2**

**Characteristic laboratory findings in PBC**
- Elevated alkaline phosphatase (AP) and \( \gamma \)-glutamyltranspeptidase (GGT, \( \gamma \)GT)
- Slight increase of the transaminases (AST and ALT)
- Often significant increase in immunoglobulin M (IgM)
- Evidence of antimitochondrial antibodies (AMA)
Primary biliary cirrhosis (PBC)

clotting factors. Bilirubin, the main pigment of the bile, however, increases and patients develop jaundice. At the beginning only in the eyes, later on all over the skin. Because bilirubin is not excreted by bile but by urine the urine is dark while the stool is getting light.

Ultrasound examination now reveals a liver surface that is irregular. There is also evidence of disturbed blood supply to the liver (collateral circulation), accumulation of fluid in the abdominal cavity (ascites) and sometimes of an enlarged spleen.

Laboratory tests should, depending on the severity of the disease, be obtained every 4–12 weeks, with follow-up ultrasound examinations every 4–8 months.

Tissue samples from the liver (liver biopsy)

Sampling of tissue obtained by ultrasound-guided puncture of the liver is done only at the time of first diagnosis for histological confirmation. Although it is currently a matter of discussion whether, given the highly reliable nature of the available laboratory tests, liver biopsy is necessary at all, the fact that PBC is a disease requiring life-long treatment and possibly liver transplantation underscores the importance of confirming the diagnosis by histological examination of the tissue. Once the diagnosis has been confirmed, further biopsies are not required unless there is suspicion of hepatocellular carcinoma. For liver biopsy, the patient is usually admitted to the hospital for one and a half days to monitor for complications, such as bleeding or bile leakage, which, however, are extremely rare. Liver puncture can also be done on an outpatient basis in cases in which timely access to medical care in the case of complications is assured.
What is the clinical course of PBC?

Common symptoms

In its earlier stages, PBC usually causes no typical complaints. Pruritus (see above), which in some patients may occur early and long before a final diagnosis of PBC is made, may in some cases not occur until later, even sometimes for the first time in a terminal disease stage. Typical for PBC is tiredness, fatigue, and a drop in productivity.

Associated “rheumatic” disorders

Some patients report symptoms affecting the joints and muscles. These are called associated rheumatic symptoms. Also considered a rheumatic disease is the so-called Hashimoto thyroiditis. In this disease, the body produces antibodies against thyroid tissue, which is gradually destroyed. Another disorder in which autoimmunological cases have been discussed is the so-called Sicca syndrome. It is characterized by reduction in the secretions of the large glands, such as the tear, vaginal and salivary glands and the pancreas (table 3).

Table 3

**Important associated disorders in patients with PBC**

- Associated rheumatic disorders
  - Joint complaints
  - Hashimoto thyroiditis
  - Sicca syndrome
- Osteoporosis
- Vitamin deficiency
- Skin changes typical for cirrhosis (see table 4)
- Hepatocellular carcinoma
Primary biliary cirrhosis (PBC)

Loss of bone mineral density (osteoporosis)

Osteoporosis, which is a loss of bone mass, occurs early in patients with PBC. Why this occurs in these patients is unknown. Because PBC most commonly affects women and because women not infrequently suffer from osteoporosis following menopause, it is sometimes not possible to distinguish between these two forms. The extent of osteoporosis can be measured radiologically (DEXA scan). In some cases, patients require treatment with medication.

Fatty stools (steatorrhea), vitamin deficiency syndromes

Sicca syndrome results in dry mucous membranes (e.g. in the eyes) and is also associated with reduced production of enzymes by the pancreas which are required for digestion of fats. Fat cannot be cleaved by enzymes in the gut and is excreted via the stool (steatorrhea). In this case, the fat content of the stool is increased (steatorrhea). Because bile acids are necessary for the absorption of fats and fat-soluble vitamins (vitamins A, D, E and K in the gut), cholestasis in the liver resulting in a deficiency of bile acids in the bowel together with Sicca syndrome contributes to fatty stools and vitamin deficiencies. A deficiency of vitamin A results in night blindness; vitamin D deficiency promotes development of osteoporosis, while reduced levels of vitamin K is associated with disorders of blood coagulation. In most patients, however, vitamin deficiency syndromes are not significant and may be mild, so that the above-mentioned symptoms do not develop and no treatment as a rule is required.
Skin changes

We have already mentioned the xanthelasmata, or subcutaneous deposits of fat in the eyelids. Small fatty tumors, called xanthomata, may also develop on the hands, feet or buttocks. As PBC progresses from its early to late stages, the classical signs of liver cirrhosis develop (table 4). On the skin, there may be star-shaped lesions called spider naevi. The color of the lips and tongue may become darker (lipstick-lips) and the skin appears thinner, especially on the face and brow.

