

Primary biliary  
cirrhosis (PBC)

Primary sclerosing  
cholangitis (PSC)



Publisher

FALK FOUNDATION e.V.



Leinenweberstr. 5  
Postfach 65 29  
79041 Freiburg  
Germany

© 2001 Falk Foundation e.V.  
All rights reserved.

Primary biliary  
cirrhosis (PBC)

Primary sclerosing  
cholangitis (PSC)

---

Author:  
Prof. Dr. U. Leuschner  
Zentrum der Inneren Medizin  
Medizinische Klinik II  
Klinikum der Universität  
Theodor-Stern-Kai 7  
D-60590 Frankfurt am Main  
Germany

2nd edition 2001

# Contents

<b>Primary biliary cirrhosis (PBC)</b> . . . . .	5
<b>What is primary biliary cirrhosis?</b> . . . . .	5
Frequency of the disease	
Stages of the disease	
<b>How to recognize primary biliary cirrhosis?</b>	9
<b>How is PBC diagnosed by the physician?</b> . .	10
Physical examination	
Laboratory tests	
Microscopic investigation of liver tissue (liver biopsy)	
<b>What do we know about the course of PBC?</b>	13
Accompanying rheumatic disorders	
Loss of bone mineral density (osteoporosis)	
Fatty stools (steatorrhea), vitamin deficiency	
Skin alterations	
Complications of complete liver cirrhosis (late stage IV of PBC)	
<b>How is PBC treated?</b> . . . . .	16
Medical therapy	
Results of therapy and side effects	
Treatment of osteoporosis, steatorrhea and vitamin deficiency	
Liver transplantation	
<b>Are there relations between PBC and chronic autoimmune hepatitis?</b> . . . . .	21
<b>Summary</b> . . . . .	22

---

<b>Primary sclerosing cholangitis (PSC)</b>	23
<b>What is primary sclerosing cholangitis?</b> . . . . .	23
Stages of the disease	
Differences between PSC and primary biliary cirrhosis (PBC)	
<b>How to recognize primary sclerosing cholangitis?</b> . . . . .	26
<b>How is PSC diagnosed by the physician?</b> . . . . .	27
Physical examination and ultrasound	
Laboratory tests	
Endoscopic retrograde cholangiography (ERC)	
Microscopic investigation of the liver tissue (liver biopsy)	
<b>What do we know about the course of PSC?</b>	30
<b>How is PSC treated?</b> . . . . .	31
Medical therapy	
Endoscopic therapy	
Liver transplantation	
Treatment of the concomitant inflammatory bowel disease	
<b>Are there relations between PSC and primary biliary cirrhosis or chronic autoimmune hepatitis?</b> . . . . .	35
<b>Summary</b> . . . . .	36

# Primary biliary cirrhosis (PBC)

## What is primary biliary cirrhosis?

Primary biliary cirrhosis (PBC) is a chronic and progressive liver disease. In the early stages PBC is unevenly distributed in the liver (patchy disease), in the late stages the complete liver is involved. PBC starts at the small bile ducts located in the liver (intrahepatic bile ducts), which are then destroyed in the course of the disease. Because, as a consequence, bile cannot be excreted into the gut, it is retained and accelerates liver damage. Since bile duct destruction is not caused by pus produced by white blood cells, the synonym for PBC is *nonsuppurative destructive cholangitis*. The name *primary biliary cirrhosis* originates from the times when diagnosis was established only in the late stages of the disease, i. e. in the cirrhotic stage. Although nowadays it is possible to diagnose PBC very early, the term primary biliary cirrhosis has not been abandoned because meanwhile it has become common. In the blood of patients with primary biliary cirrhosis typical proteins characterizing immunological reactions are found in high concentrations and the liver tissue reveals cells inducing so-called autoimmune reactions (a special type of inflammation). PBC, therefore, is an autoimmune, chronic inflammatory biliary liver disease in which specialized cells (lymphocytes) erroneously destroy the liver of the very organism (self-destruction).

### *Frequency of the disease*

The ratio between men and women is 1:9. PBC does not occur in children. PBC is seen in about 30/100.000 inhabitants or 90/100.000 women beyond 30 years of age. The number keeps rising.

---

Life expectancy of an untreated PBC patient is 12 years. Today the course of the disease can be prolonged by medical therapy. When liver transplantation becomes necessary, most of the patients can be cured.

### *Stages of the disease*

In PBC we have to differentiate between four stages (stage I–IV). At present it is unknown how long each of the four stages will last.

*Stage I:* In this stage inflammation is confined to the small intrahepatic bile ducts (nonsuppurative bile duct destruction) (Fig. 1) and the surrounding connective tissue (periportal inflammation). As already mentioned, destruction is performed by so-called immune competent cells which are able to destroy the biliary tree and later on the complete liver.

