

15.23.4 Primary sclerosing cholangitis 3135

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15.23.4 Primary sclerosing cholangitis 3135 meet the minimal listing criteria (United Kingdom Model for End- Stage Liver Disease score of 49 or greater) based on a combination of markers of disease severity including bilirubin, INR, creatinine, and sodium. Pruritus that is unresponsive to all conventional therapies (a so-called variant syndrome) is also an indication for transplantation in PBC, with very good outcomes. Fatigue is not an appropriate sole indication for transplantation as there is no symptomatic improvement after transplantation. Rising serum bilirubin correlates very well with poor survival and patients with PBC should be considered for transplantation when their bilirubin exceeds 50 $\mu\text{mol/litre}$. Once jaundice is present, clinical deterioration can be rapid, so early referral to a transplant centre is paramount. Recurrent PBC after transplantation occurs in approximately 20% of patients but rarely causes clinical problems. Liver biopsy is required for diagnosis given the frequency of raised alkaline phosphatase following transplantation and the persistence of characteristic autoantibodies. The role of UDCA after transplantation is yet to be defined. Prognosis following transplantation is very good in PBC. Prognosis/outcome Prognosis in PBC is variable. In most patients, typically presenting at older ages and showing a biochemical response to UDCA, the disease has a low impact with a small risk of progression to cirrhosis and only limited symptom impacts. Clinical assessment tools are currently being developed to aid the identification of such low-risk patients to facilitate their safe management in primary care. In up to 30% of patients, however, the disease is more aggressive and associated with a significant risk of progression. Risk is increased in patients presenting below the age of 50 and in those expressing PBC-specific ANA. Additional risk markers include inadequate biochemical response to UDCA, the presence of biochemical (low albumin and elevated bilirubin), haematological (low platelet count) features suggestive of pre-existing cirrhosis, and the presence of interface hepatitis on liver biopsy. Failure to meet UDCA response criteria should be an indication for stratified second-line therapeutic approaches, either as at present in the context of clinical trials, or in due course prescribed second-line therapeutics. In the uncommon patients with true autoimmune hepatitis overlap, both conditions should be treated. The ductopenic form of the condition has a poor prognosis due to aggressive cholestasis and typically needs transplantation. Complications Patients with PBC are at risk of the same complications of cirrhosis as seen in disease of other

aetiologies. Well-compensated cirrhotic patients can be difficult to recognize, but clinicians should be vigilant for synthetic liver dysfunction (rising bilirubin and falling albumin), evidence of portal hypertension (thrombocytopenia, splenomegaly, and/or varices), and radiological evidence of cirrhosis (including splenomegaly). Screening for hepatocellular carcinoma should be undertaken in cirrhotic patients in accordance with international guidelines (European Association for the Study of the Liver/European Organisation for Research and Treatment of Cancer and American Association for the Study of Liver Diseases): abdominal ultrasonography at 6-monthly intervals. α -Fetoprotein has recently been removed from international guidelines but is still widely used in clinical practice. All cirrhotic PBC patients require endoscopic screening for oesophagogastric varices. An initial screening endoscopy should be performed when the diagnosis of cirrhosis is made. If negative, patients with compensated cirrhosis should have further endoscopy every 2 to 3 years. If small varices are present, endoscopy should be repeated in 1 to 2 years. Patients with decompensated cirrhosis should have yearly endoscopy. Hepatic encephalopathy is unusual in PBC but if present should be treated using standard approaches. Uncertainties/controversies/future developments There are two areas of significant challenge in PBC at present. The first is how to recognize in a timely fashion and treat using stratified therapeutic approaches the typically younger patients with high-risk PBC, and then deliver those stratified approaches in normal practice in a disease where physician awareness is often limited. The second is how to treat the pervasive fatigue which is the predominant symptom of the condition and which is currently untreatable. FURTHER READING Dyson JK, et al. (2015). Novel therapeutic targets in primary biliary cirrhosis. *Nat Rev Gastroenterol Hepatol*, 12, 147–58. Dyson JK, et al. (2015). Unmet clinical need in autoimmune liver diseases. *J Hepatol*, 62, 208–18. European Association for the Study of the Liver (2009). EASL clinical practice guidelines: management of cholestatic liver diseases. *J Hepatol*, 51, 237–67. Gulamhusein AF, Hirschfield GM (2018). Best Pract Res Clin Gastroenterol, 34–35, 17–25. Harms MH, et al. (2018). Improving prognosis in primary biliary cholangitis—Therapeutic options and strategy. *Best Pract Res Clin Gastroenterol*, 34–35, 85–94. Lindor KD, et al. (2009). Primary biliary cirrhosis. *Hepatology*, 50, 291–308. Webb GJ, Siminovitch KA, Hirschfield GM (2015). The immunogenetics of primary biliary cirrhosis: a comprehensive review. *J Autoimmun*, 64, 42–52. 15.23.4 Primary sclerosing cholangitis Kate D. Lynch and Roger W. Chapman ESSENTIALS Primary sclerosing cholangitis is a chronic cholestatic liver disease caused by diffuse inflammation and fibrosis that can involve the entire biliary tree. The cause is unknown, but it is presumed to be