Table 4

Signs of liver cirrhosis (due to PBC, PSC and other causes)

- Skin changes
  - Spider naevi (dilated small blood vessels)
  - Lipstick or lacquer lips (degeneration of lip skin, darkening of the red color of the lips)
  - Red tongue (degeneration of the epithelium of the tongue)
  - Thinning of the skin (disturbance of the nutrition of the skin with degeneration)
- Ascites (fluid in the abdominal cavity)
- Edema (swelling of the legs)
- Black and blue marks after very minor injuries (tendency to bleed)
- Loss of body hair (chest and abdomen) in males
- Signs that are not observable by the patient:
  - Esophageal varices (varicose veins in the esophagus)
  - Reduced brain function (hepatic encephalopathy)
Complications of complete cirrhosis

The complete or near-complete transformation of the liver into scar tissue results in a significant reduction in blood flow through the organ. Instead, the blood flows through so-called collateral pathways that bypass the liver. These include varices of the esophagus, which may bleed profusely. There may also be accumulation of fluid in the abdominal cavity (ascites) and brain function may also be affected (hepatic encephalopathy), which can further complicate the clinical picture. In the terminal stage about 3% of patients develop hepatocellular carcinoma.
How does one treat PBC?

As late as 1985, PBC was considered an untreatable disease. Today, this disease is amenable to both treatment with drugs and with liver transplantation.

Drug treatment

Treatment with medication begins as soon as the diagnosis is confirmed, regardless of disease stage. Treatment consists in the administration of ursodeoxycholic acid (UDCA), a bile acid that normally occurs in only small amounts in humans. The daily UDCA dose is 13–15 mg per kilogram of body weight. UDCA should be taken in two to three doses per day, treatment should not be interrupted. Interruption of therapy results in a renewed worsening (rebound effect) in laboratory values (table 5). Recent studies have shown that in some patients a combination of UDCA with a cortisone preparation (prednisone, budesonide) or, at least initially, with the immunosuppressant medication, azathioprine, is superior to the effects of UDCA alone. Further data are needed before this combination can be recommended as standard therapy. In

Table 5

<table>
<thead>
<tr>
<th>Drug therapy of PBC</th>
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<tbody>
<tr>
<td>• Ursodeoxycholic acid (UDCA): 13–15 mg per kilogram of body weight daily</td>
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<tr>
<td>• Therapy starts immediately after the diagnosis is confirmed</td>
</tr>
<tr>
<td>• Duration of therapy: life long or until liver transplantation</td>
</tr>
<tr>
<td>• If response to UDCA is inadequate, combination with cortisone, budesonide or azathioprine (still being tested in studies)</td>
</tr>
</tbody>
</table>
patients who do not respond sufficiently to UDCA alone a combination therapy should be initiated already now. Combination therapy should only be started in patients with the early stages I or II of PBC.

**Results and side effects of therapy**

In infrequent cases, UDCA is associated with diarrhea. As a rule, however, the drug is taken without any side effects. Many patients have been treated with UDCA over a period of 12–22 years without any need to interrupt or discontinue the drug due to side effects.

As an effect of treatment during the first six months the liver enzymes γGT and GLDH drop by up to 80%, followed by improvements in AP and IgM by 30–60% and finally of the inflammation parameters, AST and ALT. Only the concentrations of AMAs remain unchanged. In 30% of patients with relatively low initial concentrations, value return to normal after three to five years of therapy, while in the remaining 70% they improve significantly but never completely return to normal.

It has been shown that therapy with UDCA improves not only the laboratory values but also histological findings. The development of esophageal varices is slowed, the need for liver transplantation is delayed and patients’ life expectancy is improved.