*Stage II:* In this stage besides bile duct destruction the number of small bile ducts is increased (bile duct proliferation). Inflammatory infiltrates in the surrounding of bile ducts and small blood vessels are dense and in some areas invade the neighbouring liver lobule (Fig. 2).

*Stage III:* Increasing numbers of bile ducts are being destroyed and occluded (bile duct rarification), again inflammatory cells invade the liver lobule and the amount of fibres, the so-called connective tissue is augmented (Fig. 3).

*Stage IV:* The amount of connective tissue has further increased and divides the liver tissue into areas of different size. So-called regeneration nodules of varied diameters will develop (Fig. 4). In this late stage of the disease destruction of the small bile ducts and inflammation is reduced or even ceases. Finally, the classical picture of liver cirrhosis (PBC) has developed.

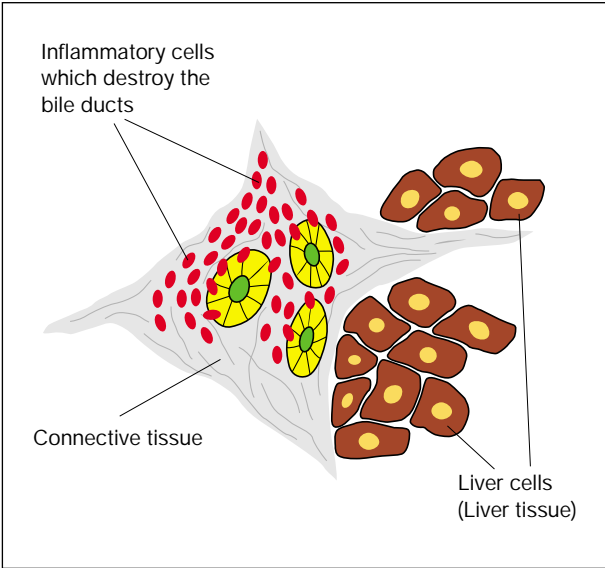


Figure 1: PBC stage I

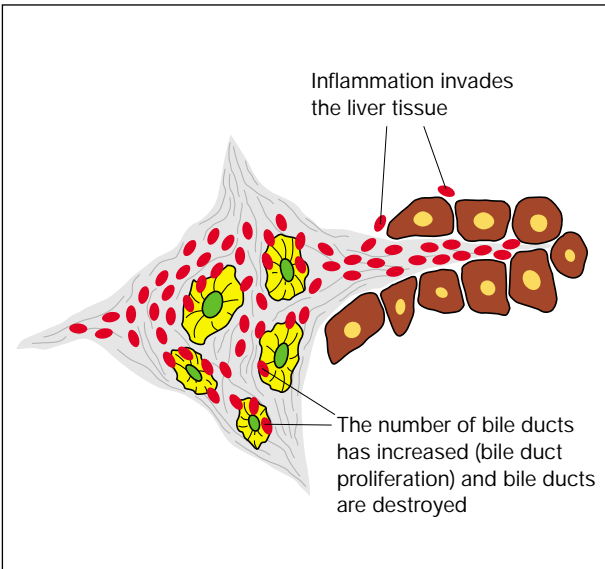


Figure 2: PBC stage II

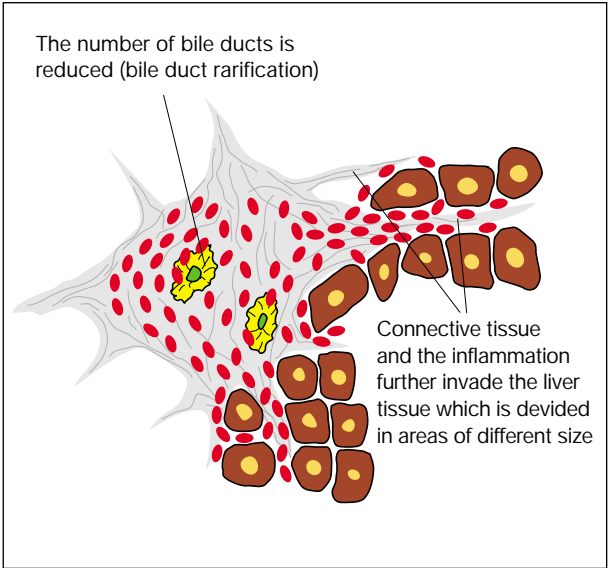


Figure 3: PBC stage III

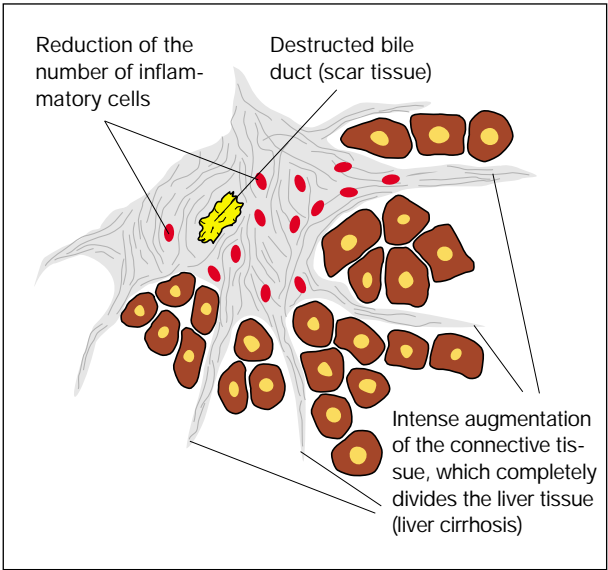


Figure 4: PBC stage IV

### How to recognize primary biliary cirrhosis?

One of the first symptoms of primary biliary cirrhosis may be a mild, stronger or even excessive itching, which occurs predominantly at night. This pruritus affects the arms, the back and the lower part of the legs. Further characteristic signs are cumbersome fatigue and a reduction of vitality (Table 1). In the course of progression of the disease yellow-greyish fat deposits (xanthelasma) can develop in the nasal area of the eye lids.

In some patients first diagnosis of PBC is established after pregnancy. In the last trimenon women suffered from cholestasis (so-called cholestasis of pregnancy) which disappeared spontaneously after delivery and returned a couple of weeks later accompanied by fatigue and pruritus. In these patients the recurrence of cholestasis is caused by PBC, as can easily be seen by the typical alterations of liver function tests and the blood proteins characterizing immunological reactions (see below).

Table 1

#### **Characteristics of primary biliary cirrhosis**

- Mainly women, seldom men
- Sometimes develops after pregnancy
- Itching (arms, legs, back)
- Fatigue
- Sometimes fat deposits in the nasal area of the eye lids

---

## How is PBC diagnosed by the physician?

Formerly the diagnosis of PBC was rather difficult. Since the correct diagnosis then was established only in late stages of the disease, it was called „primary biliary cirrhosis“. Today simple blood examinations permit an early diagnosis, usually in the stages I or II, which means long before the development of liver cirrhosis.