section 15 Gastroenterological disorders 3136 immune mediated, and there is a close association with inflammatory bowel disease, particularly ulcerative colitis. The disorder tends to affect men (male:female, 2:1), some presenting with fatigue, intermittent jaundice, weight loss, right upper quadrant pain, and pruritus, but many are asymptomatic at diagnosis, which is made incidentally when a persistently raised serum alkaline phosphatase is discovered, usually in the clinical setting of ulcerative colitis. Serum biochemical tests usually indicate cholestasis, but diagnosis is based on three criteria: (1) generalized beading and stenosis of the biliary system on cholangiography; (2) absence of choledocholithiasis or a history of bile duct surgery; and (3) exclusion of bile duct cancer, usually by prolonged follow-up. There is no curative medical treatment. Pruritus is initially managed with cholestyramine, with second-line treatments including rifampicin and naltrexone. Orthotopic liver transplantation is the only option available for young patients with advanced liver disease. Introduction Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease caused by diffuse inflammation and fibrosis that can involve the entire biliary tree. The

progressive pathological process obliterates intrahepatic and extrahepatic bile ducts, ultimately leading to biliary cirrhosis, portal hypertension, and hepatic failure. Cholangiocarcinoma develops in approximately 10% of patients. PSC was initially considered to be a rare disease, but the advent of endoscopic retrograde cholangiopancreatography (ERCP) in the early 1970s established the diagnosis in a progressively larger number of patients. This led to the realization that PSC has a much wider clinical and pathological spectrum than was previously recognized. Serum biochemical tests usually indicate cholestasis, but diagnosis is based on three criteria: (1) generalized beading and stenosis of the biliary system on cholangiography; (2) absence of choledocholithiasis or a history of bile duct surgery; and (3) exclusion of bile duct cancer, usually by prolonged follow-up.

Aetiopathogenesis The cause of PSC remains unknown. There is a very close association, however, between PSC and inflammatory bowel disease (IBD), particularly ulcerative colitis. Approximately two-thirds of northern European patients with PSC have coexisting ulcerative colitis, and PSC is the most common form of chronic liver disease found in ulcerative colitis. In southern Europeans, about one-half of patients with PSC will have ulcerative colitis. However, in Japan only 20% of patients will also have IBD. This difference in populations may be real or may represent differences in case finding as not all the patients studied had had colonoscopy and colonic biopsies performed. Approximately 3 to 10% of patients with ulcerative colitis will develop PSC, with greater risk associated with pancolitis as compared with only distal disease. Any proposed aetiopathogenic factor must explain the close association with IBD. Current evidence suggests that PSC is an immunologically mediated disease, probably triggered in genetically susceptible subjects by acquired toxic or infectious agents arising from the biome, which may then gain access through the 'leaky' diseased colon.

Immunogenetic factors Case reports of families in whom members developed ulcerative colitis and PSC led to the search for a human leucocyte antigen (HLA) association. A close link with the HLA A1-B8-DR3 haplotype has been found, in common with other organ-specific autoimmune diseases such as autoimmune chronic active hepatitis. Independent associations with HLA DR2 and DR6 have also been documented. HLA A1-B8-DR3, DR2, and DR6 are equally distributed in patients with PSC, with or without ulcerative colitis. It has been suggested that DR3, DR6, and DR2 encode for amino acids in the HLA β -chain that may enhance antigen presentation by the HLA molecule to the T-cell receptor. Further evidence of an immune-mediated basis for this condition has been provided by recent, large genome-wide association studies and Immunochip studies. These have both confirmed the HLA associations found in initial candidate gene studies and also a further 22 non-HLA risk loci have been identified, including FUT2 involved in regulating bacteria in the intestine and interleukin-2 loci and other genes found in other autoimmune diseases. These emphasize the importance of the acquired and innate immune responses and interaction with the biome in the pathogenesis of PSC.