Less clear is the effect of UDCA on symptoms such as fatigue and pruritus, which may sometimes become intolerable (table 6). The treatment of these two symptoms has been shown to be especially difficult, requiring much patience and endurance from both physician and patient. It appears to be the case that patients with mild cholestasis (slight elevation of AP and GGT, but normal bilirubin) are more often free of complaints than are patients with high values.
Treatm ent of osteoporosis, steatorrhea and vitamin deficiencies

Osteoporosis, which develops at an early disease stage, can today be treated very effectively with bisphosphonates. In women with postmenopausal osteoporosis, bisphosphonates resulted in prevention of bone loss and even in restoration of bone mass. This effect has not yet been proven in patients with PBC but is considered very likely. For this reason, these drugs are also used in patients with PBC. Treatment with vitamin D and calcium is also effective. In all cases patients should maintain a regular, balanced Western diet and get plenty of outdoor exercise, which also helps prevent osteoporosis (table 7). Female sex hormones (estrogens) also prevent osteoporosis. Because estrogens, however, also promote cholestasis, their use in PBC is controversial.

Table 6

Treatment of pruritus
- Ursodeoxycholic acid (UDCA)
- Colestyramine or
- Colestipol or
- Opiate antagonists or
- Combination of the above treatments

Table 7

Treatment of osteoporosis in PBC
- Adequate physical exercise outdoors
- Well-balanced diet
- Bisphosphonates and/or calcium and vitamin D
- Estrogens (in females)
Fatty stools, which occur less frequently, can be combated by reducing the fat content of the diet to 40–50 grams daily. If this is not sufficient, patients can be given enzyme-containing medications. If these, in turn, do not produce the desired effect, patients are advised to prepare their food with modified, easily absorbable fat such as Ceres margarine. These modified fats do not require to pancreatic enzymes to be broken down before they are absorbed in the small bowel.

If patients experience vitamin deficiencies, regular injections of the fat-soluble vitamins A, D, E and K are recommended, but unfortunately these drugs are no longer available. Because they are injected into muscle, they cannot be lost with fatty stools.

Liver transplantation

As the disease progresses and liver function cannot be maintained, or if there are complications or itching becomes unbearable, liver transplantation represents the most effective option. Although transplantation of the liver is one of the most major operations in modern medicine, the technique has become very refined and is very effective. Following liver transplantation, patients undergo follow-up treatment with the long-term goal of preventing rejection of the transplanted organ. This treatment consists of administration of so-called immunosuppressants (table 8), which many physicians give in combination with UDCA.

Following transplantation, PBC may recur in a small number of patients in the transplanted liver or they may develop a different type of liver damage (e.g. rejection, changes in blood vessels). In these cases, patients are treated with medications as long as possible but in some cases a second liver transplantation may be necessary.
Immunosuppressive therapy options following liver transplantation

- Cortisone preparations (e.g. prednisolone or prednisone)
- Cyclosporin A
- Tacrolimus
- Azathioprine
- Mycophenolate Mofetil
- Combination of the above medications
Is primary biliary cirrhosis related to autoimmune hepatitis?

Indeed, there is a small proportion of patients with PBC whose laboratory parameters and findings from microscopic analysis of liver tissue point equally to PBC and to autoimmune hepatitis. Other patients, who suffered initially from PBC, later showed signs of increasing inflammation, and finally they showed signs of both PBC and chronic autoimmune hepatitis. Such cases of mixed disease are called “overlap syndromes”.

The small number of patients with overlap syndrome may respond to a combination of UDCA (13–15 mg per kilogram of body weight per day) and a low-dose cortisone preparation, possibly in combination with the immunosuppressant azathioprine.
Summary

- Primary biliary cirrhosis (PBC) is a chronic inflammatory autoimmune disease of the liver.
- Beginning at the small bile ducts and gradually extending to the liver tissue, PBC leads ultimately to liver cirrhosis.
- The average survival of untreated patients is 12–20 years from first diagnosis.
- Because of improvements in laboratory diagnostics, PBC can today be identified in an early disease stage.
- Drug therapy consists in life-long administration of ursodeoxycholic acid (UDCA) beginning immediately after confirmation of diagnosis.
- UDCA improves liver enzyme values and histological findings, postpones the need for liver transplantation and extends life expectancy.
- Liver transplantation remains as an option when therapy with medications is no longer effective.
- Results of liver transplantation are very good and are steadily improving.
Primary sclerosing cholangitis (PSC)

What is primary sclerosing cholangitis?