### *Physical examination*

In the early stages of the disease the physician is unable to find any characteristic alterations. Jaundiced eyes (icterus: increase of serum bilirubin) or jaundiced skin cannot be found, the liver is not enlarged. Ultrasonography shows a normal image of the liver or only minor alterations which may correlate with fatty liver, acute hepatitis or any other liver disease. In a later stage the liver can be enlarged and in the last stage signs of liver cirrhosis can be seen (Table 4). The ultrasound image shows the characteristic irregular surface of the organ.

### *Laboratory tests*

Characteristic alterations can be seen in the serum of the patients: in nearly 100 % the so-called antimitochondrial antibodies (AMA) are present. AMAs are circulating proteins (antibodies) directed against cell organelles of the energy threshold (mitochondria) of the liver cell. AMAs are not the cause of PBC, they do not reflect the severity of the disease, but as special markers they prove the existence of primary biliary cirrhosis (Table 2). Further, the typical markers for bile duct inflammation and cholestasis are increased in the serum: alkaline phosphatase (AP) and  $\gamma$ -glutamyl transpeptidase (GGT or  $\gamma$ -GT). Also typical for PBC is

an increase of another serum protein, the immunoglobulin M (IgM). When serum concentrations of these parameters are augmented and when a second investigation confirms the existence of AMAs, the diagnosis of PBC is certain even when the patient is without any symptoms. On the other hand, parameters indicating inflammation of the liver lobule (the so-called aminotransferases: alanine aminotransferase, ALT, aspartate aminotransferase, AST) are increased to a lesser degree. The explanation for this phenomenon is that PBC mainly is a disease of the biliary tree and not of the liver tissue.

In later stages of the disease (stage III and IV) laboratory parameters do not further change, but finally in the late stage of cirrhosis (stage IV) the total liver function deteriorates, which is best seen by the decrease of serum albumin concentrations and the blood clotting factors. Bilirubin (yellow colour of bile) increases in the blood and jaundice develops.

Table 2

### **Characteristic laboratory findings in PBC**

- Elevation of alkaline phosphatase (AP) and  $\gamma$ -glutamyl transpeptidase (GGT or  $\gamma$ -GT)
- Moderately increased transaminases AST and ALT
- Marked increase of immunoglobulin M (IgM)
- Antimitochondrial antibodies (AMA) in the serum

---

At that time ultrasound tomography may demonstrate an irregularly shaped liver surface, an altered blood supply of the liver, water in the abdominal cavity (ascites) and an enlarged spleen. Endoscopically esophageal varices can be diagnosed in the lower third of the esophagus.

Depending on the stage of the disease laboratory controls should be performed every three months, ultrasound tomography every 6–8 months.