Cellular immune abnormalities Elevated circulating immune complexes associated with activation of complement via the classic pathway have been found in the serum and bile of patients with PSC. In common with other autoimmune diseases there are reduced levels of T-regulatory cells circulating in the serum of these patients, leading to an increased ratio of T-helper to T-regulatory cells. Infiltration of portal tracts by increased numbers of mononuclear cells is seen in liver biopsies from patients with PSC, and most of these cells are activated T lymphocytes. Current evidence suggests that PSC is an immunologically mediated disease, perhaps triggered in genetically susceptible subjects by acquired toxic or infectious agents which are presented through antigen-presenting cells to activated T lymphocytes. Unlike normal biliary cells, the biliary epithelial cells in PSC express HLA class II molecules and also intercellular adhesion molecules (ICAM) such as ICAM-1. It has been suggested that the biliary disease is mediated by long-lived memory T cells derived

from the inflamed gut which enter the enterohepatic circulation, hence gaining access to the liver. Aberrant expression of gut homing chemokines (such as CCL25) and adhesion molecules (such as MAdCAM-1) on biliary cells cause recruitment of these gut-derived T cells to the liver, which in turn leads to biliary inflammation and damage. However, the reason ('trigger factor') for the aberrant bile duct expression is unknown. Alternative hypothesis—exposure to bacterial components An alternative hypothesis has been proposed in which the initial event is the reaction of an immunologically susceptible host to bacterial cell wall products, resulting in hepatic macrophages producing tumour necrosis factor- α and endotoxin. The exposure to bacterial components and increased gut permeability

15.23.4 Primary sclerosing cholangitis 3137 would be increased by the presence of IBD, but could also, in theory, occur during episodes of gut infection. The resulting increase in peribiliary cytokine and chemokine secretion would attract activated neutrophils, monocyte/macrophages, T cells, and fibroblasts. The deposition of concentric fibrosis could result in atrophy of the biliary epithelial cells secondary to ischaemia. The resulting bile duct loss would lead to progressive cholestasis, fibrosis, and secondary biliary cirrhosis. This hypothesis does not, however, explain the relative scarcity of patients with Crohn's colitis and PSC, and does not take into account the strong circumstantial evidence of immune mediation and autoimmunity, previously described.

Epidemiology The incidence and prevalence of PSC varies depending on geographic location. For unknown reasons, the prevalence appears to be higher in Europe the further north one lives, with some of the highest figures reported from cohorts in Scandinavia. In a Swedish study, the prevalence of ulcerative colitis was 171 per 100 000 population and that of PSC 6.3 per 100 000 population. A recent population study from New Zealand demonstrated a prevalence of PSC of 11.7 per 100 000, while studies from North America and South Wales have demonstrated a prevalence of 20 per 100 000 population in men. The incidence of PSC appears to be increasing, though whether this represents a true increase in incidence or a higher awareness/detection rate is unclear. There is a clear male predominance, with a male:female ratio of 2:1. Most patients present between the ages of 25 and 40 years, although PSC may be diagnosed at any age. Indeed, it is recognized as an important cause of chronic liver disease in children. Clinical features The clinical presentation is variable: some patients may present with fatigue, intermittent jaundice, weight loss, right upper quadrant pain, and pruritus. Attacks of acute cholangitis are surprisingly rare and usually follow instrumental biliary intervention, such as ERCP. Physical examination is abnormal in approximately one-half of symptomatic patients; the most common findings are jaundice and hepatosplenomegaly. Most patients with PSC are asymptomatic at diagnosis, which is made incidentally when a persistently raised serum alkaline phosphatase is discovered, usually in the clinical setting of ulcerative colitis. Later, as the disease progresses, portal hypertension is a prominent feature of liver decompensation, with the presence of ascites and oesophageal varices usually preceding the onset of liver synthetic dysfunction (such as hypoalbuminaemia and coagulopathy). Hyperbilirubinaemia/jaundice occurs with progression of liver disease, due to both cholestasis from strictures and liver synthetic dysfunction. Intermittent ascending cholangitis and development of cancer are features which can occur (see 'Malignancy'), and the sudden deterioration with jaundice, itching, and worsening liver enzymes should prompt investigation for complications. Differential diagnosis The term 'secondary sclerosing cholangitis' is used to describe the typical bile duct changes when a clear predisposing factor to duct fibrosis, such as previous bile duct surgery, can be identified, and these must be considered and excluded before a diagnosis of PSC is made. The causes of secondary sclerosing cholangitis are shown in Box