Primary sclerosing cholangitis (PSC) is a chronic liver disease that is characterized by inflammation during which onion skin-like layers of connective tissue develop around the small bile ducts. As the amount of connective tissue increases, the bile ducts are occluded (closed off) and cholestasis develops, which, if extensive, leads to jaundice. These areas of inflammation subsequently involve neighboring liver tissue, leading to cirrhosis as the terminal stage of the disease. Although PSC is an autoimmune disease, there are no specific immune markers in serum. There are, however, cells known as immunocompetent cells that are capable of attacking the body’s own tissue, such as bile ducts or liver tissue. The frequency of PSC is not exactly known but it is being much more frequently diagnosed.

Staging

PSC is divided into four stages (stages I–IV; table 9).

Table 9

<table>
<thead>
<tr>
<th>Stages of PSC</th>
<th>Description</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Inflammation and connective tissue proliferation around the small bile ducts</td>
</tr>
<tr>
<td>Stage II</td>
<td>Inflammation passes into the liver with further scar tissue formation</td>
</tr>
<tr>
<td>Stage III</td>
<td>More severe scar tissue formation</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Biliary liver cirrhosis</td>
</tr>
</tbody>
</table>
Differences between PSC and primary biliary cirrhosis (PBC)

Despite superficial similarities, PSC differs from PBC not only in terms of the above mentioned histological or microscopic changes but also in other aspects. In PSC, the bile duct changes develop not only in the intrahepatic bile ducts but may also affect the large common bile duct outside the organ leading from the undersurface of the liver to its entrance into the bowel and may occur simultaneously both intra- and extrahepatically. The gallbladder, however, is rarely affected.

A further important difference between PSC and PBC is that, in PSC, 80–90% of patients also suffer from inflammatory bowel disease (IBD) characterized by inflammation and ulceration of the mucosal membrane of the bowel. In 10–15% of cases, this inflammatory bowel disease is of the type known as Crohn’s disease, while the remaining 80–85% of patients show signs of ulcerative colitis.

A further important difference is that PSC may also attack children and adolescents, while PBC occurs almost exclusively in adults. Up to 80% of PSC patients are men, unlike PBC which, in 90% of cases, affects women (table 10). And finally, in PSC different types of malignancies can develop, while in PBC only liver cell carcinoma has been described.

Cancer risk

Patients with PSC are at an increased risk of developing cancer, which means that regular follow-up is advisable. About 10% of patients develop carcinoma of the bile ducts, which in 30% of patients develops early and later is seen less often. The risk of developing colon carcinoma in patients with associated ul-
Differences between PBC and PSC

- PSC: Bile duct changes both intra- and extrahepatic
- PSC: Antimitochondrial antibodies (AMA) absent
- PSC: 80–90% of patients also have inflammatory bowel disease
- PSC: Predominantly affects men
- PSC: May also affect children and adolescents
- In PSC different types of malignancies can develop

Celiac colitis is higher than in patients with ulcerative colitis but without PSC. For this reason, patients should undergo colonoscopy at regular intervals. According to the most recent studies, the risk of developing carcinoma of the pancreas is 14 times higher than in the general population, underscoring the importance of regular ultrasound examinations. And finally also the development of gallbladder carcinoma has been described more often, especially in patients with gallbladder polyps.
How does one recognize primary sclerosing cholangitis?

The disease course of PSC is usually more severe and varied than that of PBC. Patients frequently report feeling generally unwell, with reduced performance and tiredness as the first symptoms. Pruritus (itching) is common. Fever indicates a concomitant bacterial inflammation of the bile ducts. Transient or more persisting yellow discoloration of the eyes (scleral icterus), sometimes with mild skin jaundice, can occur as a result of occlusion of the bile ducts (table 11). Such occlusions may occur because of inflammation, narrowing of the ducts caused by scar tissue formation or because of the presence of sludge (thickened bile) or small stones, which may occur in high-grade changes of the bile ducts.