*Microscopic investigation of liver tissue (liver biopsy)*

An ultrasound-guided liver biopsy is taken before onset of therapy to secure the diagnosis. At present it is discussed whether liver biopsy is necessary at all, because laboratory investigations are easy to perform and usually permit a correct diagnosis. Considering that life-long medical therapy is required and eventually liver transplantation has to be done there is more certainty when the diagnosis has been confirmed microscopically. Follow-up liver biopsies during the course of the disease are not necessary as a rule, except when liver cell carcinoma is suspected.

## What do we know about the course of PBC?

Early stages of the disease usually are asymptomatic. Itching (pruritus), which is characteristic for PBC, can be observed in some patients long before the correct diagnosis of PBC will be established. In other patients itching starts in the late stages, or not at all.

### *Accompanying rheumatic disorders*

In many patients PBC is accompanied by rheumatic alterations and complaints. In Hashimoto-thyreoiditis, which is also counted as rheumatic complication, antibodies against the thyroid gland exist and function of the gland slowly deteriorates. When secretion of other great glands (e.g. pancreas, salivatory glands) are progressively reduced, this phenomenon is called Sicca-syndrome (Table 3).

Table 3

### **Important concomitant alterations in PBC**

- Rheumatic alterations
  - Joint pain
  - Hashimoto-thyreoiditis
  - Sicca-syndrome
- Bone mineral loss (osteoporosis)
- Vitamin deficiency
- Skin alterations typical for liver cirrhosis (see Table 4)
- Liver cell carcinoma

---

### *Loss of bone mineral density (osteoporosis)*

Already at the beginning of the disease osteoporosis may develop. Since PBC is predominantly seen in women and women develop osteoporosis during menopause, it remains unclear whether PBC or menopause initiated bone mineral loss.

### *Fatty stools (steatorrhea), vitamin deficiency*

The so-called Sicca-syndrome reduces the secretion of fluids and of fat-cleaving enzymes of the pancreatic gland. This results in a reduced resorption of fat in the intestine and an excretion of fat via the stool (fatty stools: steatorrhea). Furthermore, since also bile acids are mandatory for the resorption of fat and fat-soluble vitamins (vitamin A, D, E and K), bile acid deficiency during cholestasis (biliary liver disease!) and the Sicca-syndrome together accelerate fatty stools and vitamin deficiency. Vitamin A deficiency may induce night blindness, vitamin D deficiency supports the development of osteoporosis and vitamin K deficiency may be followed by blood clotting disorders. In most PBC patients vitamin deficiency is not pronounced. Therefore, complications based on vitamin deficiency are rare and usually do not require treatment.

### *Skin alterations*

When PBC develops from early stages to late stage IV, typical alterations of the skin can be observed (Table 4). So-called spider naevi (dilatation of small blood vessels of the skin) are located on the arms, the chest and the back; the red colour of lip and tongue is intensified and seems to be darker (lacquer lips). The skin appears to be thinner, predominantly seen in the face and the forehead.

### *Complications of complete liver cirrhosis (late stage IV of PBC)*

When the liver tissue has changed to scar tissue the blood supply is heavily reduced and blood circulation bypasses the liver. Best-known bypasses are esophageal varices which may bleed. Hemorrhage from esophageal varices is one of the risk factors of final stage PBC. Water in the abdominal cavity (ascites) and a disturbance of the brain function (hepatic encephalopathy) will further complicate the disease. In about 3 % of the patients liver cell carcinoma will develop.

Table 4

#### **Typical findings in patients with complete liver cirrhosis (all types of cirrhosis, not only in patients with PBC or PSC)**

- Skin alterations
  - Dilated blood vessels of the skin (spider naevi)
  - Lacquer lips (red coloured lips)
  - Red tongue
  - Thin skin on forehead and face
- Water in the abdominal cavity (ascites)
- Swollen legs
- Blue patches of skin after trivial injuries
- Loss of hair of chest and belly
- Not seen by the patients:
  - Esophageal varices
  - Impaired brain function (encephalopathy)

---

## How is PBC treated?

Until 1985 we were unable to treat primary biliary cirrhosis. Nowadays medical therapy and liver transplantation are available.

### *Medical therapy*

Medical treatment starts immediately after establishing the diagnosis. Treatment is independent from the stage of the disease and any concomitant disease and consists of the intake of the bile acid ursodeoxycholic acid (UDCA). UDCA is a physiologically occurring bile acid found in small concentrations in human bile. The dosage of UDCA is 12–15 mg/kg body weight daily. Treatment should not be interrupted. Treatment interruption will induce severe rebound effects (Table 5). Recent investigations have shown that the combination of UDCA with glucocorticoids or the also immunosuppressive azathioprine may produce better results than UDCA alone; but further data have to be awaited until this combination therapy can be accepted as standard medication. Only when ursodeoxycholic acid monotherapy seems to be inefficient combination therapy UDCA/glucocorti-

Table 5

#### **Medical therapy of PBC**

- Ursodeoxycholic acid (UDCA):  
12–15 mg/kg daily
- Onset of therapy: immediately
- Treatment period: life-long or until liver transplantation
- When UDCA insufficient, combination with glucocorticoids and azathioprine recommended (at present under investigation)

coids or UDCA/glucocorticoids/azathioprine should be initiated already now.