15.23.4.1. IgG4-related sclerosing cholangitis An important differential diagnosis to recognize and rule out is IgG4-related sclerosing cholangitis (IgG4-SC), which tends to induce a longer stenosis on cholangiography in contrast to the short stenosis of patients with PSC. At the time of diagnosis, it is therefore important to test for the subtypes of IgG, and in particular IgG4. IgG4-SC is a disorder characterized often (but not always) by raised serum IgG4 levels, involvement of other organs with IgG4-related disease (such as type 1 autoimmune pancreatitis), and characteristic findings on liver biopsy (fibroinflammatory involvement is observed mainly in the stroma of the bile duct wall, whereas the bile duct epithelium is intact). Raised serum IgG4 levels (>1.4 g/litre) are found in 7 to 22% of patients with PSC, as opposed to only 0 to 1% with other liver diseases/healthy controls. By itself, however, a raised serum IgG4 level is not sufficient to make the diagnosis of IgG4-SC. A recent study found that a serum IgG4 level of greater than four times the upper limit of normal had an excellent positive predictive value for differentiating IgG4-SC from PSC, but this only occurs in 42% of patients with IgG4-SC. Additionally, in the setting of a marginally raised IgG4 level (one to two times the upper limit of normal), an IgG4:IgG1 ratio of greater than 0.24 supports a diagnosis of IgG4-SC. It is important to diagnose IgG4-SC where present, as this has an excellent response to systemic corticosteroid therapy, unlike PSC. Interestingly, if the criteria are not met for a diagnosis of IgG4-SC, elevated serum IgG4 levels (>1.4 g/litre) confers a poorer prognosis in patients with PSC, the explanation for which is unknown.

Box 15.23.4.1 Causes of secondary sclerosing cholangitis

- Previous bile duct surgery with stricturing and cholangitis
- Bile duct stones causing cholangitis
- Intrahepatic infusion of 5-fluorodeoxyuridine
- Formalin insertion into hepatic hydatid cysts
- Alcohol insertion into hepatic tumours
- AIDS/immunodeficiency states—probably infective (chronic cytomegalovirus or cryptosporidial infection)
- IgG4-associated cholangitis
- Cholangiocarcinoma
- Diffuse intrahepatic metastasis
- Eosinophilic cholangitis
- Histiocytosis C
- Mast cell cholangiopathy
- Portal hypertensive biliopathy
- Recurrent pancreatitis

Adapted from American Association for Study of the Liver (AASLD) guidelines.

section 15 Gastroenterological disorders 3138 Clinical investigation A summary of investigations performed in the work up of PSC is shown in Box 15.23.4.2. Blood tests Serum biochemical tests usually indicate cholestasis, but PSC may cause no abnormalities of serum biochemistry. The serum alkaline phosphatase is often raised to more than three times normal, and mild elevations in liver transaminases are seen in most patients. Serum bilirubin is not usually elevated until later stages of the disease. Levels of bilirubin and alkaline phosphatase may fluctuate widely in an individual patient during the course of the disease. Hypoalbuminaemia is unusual until the disease becomes advanced. Like primary biliary cirrhosis, a disease with which it shares many features, symptomatic PSC is characterized by hypergammaglobulinaemia; high concentrations of serum IgM are found in patients with advanced disease, and high levels of IgG are found in all children with PSC. Smooth muscle antibody and antinuclear factor are also found in approximately one-third of patients with PSC, usually in low titres. Serum mitochondrial antibodies are absent. A cytoplasmic antineutrophil antibody is found in the serum of 80% of patients with PSC and approximately 30 to 40% of patients with ulcerative colitis. However, the antibody is not specific for PSC and is found in 50% of patients with autoimmune chronic active hepatitis (type 1). The antigen(s) are distinct from those found in granulomatosis with polyangiitis (previously known as Wegener's granulomatosis) and microscopic polyangiitis, which have been shown to be proteinase 3 and myeloperoxidase. Current evidence suggests that the antigen may be a nuclear envelope protein. The pathogenetic significance of the circulating antibody is not clear, and it is not clinically useful as a diagnostic test. Titres of the antibody do not change after hepatic transplantation.