If patients at the same time suffer from one of the above mentioned inflammatory bowel diseases (ulcerative colitis or Crohn’s disease), they may experience abdominal pains of varying severity, diarrhea

<table>
<thead>
<tr>
<th>Symptoms and findings in PSC</th>
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<tbody>
<tr>
<td>• Tiredness, fatigue, reduced performance</td>
</tr>
<tr>
<td>• Significant feeling of general illness</td>
</tr>
<tr>
<td>• Subfebrile or febrile temperatures</td>
</tr>
<tr>
<td>• Itching (pruritus)</td>
</tr>
<tr>
<td>• Recurring jaundice</td>
</tr>
<tr>
<td>• Joint complaints</td>
</tr>
<tr>
<td>• Weight loss</td>
</tr>
<tr>
<td>• Upper abdominal complaints*</td>
</tr>
<tr>
<td>• Soft stools, bleeding, diarrhea*</td>
</tr>
</tbody>
</table>

*) Symptoms of concomitant ulcerative colitis or Crohn’s disease
and weight loss. The severity of IBD associated with PSC, however, may be mild and may come to light only upon questioning by the physician. In addition, there may be rheumatic changes in the joints and other associated symptoms (see table 3). In a later disease phase, patients develop the symptoms of liver cirrhosis (see table 4).
How does your physician diagnose PSC?

*Physical examination and diagnostic ultrasound*

In early stages of PSC, physical examination may often reveal no evidence of the underlying disease. The liver may be slightly enlarged but may also be normal in size. In the late stages characteristics of liver cirrhosis can be detected (see PBC, table 4). If patients at the same time suffer from one of the inflammatory bowel diseases, they may experience pain with pressure to the abdomen. The physician may feel a lump representing several bowel loops or hear gurgling and other noises throughout the whole abdomen. If the disease has progressed as far as cirrhosis, the changes given in table 4 will often be found.

Ultrasound examination of the liver initially finds only uncharacteristic changes, but as the disease progresses, ultrasound demonstrates widening and outpouching of the bile ducts. In the final stage we have the picture of complete cirrhosis with an irregular liver surface, shrinkage and enlargement of the spleen.

*Laboratory tests*

In PSC, laboratory tests show significant increases in serum especially of the enzymes that point to cholestasis, such as alkaline phosphatase (AP) and $\gamma$-glutamyl-transpeptidase (GGT or $\gamma$GT), and to a lesser extent of the hepatic transaminases (alanine aminotransferase: ALT; aspartate aminotransferase: AST). The serum concentration of the bile pigment bilirubin depends on the disease stage and on the associated complications, such as gallstones. Unlike primary biliary cirrhosis (PBC), the other important liver disease associated with cholestasis, PSC, is not characterized
by increased titers of antimitochondrial antibodies (AMA), which is typical for PBC (in PSC there are no typical antibodies at all). In addition, the erythrocyte sedimentation rate (ESR) and the number of white blood cells may be elevated. In a more advanced stage of the disease, there may be a reduction in the number of blood platelets, which are trapped in the enlarged spleen and destroyed and which can be observed in all types of liver cirrhosis. Bilirubin increases and the protein synthesis of the liver and the formation of coagulation factors is reduced (see PBC).

Endoscopic retrograde cholangiography (ERC)

The decisive diagnostic method consists of the radiological imaging of the intra- and extrahepatic bile duct system (endoscopic retrograde cholangiography). With this method, similar to gastroscopy, an endoscope is passed through the mouth and advanced into the duodenum. Radiological contrast medium is injected directly into the bile duct through the endoscope. ERC visualizes the typical outpouchings and interruptions in both the intra- and extrahepatic bile ducts that occur even at early stages of the disease. These changes are so typical that a single look at the radiological images permits the correct diagnosis. The only entities which must still be excluded are AIDS-related inflammation of the bile ducts, changes following liver transplantation and changes due to the local use of anti-cancer medications (table 12). Because these other diagnoses are easily excluded by a careful case history, ERC represents the most reliable method for diagnosing PSC.

The bile ducts and changes due to PSC can also be visualized using magnetic resonance cholangiography (MRC). Although this spares the patient from “swallowing the tube” the images that are possible
with the method at the present time are less satisfactory than those provided by ERC. In addition, MRC is a purely radiological technique which, unlike ERC, does not include the capability for any instrumental intervention (e.g. dilatation) of the bile ducts. In 10–15% MRC is unable to diagnose PSC.