### *Results of therapy and side effects*

In few cases ursodeoxycholic acid induces diarrhea, in most patients there are no side effects at all. Many patients have been treated over a period of 12–18 years without any therapy-related unwanted reactions.

During the first 6 months of treatment the liver enzymes  $\gamma$ -GT and GLDH decrease by 80%, later on AP and IgM by 30–60% and finally the inflammatory parameters AST and ALT. Only the concentrations of the antimitochondrial antibodies (AMAs) will not change. In about 30% of the patients with relatively low pretreatment liver function tests there will be complete normalization of liver biochemistries within 3–5 years (except AMAs), in 70% we see a significant improvement, but values do not normalize. As could be shown, UDCA therapy not only improves the laboratory data but also liver histology, prevents the development of esophageal varices and prolongs life expectancy.

Table 6

### **Treatment of itching (pruritus)**

- Ursodeoxycholic acid (UDCA)
- Colestyramine, or
- Opiate antagonists, or
- Combination of all three treatment options

---

The effect of UDCA on symptoms, such as fatigue or pruritus (Table 6) is discussed controversially. Treatment of fatigue and pruritus may be very difficult. Patience and endurance are expected from both the patient and the physician. Probably patients with less increased initial laboratory data (AP, GGT and normal bilirubin concentrations) respond better to UDCA therapy than those with high pretreatment findings.

*Treatment of osteoporosis, steatorrhea and vitamin deficiency*

Demineralization of the bones (osteoporosis) can be treated adequately. The administration of bisphosphonates in women with postmenopausal osteoporosis not only stopped the progression of osteoporosis but induced an increase of bone mineral density. This has not yet been shown for patients with primary biliary cirrhosis, but probably a similar effect can be expected. Therefore, bisphosphonates are also used in the treatment of patients with PBC. Treatment with vitamin D and calcium preparations seems to be less successful. Whether estrogens can be prescribed or not depends on the liver function tests and has to be decided by the physician. In any case patients with PBC should have a well-balanced mixed diet and should have regular work-out in fresh air (Table 7).

Table 7

**Treatment of bone mineral loss (osteoporosis)**

- Work-out in fresh air
- Well-balanced mixed diet
- Bisphosphonates and calcium
- Estrogens (women only)

Fatty stools (steatorrhea) are rare and can be treated successfully by reduction of the fat content in the diet to 40–50 g/day. If this is not sufficient, the usual enzyme containing drugs are added to the meals and should this measure fail the meals should be prepared with medium-chain triglycerides (MCT-Ceres). These triglycerides need not be cleaved by enzymes of the pancreatic gland and, therefore, can rapidly be absorbed by the intestine.

Should vitamin deficiency be accompanied by symptoms, regular injection with the fat soluble vitamins A, D, E and K are recommended. Since vitamin therapy is done intramuscularly, vitamins cannot be excreted with the fatty stools.

### *Liver transplantation*

Liver transplantation is indicated when liver function deteriorates rapidly, when unmanageable complications develop or a disabling pruritus persists even when treated. Liver transplantation is one of the most demanding surgical procedures in medicine, but the technique has been optimized and the results, there-

Table 8

#### **Immunosuppressants after liver transplantation**

- Glucocorticoids (e.g. prednisone or prednisolone)
- Cyclosporin A (CsA)
- Tacrolimus (FK506)
- Azathioprine
- Mycophenolate mofetil
- Combination therapies with the above mentioned drugs

---

fore, are excellent. Liver transplantation is followed by medical treatment with the aim to prevent transplant rejection. Drugs are listed in Table 8.

## **Are there relations between PBC and chronic autoimmune hepatitis?**

Indeed, in some patients with primary biliary cirrhosis laboratory data and histological alterations are similar to those found in patients with chronic autoimmune hepatitis. Occurrence of two different clearly marked liver diseases in one patient is called overlap-syndrome. Further, in a few patients diagnosis may change. After a flare-up of the disease, besides the typical signs of PBC, laboratory markers and a histological picture may develop resembling chronic autoimmune hepatitis.

For the patients with the so-called overlap-syndrome combination therapy with ursodeoxycholic acid (12–15 mg/kg body weight/day) and a glucocorticoid or even a triple therapy adding the immunosuppressant azathioprine may be helpful.