Radiological features Magnetic resonance cholangiopancreatography (MRCP) provides a noninvasive method of imaging the biliary tree, and has become established as the standard technique for the diagnosis of PSC as there is a significant risk of cholangitis or acute pancreatitis after diagnostic ERCP. MRCP has a high sensitivity (86%) and very high specificity (94%) for diagnosing PSC. ERCP is reserved for the few patients in whom there is diagnostic uncertainty after MRCP. The cholangiographic appearances on MRCP and/or ERCP are usually diagnostic and consist of multiple, irregular stricturing and dilatation (beading of the intrahepatic and extrahepatic biliary ducts) (Figs. 15.23.4.1 and 15.23.4.2). In some patients, the involvement is localized to the intrahepatic system, and rarely only the extrahepatic bile ducts may be involved. Small diverticula are found along the common bile duct in about 20% of patients and are pathognomonic. Transabdominal ultrasonography should also be informed in the initial investigations to rule out choledocholithiasis.

Box 15.23.4.2 Investigations to perform at diagnosis of PSC

- Liver enzymes— γ -glutamyl transferase, alkaline phosphatase, alkaline transaminase
- Bilirubin
- Complete blood count
- IgG and IgM levels
- Antineutrophil cytoplasmic antibody
- Antinuclear antibody
- Smooth muscle antibody
- IgG1 and IgG4 levels
- Ultrasonography
- MRCP (with or without ERCP)
- Liver biopsy

a Liver biopsy is only indicated when MRCP/ERCP is normal and/or suspicion of overlap syndrome. Fig. 15.23.4.1 Endoscopic retrograde ERCP demonstrating diffuse stricturing and dilatation of the biliary tree. Fig. 15.23.4.2 MRCP with diffuse intrahepatic strictures indicating sclerosing cholangitis.

15.23.4 Primary sclerosing cholangitis 3139 **Liver biopsy** Liver biopsy is reserved for cases where there is a question of overlap with autoimmune hepatitis or the MRCP is normal (in which case the variant small duct PSC is considered—see ‘Prognosis’). It is important to note that PSC, pathologically, is a patchy, focal disease, and there is a risk that sampling at percutaneous liver biopsy may miss the diagnosis. The histological appearances on liver biopsy are only diagnostic for PSC in one-third of patients, although some form of biliary disease can usually be identified. The characteristic early features of PSC are periductular ‘onion skin’ fibrosis and inflammation, portal oedema, and bile ductular proliferation resulting in the expansion of the portal tracts (Fig. 15.23.4.3). Later, fibrosis spreads into the liver parenchyma to form fibrous septa, leading inevitably to biliary cirrhosis. As in primary biliary cirrhosis, with disease progression an obliterative cholangitis occurs, leading to complete replacement of the intralobular bile ducts by connective tissue—the so-called vanishing bile duct syndrome. In addition, piecemeal necrosis, copper-binding protein, cholestasis, and occasional portal phlebitis may be present. **Association with other diseases** Many diseases have been associated with PSC (Box 15.23.4.3). The most important association is with IBD, occurring in approximately 70% of patients. 70% of the IBD in PSC is due to ulcerative colitis, 15% due to Crohn’s disease, and 5% due to IBD-unspecified. Regardless of subtype, the IBD is usually a pancolitis, often with rectal sparing and mild involvement of the ileum, and is usually fairly mild to quiescent in nature with minimal to no symptoms. Given the fairly specific IBD phenotype in PSC, it is often postulated that the colitis associated with PSC may represent a distinct form of colitis, namely PSC/IBD with a distinct genetic background. This hypothesis has been strengthened by recent studies which have shown distinct genetic differences between ulcerative colitis and Crohn’s disease and PSC/IBD. Although the symptoms of ulcerative colitis usually develop before those of PSC, the onset of the latter may precede the symptoms of colitis by some years. The outcome of PSC is completely unrelated to the activity, severity, or clinical course of the colitis, and colectomy has no effect on the progression of the cholangitis. **Management** There is no curative medical treatment for PSC. This is indicated by

the plethora of medical, endoscopic, and surgical approaches that have been advocated. Treatment of cholestasis, complications, and specific disease processes may all be required in the management of an individual patient.