Tissue samples from the liver (liver biopsy)

A histologic-microscopic confirmation of the disease is not actually obligatory. However, because of the need for life-long medication therapy and the possibility of the future need for liver transplantation, the histologic confirmation of the diagnosis is desirable. Tissue is obtained by fine needle puncture of the liver in local anesthesia under ultrasound guidance.

<table>
<thead>
<tr>
<th>Diseases with endoscopic (ERC) findings of the bile ducts similar to those seen in primary sclerosing cholangitis (PSC), which must be differentiated from PSC and further differential diagnoses of PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• AIDS cholangitis</td>
</tr>
<tr>
<td>• Bile duct inflammation due to local application of cytostatic (anticancer) agents</td>
</tr>
<tr>
<td>• Blood circulation problems in the area of the bile ducts after liver transplantation</td>
</tr>
</tbody>
</table>

To be differentiated on the basis of ERC, clinical picture and laboratory values (differential diagnosis):

- Primary biliary cirrhosis (PBC: ERC normal)
- Bacterial bile duct inflammation (ERC, blood tests similar)
- Bile duct inflammation caused by parasites (ERC, blood tests similar)
What is the clinical course of PSC?

PSC is more seldom when compared to PBC, but if one looks for PSC in patients with inflammatory bowel disease its number rises. PSC follows a chronic clinical course with numerous disease flares and within 15–20 years it progresses to liver cirrhosis. In its early stages, however, even over several years, it may go unnoticed. If, however, the laboratory parameters of cholestasis (AP, GGT) are elevated in the presence of unexplained upper abdominal complaints, stool irregularities, and especially soft stools, PSC with associated chronic bowel disease must always be suspected (table 13).

In rare cases (8–10%), patients with PSC may develop carcinoma of the bile ducts. The diagnosis of carcinoma of the biliary system is not easy. If this disease is suspected, every effort must be made to exclude it using all methods available, including blood tests, ERC (mentioned above), biopsy (tissue sample from the suspected region) and a brush biopsy of the suspicious area. The risk of cancer has already been discussed above.
Symptoms of PSC associated with ulcerative colitis or Crohn’s disease

- Abdominal pain
- Porridgy, watery, sometimes bloody diarrhea: 3–10 or more times daily
- Weight loss
- Conjunctivitis
- Joint complaints
- Open tracks at the end of the bowel (fistulas)
- Dough-like, red swellings of the legs (erythema nodosum)

For further details see table 11

Table 13
How does one treat PSC?

Drug treatment

Previous pilot studies with a low dose of ursodeoxycholic acid (UDCA, 10–15 mg/kg of body weight daily) have shown that UDCA positively influenced some laboratory data, but had no effect on liver histology or life expectancy. Since in a recent study a higher dose of UDCA was associated with unwanted negative results when compared to placebo, the “European Association for the Study of the Liver” (EASL) does not recommend the general use of UDCA in PSC. Unlike in PBC, combination regimens, e.g. of UDCA with prednisone or with azathioprine, have not been shown to be effective or have not yet been adequately tested. Details regarding the treatment of symptoms and associated health problems can be found in tables 6 and 7, where UDCA should be omitted. The treatment of PSC has neither a positive nor a negative effect on the associated bowel disease and vice-versa.

Endoscopic treatment

Since at present there is no medicamentous treatment which is able to re-open bile duct stenoses and strictures, for these patients endoscopic balloon dilatation is to be recommended. In endoscopic balloon dilatation, as in gastroscopy, an endoscope is passed through the mouth and advanced into the bowel to the site of the opening of the common bile duct. From here, a thin catheter is inserted into the bile duct. At the end of the catheter is a balloon, which can be expanded by injection of fluid (figure 5). This process widens the bile duct and areas of narrowing are expanded and made passable for bile
When endoscopic treatment was combined with UDCA in some patients, general condition, laboratory findings and life expectancy improved; but also these data have to be confirmed in future studies until combination treatment can be recommended for general use.

Figure 5: Typical situation in PSC with significant changes in both the intra- and extrahepatic bile duct system. The catheter has been advanced through the endoscope, but the balloon has not yet been inflated.
Liver transplantation

If, after sometimes many years, patients with PSC can no longer be effectively treated with drug and endoscopic therapy, liver transplantation is the last treatment option. Following transplantation, patients receive so-called immunosuppressants, as shown in table 14.