---

## Summary

- Primary biliary cirrhosis is a chronic inflammatory autoimmune liver disease.
- Inflammation starts at the small intrahepatic bile ducts, invades the liver lobule and eventually leads to liver cirrhosis.
- The mean life expectancy in untreated patients is 12 years.
- Since diagnostic procedures have improved today PBC can be diagnosed in an early stage of the disease.
- Medical treatment starts immediately after the diagnosis has been established, the treatment of choice is the administration of ursodeoxycholic acid. Therapy is a life-long one.
- Ursodeoxycholic acid improves laboratory tests, liver histology, delays the time until liver transplantation and prolongs life expectancy.
- Liver transplantation is necessary when medical treatment is not successful.
- The results of liver transplantation are excellent and are constantly improving.

# Primary sclerosing cholangitis (PSC)

## What is primary sclerosing cholangitis?

Primary sclerosing cholangitis (PSC) is a chronic inflammatory liver disease in which onion skin-like layers of connective tissue surround the intrahepatic and extrahepatic bile ducts. Later on, inflammation invades the liver tissue, the amount of connective tissue increases and bile ducts become obstructed. When bile duct obstruction and strictures are distributed all over the liver or when relevant stricture has developed in the extrahepatic biliary tree, jaundice (yellow eyes and skin: icterus) is visible. The final stage of primary sclerosing cholangitis is liver cirrhosis. Although PSC is an autoimmune disease of the liver there are no typical proteins (immune markers) found in the serum, but different types of so-called im-

Table 9

### Classification of primary sclerosing cholangitis (PSC)

Stage I	Inflammation Connective tissue around small bile ducts
Stage II	Inflammation invades the liver tissue Further increase of connective tissue around bile ducts
Stage III	Obliteration of bile ducts, irregularities in the biliary tree Increase of connective tissue, regeneration nodules (see page 6)
Stage IV	Complete biliary cirrhosis

---

mune-competent cells can be seen in the liver tissue. These cells (lymphocytes) are able to destroy the biliary tree and the liver lobule. Figures on the frequency of PSC are uncertain, but nowadays PSC is diagnosed more often than in previous years.

### *Stages of the disease*

In PSC we differentiate four stages (stage I–IV) of the disease (Table 9).

### *Differences between PSC and primary biliary cirrhosis (PBC)*

Primary sclerosing cholangitis differs from PBC apart from the already mentioned microscopical aspects of the liver tissue as follows: In patients with PSC bile duct alterations are found in the liver itself but also in the large common bile duct which drains bile from the liver into the small intestine (duodenum). The gallbladder is not affected

Another important difference between PBC and PSC is, that PSC is accompanied in 80–90% by an in-

Table 10

#### **Differences between PBC and PSC**

- PSC: Predominantly in men
- PSC: Sometimes in children and adolescents
- PSC: Bile duct damage inside and outside of the liver
- PSC: Antimitochondrial antibodies (AMA) absent
- PSC: In 80–90% accompanied by inflammatory bowel disease
- PSC: In 8% cancer of the bile ducts

inflammatory ulcerative bowel disease. In 10–15 % it is Crohn's disease, in 80–85 % it is an ulcerative colitis.

Another interesting aspect is that PSC can also be found in children and adolescents, while PBC has been observed in adults only. And finally, 80 % of patients with PSC are men, in contrast 90 % of patients with PBC are women (Table 10).

---

## How to recognize primary sclerosing cholangitis?

In most patients the course of PSC is more complicated than that of PBC. Malaise and fatigue are early symptoms, itching (pruritus) is frequent. Fever indicates an additional bacterial infection of the bile ducts. Short- or long-lasting jaundiced eyes and a sometimes transitory jaundice of the skin indicate bile duct occlusion (Table 11). Bile duct occlusion is caused by the inflammation itself, by scar tissue, bile sludge or bile duct stones, which can develop in the extremely altered biliary tree.

When PSC is accompanied by one of the inflammatory bowel diseases (ulcerative colitis, Crohn's disease), bowel movements, pain, diarrhea and loss of body weight can be observed. Usually the PSC accompanying bowel disease is not very pronounced and in many patients will only be diagnosed when the patient is questioned about stool alterations.

Furthermore, rheumatic alterations of the big joints and finally the classical symptoms of complete liver cirrhosis will develop (Table 4).

Table 11

### Symptoms and findings in PSC

- Fatigue
- Malaise
- Increased temperature and fever
- Itching (pruritus)
- Recurrent yellow eyes and yellow skin (jaundice)
- Joint pain
- Loss of body weight
- Pain in the upper abdomen\*
- Loose stools or diarrhea\*

---

\* when associated with inflammatory bowel disease

## How is PSC diagnosed by the physician?

### *Physical examination and ultrasound*

Physical examination in the early stages of the disease may be without any abnormalities. Later on, the liver can be slightly enlarged. Pain in the abdomen is found when the liver disease is accompanied by one of the inflammatory bowel diseases. Sometimes the physician is able to palpate different parts of the intestine which adhere together because of the severe inflammation or he hears rumbles and murmurs in the abdomen. Table 4 shows the abnormal findings in patients with final stage of the disease, i. e. liver cirrhosis.