Symptomatic measures

Management of cholestasis A few PSC patients may be troubled by pruritus. This is best managed initially by the bile acid sequestrant, cholestyramine, administered orally. The dose should be increased until relief is obtained. Second-line treatments include rifampicin and the opioid antagonist naltrexone. Replacement of fat-soluble vitamins is necessary when patients become jaundiced. Metabolic bone disease (usually osteoporosis) is a common complication of advanced PSC. Calcium supplementation with vitamin D3 should be given prophylactically in jaundiced patients, and bisphosphonates considered in those with osteoporosis.

Management of complications Broad-spectrum antibiotics such as ciprofloxacin should be given for acute attacks of cholangitis. If cholangiography shows a well-defined obstruction to the main extrahepatic bile ducts, then mechanical relief must be considered. Balloon dilatation of the strictures performed at ERCP may prove useful in symptomatic patients with well-defined localized particularly 'main duct' strictures, and can lead to a striking improvement in symptoms and serum biochemistry. In a few patients, the best approach is to introduce a temporary prosthesis (stent) through the obstruction. This may be placed nonoperatively by the percutaneous transhepatic route or at ERCP. Another common complication is the development of small biliary stones (brown pigment) and biliary sludge, which can lead to a rapid clinical or biochemical deterioration. In these patients,

Fig. 15.23.4.3 The hepatic histological changes of early PSC showing a concentric (onion skin) fibrosis around the bile ducts. Long arrow, bile duct; short arrow, hepatic artery. Box 15.23.4.3

Diseases associated with primary sclerosing cholangitis • Ulcerative colitis • Crohn's colitis • Chronic pancreatitis • Retroperitoneal fibrosis • Riedel's struma • Autoimmune pancreatitis • Retro-orbital tumours • Sjögren's syndrome • Angioimmunoblastic lymphadenopathy • Histiocytosis X • Autoimmune haemolytic anaemia

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endoscopic sphincterotomy with extraction of the biliary debris can be beneficial. Specific treatment

Medical The medical treatment of PSC has included trials of corticosteroids, immunosuppressive drugs, synthetic bile acids, and antibiotics, either alone or in combination. The results have been universally disappointing, although assessment of treatment of this uncommon disease is difficult because the clinical course fluctuates, survival is variable, and some patients may remain asymptomatic for long periods of time. In general, corticosteroids are not indicated in PSC because clinical trials have not demonstrated efficacy. Moreover, there is evidence that, even in male patients, metabolic bone disease may be accelerated by corticosteroids. They should be reserved for the few patients who also exhibit features of autoimmune hepatitis (PSC/autoimmune overlap) confirmed on liver biopsy, or in those patients with IgG4-associated cholangitis. Ursodeoxycholic acid (UDCA) is a nonhepatotoxic hydrophilic bile acid which has been used widely for the treatment of cholestasis—it reduces levels of cholestatic liver enzymes. Doses of 15 to 20 mg/kg daily have been shown to improve liver blood tests and have shown a trend towards increased survival, though not to statistical significance. Unfortunately, in a large randomized controlled trial, while improvements were seen biochemically, high-dose UDCA (28–30 mg/kg) was shown to be associated with a worse clinical outcome (composite endpoint of death, liver transplantation, cirrhosis, oesophageal varices, or cholangiocarcinoma) compared with those on placebo. There is limited data which suggest that UDCA may lower the prevalence of colonic dysplasia and possibly cholangiocarcinoma, although this has not been shown in all studies. Current international