Treatment of associated inflammatory bowel disease

Patients with PSC who simultaneously suffer from Crohn’s disease of the small intestine are treated with a cortisone preparation, such as prednisolone, in the acute phase. Once the bowel disease has gone into remission, the cortisone is gradually withdrawn. If Crohn’s disease is restricted to the colon, patients can undergo long-term treatment with mesalazine (table 15). That mesalazine is able to prevent disease recurrence remains unclear.

If, as is much more common, PSC is associated with ulcerative colitis, treatment of an acute flare is like that in Crohn’s disease, but with the addition of mesalazine. Maintenance treatment for prophylaxis against a new disease flare also consists of mesalazine.

Table 14

**Immunosuppressive agents after liver transplantation**

- Cortisone preparations (e.g. prednisolone or prednisone)
- Cyclosporin A
- Tacrolimus
- Azathioprine
- Mycophenolate Mofetil
- Combination of the above medications
In Crohn’s disease, surgery is indicated only in the case of severe complications. Because Crohn’s disease may recur after surgery in another, previously unaffected segment of the bowel, it is advisable to postpone surgery as long as possible in order that patients do not develop a short-bowel syndrome.

If serious complications require surgery in patients with ulcerative colitis, however, the total removal of the colon (total colectomy) cures the disease. Naturally, one attempts to avoid this large operation, which is possible in most patients. Neither the medical nor the surgical treatment of the bowel disease appears to have any effect on the biliary disease.

Treatment must be flexible and tailored to the patient’s exact situation.

Table 15

<table>
<thead>
<tr>
<th>Treatment of inflammatory bowel diseases in patients with PSC</th>
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<tbody>
<tr>
<td>• Cortisone preparations in acute flares and in small bowel involvement</td>
</tr>
<tr>
<td>• Cortisone preparations are “tapered” over one year</td>
</tr>
<tr>
<td>• Mesalazine with colon involvement</td>
</tr>
<tr>
<td>• Reduced-dose mesalazine as maintenance therapy</td>
</tr>
<tr>
<td>• Combination of both drugs</td>
</tr>
<tr>
<td>• Local treatment with enemas and suppositories</td>
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<tr>
<td>• Surgery</td>
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</tbody>
</table>

Treatment must be carried out very carefully.
Is primary sclerosing cholangitis related to primary biliary cirrhosis or autoimmune hepatitis?

This question cannot yet be answered with certainty, although there are cases described in which chronic autoimmune hepatitis has transitioned to PSC or of patients with PSC or PBC who simultaneously had chronic autoimmune hepatitis. These data might cause one to postulate that PSC, PBC and chronic autoimmune hepatitis may somehow be related. Because our understanding of the possible relationships between these diseases is limited, we will not discuss them at this point.
Summary

- Primary sclerosing cholangitis (PSC) is a chronic inflammatory autoimmune disease of the liver.
- PSC leads to connective tissue encasement of the small and large bile ducts both within and outside the liver and gradually results in liver cirrhosis.
- PSC most commonly affects males.
- About 80–90% of patients also suffer from an inflammatory bowel disease (IBD: ulcerative colitis or Crohn’s disease)
- Bile duct carcinoma develops in about 10% of patients; patients also have a higher risk of cancer of the colon, pancreas and gallbladder.
- At present there is no medicamentous therapy for PSC. Although with a low dose of UDCA some positive results have been described, the limited data base does not yet allow a specific recommendation for the general use in PSC. A higher dose of UDCA was associated with unwanted reactions. Therefore, the only treatment option we have is endoscopic dilatation of bile duct strictures.
- When endoscopic treatment is not successful or the risk of complications exists, liver transplantation will become necessary.
- The success rate of liver transplantation is very good.
Further information for patients with liver and biliary diseases:

- Autoimmune Hepatitis (Bu83e)
  28 pages
  NEW

- A Guide for Patients with Liver Diseases including Guidelines for Nutrition (F80e)
  70 pages

- What you should know about gallstone treatment (Li82e)
  30 pages

These brochures can be ordered free of charge from Falk Foundation e.V. or the local Falk partner.

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