In the early stages ultrasound will not be able to detect characteristic changes of the biliary tree, later on sacculations and strictures can be seen, in some patients even sludge or tiny bile duct stones in the irregularly shaped bile ducts.

### *Laboratory tests*

In PSC predominantly bile stasis (blockade) indicating enzymes, such as alkaline phosphatase (AP) and  $\gamma$ -glutamyl transpeptidase (GGT or  $\gamma$ -GT) are increased in the blood. Aminotransferases (alanine aminotransferase, ALT; aspartate aminotransferase, AST) are increased to a lesser extent. The increase of bilirubin in the blood depends on the extent of bile duct alterations. Antimitochondrial antibodies (AMA) in contrast to primary biliary cirrhosis (PBC) are absent. In addition, blood sedimentation rate and white blood cell count (which are a hint for an inflammation) may be increased. When the disease progresses to cirrhosis blood platelets (thrombocytes) needed for blood clotting are reduced because they are degrad-

---

ed in the spleen. Liver synthesis of serum proteins and blood clotting factors are impaired.

*Endoscopic retrograde cholangiography (ERC)*

The most important diagnostic measure is the radiological visualization of the biliary tree by an endoscopic procedure (endoscopic retrograde cholangiography, ERC). Like in endoscopy of the stomach, the endoscope is introduced via the mouth and the stomach into the small intestine (duodenum). Via the endoscope an X-ray contrast medium is instilled into the bile ducts. Already in the early stages of PSC, sacculations, strictures and irregularities can be detected. These alterations are typical for PSC so that the diagnosis can be established at first glance. PSC-like findings need to be differentiated only from inflammation in patients with AIDS, in a few patients after liver transplantation and after instillation of anti-cancer drugs into the common bile duct (Table 12). Since these aspects can be excluded merely by

Table 12

**Differential diagnosis of PSC due to the finding of endoscopic imaging of the biliary tree. Further differential diagnoses.**

- AIDS-cholangitis
- Local therapy with cytostatics
- Insufficient blood supply after liver transplantation

---

due to the clinical picture and laboratory data

- Primary biliary cirrhosis (PBC)
- Bile duct infections with bacteria
- Bile duct infections with parasites

questioning the patient, ERC is the method of choice in the diagnosis of primary sclerosing cholangitis.

### *Microscopic investigation of the liver tissue (liver biopsy)*

In most patients liver biopsy is not necessary. Because PSC requires life-long medical treatment and liver transplantation may become necessary in the future, most physicians believe that at least one biopsy for securing the diagnosis should be taken. Liver biopsy is carried out under ultrasound guidance with a thin needle in local anesthesia.

---

## What do we know about the course of PSC?

PSC is a chronic liver disease with intermittent phases of inflammation. In the beginning PSC may be without any remarkable symptoms and alterations for some years. When alkaline phosphatase and  $\gamma$ -glutamyl transpeptidase are increased, when discomfort in the upper abdomen occurs, when the stools become irregular and soft, the patient is suspected to have PSC, probably associated with chronic bowel disease. All symptoms can also originate from the accompanying chronic inflammatory bowel diseases (Table 13). The stage of PSC is not correlated to the stage and the course of the bowel disease.

In rare cases (8%) bile duct cancer can develop. Diagnosis of bile duct carcinoma is difficult. If malignancy is suspected, the following investigations have to be performed: blood tests, endoscopic retrograde cholangiography (ERC), biopsy of the suspicious area and brush cytology from the suspicious region.

Table 13

### **Symptoms and typical findings in patients with ulcerative colitis and Crohn's disease**

- Abdominal pain
- Loose, watery (diarrhea) or bloody stools: 3–10 times daily or more
- Loss of body weight
- Inflammation of the conjunctiva
- Joint pain
- Fistulae around the anus and in other places
- Focal reddened and warm swellings of legs (erythema nodosum)

### How is PSC treated?

#### *Medial therapy*

Basic treatment and therapy of choice is the administration of ursodeoxycholic acid (UDCA) in a dosis of 12–15 (or more) mg/kg body weight daily. UDCA can be given either three times per day with meals or in a single bedtime dose. Except for diarrhea in 2 % of the patients, UDCA is without any side effects. UDCA induces a decrease of the bile stasis indicating enzymes AP and GGT as well as of the inflammation parameters ALT and AST. In many patients serum bilirubin decreases and well-being increases. In contrast to PBC, combination therapies of UDCA and prednisone or prednisolone and azathioprine have not yet been tested. Details on the treatment of symptoms in concomitant diseases are given in Tables 6 and 7. Treatment of PSC has no influence at all on the concomitant bowel disease and vice-versa.

#### *Endoscopic therapy*

The drug ursodeoxycholic acid is unable to unplug strictures and stenoses in the biliary system. In these cases the combination of UDCA with the endoscopic balloon dilatation proved helpful. Via the endoscope located opposite the orifice of the common bile duct a balloon catheter is introduced into the biliary system and the balloon is placed into the strictured part of the bile duct. When the localization is correct the balloon is filled with air or water and dilates the stricture. When UDC therapy is combined with endoscopic balloon dilatation, life expectancy of treated patients is prolonged compared to a treatment group with UDCA monotherapy (Fig. 5).



Figure 5: Typical picture of PSC showing severe alterations of bile ducts outside the liver (common bile duct) and inside. The balloon catheter has been introduced into the common bile duct but the balloon is not yet filled with air or water.

### *Liver transplantation*

Liver transplantation is indicated when medical therapy (UDCA plus balloon dilatation) is unable to improve the situation or at least to keep it in a steady state. To prevent rejection of the transplant treatment with so-called immunosuppressants (Table 14) is necessary.

### *Treatment of the concomitant inflammatory bowel disease*

When PSC is accompanied by Crohn's disease in the small intestine, patients are treated with glucocorticoids, such as prednisolone or budesonide. When the disease improves (remission), the dosage is reduced slowly. When Crohn's disease is located in the large bowel (colon), long-term treatment with mesalazine will be necessary (Table 15). After remission mesalazine prevents flares of the inflammation.

When PSC is accompanied by ulcerative colitis, which is more frequently seen than with Crohn's disease, treatment is the same as in the acute-phase of Crohn's disease, but simultaneously to the immunosuppressants mesalazine is administered. To prevent

Table 14

#### **Immunosuppressants after liver transplantation**

- Glucocorticoids (e.g. prednisone or prednisolone)
- Cyclosporin A (CsA)
- Tacrolimus (FK506)
- Azathioprine
- Mycophenolate mofetil
- Combination therapies with the above mentioned drugs

---

a relapse following remission mesalazine is given as long-term treatment.

Crohn's disease needs surgery only in severe complications. Operation should be used with utmost reluctance because after surgery Crohn's disease may recur in a distant so far healthy section of the intestine.

When severe complications render surgery of ulcerative colitis necessary, total colectomy (which will be necessary only in a few patients) cures the disease. This is in contrast to surgery in patients with Crohn's disease. It is well understood that one tries to avoid this major surgery, which can be achieved in most patients.

Table 15

**Treatment of inflammatory bowel disease in patients with PSC**

- Glucocorticoids during the acute phase of the disease and when the small bowel is involved
- Tapering off of glucocorticoids during the following year
- Mesalazine when the large bowel (colon) is involved
- Mesalazine long-term treatment with reduced dose
- Combination of glucocorticoids and mesalazine
- Local treatment with enemas and suppositories
- Surgery

## **Are there relations between PSC and primary biliary cirrhosis or chronic autoimmune hepatitis?**

This question cannot be answered at present. In the literature only few cases have been described in which chronic autoimmune hepatitis changed to primary sclerosing cholangitis and on the other hand there are only few patients who primarily had PBC which changed to chronic autoimmune hepatitis. From these observations one could conclude that PSC, PBC and chronic autoimmune hepatitis belong together in a certain way, but since the relations between these chronic autoimmune liver diseases are not well understood, they will not be discussed in this booklet.

---

## Summary

- Primary sclerosing cholangitis is a chronic inflammatory autoimmune disease of the liver.
- PSC is characterized by inflammation and onion skin-layers of connective tissue around the biliary system, which finally leads to liver cirrhosis.
- PSC is mainly seen in men and seldom in women.
- In 80–90% PSC is accompanied by inflammatory bowel disease (ulcerative colitis, Crohn's disease).
- Bile duct carcinoma is seen in about 8% of the patients with PSC.
- PSC is treated with ursodeoxycholic acid. Treatment starts immediately after establishment of diagnosis. In combination with endoscopic balloon dilatation ursodeoxycholic acid prolongs life expectancy.
- When medical and endoscopic therapy are not successful, liver transplantation is recommended.
- The success rates of liver transplantation are very good.

---

## Further information for patients with liver diseases

- **Information for patients with liver diseases including guidelines for nutrition (F80e)**  
*67 pages*
- **Nature helps liver and biliary tract diseases (HP80e)**  
*32 pages*
- **Biliary stasis – what to do? (U80e)**  
*39 pages*

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

FALK FOUNDATION e.V.



Leinenweberstr. 5  
Postfach 65 29  
79041 Freiburg  
Germany

FALK FOUNDATION e.V.



Leinenweberstr. 5  
Postfach 65 29  
79041 Freiburg  
Germany

U82e 2-6/2001/5.000 Konk