guidelines differ in their recommendations as to the use of ursodeoxycholic acid in PSC. While high-dose UDCA should never be prescribed, lower doses of 15 to 20 mg/kg appear to be safe in clinical trials, and are associated with a greater proportion of patients having normalization of alkaline phosphatase compared with placebo. A firm recommendation regarding UDCA use in PSC cannot be made, and practice varies among different centres and countries. Transplantation Liver transplantation is the only management option available in patients with end-stage PSC and decompensated liver disease, and PSC is in the top five most common indications for this procedure in the United Kingdom and United States of America. Recent results have been very encouraging, with 5-year survival rates of 75 to 90% being obtained in most centres, comparing favourably with those for other forms of chronic liver disease. PSC recurs in the transplanted liver in 30% of patients at 5 years after transplantation, and in a few patients recurrence has led to problems with liver decompensation, requiring retransplantation. It has been shown recently that graft survival is optimized if patients have previously had a colectomy with end ileostomy. Furthermore, in patients with a colectomy and ileal pouch anal anastomosis, graft survival was reduced, indicating a potential role for the microbiota in the setting of graft survival in PSC. Proven cholangiocarcinoma is a contradiction to transplantation because the tumour recurs rapidly after transplantation with immunosuppression, although there are a few centres in the United States of America and Europe who transplant highly selected cases after neoadjuvant chemotherapy with reasonable outcomes. Prognosis and complications The course of PSC is highly variable and unpredictable. The median survival from presentation to death or liver transplantation in symptomatic patients was previously quoted as approximately 10 to 12 years; however, these data were from transplant-centre cohorts of patients with PSC and subsequent epidemiological observational studies incorporating non-liver transplant centres suggest a longer median survival of 22 years. In the past, most patients died of hepatic failure following deepening cholestatic jaundice, but with the advent of successful liver transplantation the majority of patients die of malignancy, either hepatobiliary or colonic. Large epidemiological studies, predominantly retrospective, have identified various features which convey a poorer clinical outcome. These include a persistently raised alkaline phosphatase above 1.5 times the upper limit of normal; raised bilirubin; the presence of a dominant stricture; older age at diagnosis; and the presence of ulcerative colitis (as opposed to Crohn's disease). Gender and the presence or not of IBD have not been associated with transplant-free survival. Several prognostic risk scores encompassing some of these factors have been put forward, including the Mayo Risk Score, the Amsterdam-Oxford Model for PSC, and the UK-PSC Risk Score. Whilst these are mainly used in the clinical trial setting, they may be useful in risk stratifying patients in clinical practice, and identifying patients who should be put forward for clinical trials of new therapeutic agents in PSC. Malignancy About 7 to 13% of patients with long-standing PSC develop cholangiocarcinoma, which usually follows a very aggressive course, with mean survival after the diagnosis of cholangiocarcinoma of only 9 months. Unfortunately, there are no factors that will predict which patients will develop this cancer. Tumour markers such as carcinoembryonic antigen and carbohydrate antigen 19-9 have not proven to be useful as potential early serum markers of the development of bile duct cancer in PSC. Annual MRCP examinations have been advocated as surveillance in PSC, but clinical evidence of effectiveness is lacking. Patients are also at increased risk of developing gallbladder cancer and hepatocellular carcinoma, and annual transabdominal ultrasound surveillance is recommended, with cholecystectomy should gallbladder polyps be present, particularly those greater than 0.8 cm in size. Patients with PSC and IBD are at greater risk of developing colorectal dysplasia and colonic cancer than those with ulcerative colitis alone. In a Swedish study, the absolute accumulative risk

of developing colorectal dysplasia/cancer in the PSC/ulcerative colitis group was 9%, 31%, and 50%, respectively, after 10, 20, and 25 years of disease duration. In the group with ulcerative colitis alone, the corresponding

15.23.4 Primary sclerosing cholangitis 3141 risk was 2%, 5%, and 10%, respectively. Several studies suggest the increased risk of colorectal cancer is only in those PSC patients with ulcerative colitis, and not those with Crohn's disease. Colorectal cancer in patients with PSC predominates in the right colon. Liver transplantation does not reduce the risk of colorectal neoplasia and may increase it because of the need for long-term immunosuppression. Guidelines recommend that patients with PSC and concomitant colitis (regardless of subtype) should have annual surveillance colonoscopies for early detection and prevention of colorectal dysplasia and carcinoma. Special circumstances—small duct PSC A variant of the disease called 'small duct PSC' is applied to the approximately 10% of patients with characteristic clinical and histological findings but who have normal cholangiography. These patients usually present with abnormal cholestatic biochemical tests in the context of IBD. The absence of macroscopic cholangiographic abnormalities necessitates liver biopsy for the diagnosis of small duct PSC. Their prognosis is very good, with no reports of malignancy in this group, and progression to advanced liver disease is rare. Median survival is 29.5 years compared to 10 to 22 years for classical PSC. However, 20 to 25% of patients with small duct PSC may progress to classical PSC over time, which then confers the usual prognosis outlined earlier. Patients with small duct PSC should be monitored for any deterioration (such as a sudden rise in alkaline phosphatase or bilirubin concentration, or new symptoms), which should prompt repeat imaging of bile ducts. Areas of uncertainty, controversy and future developments There are a range of new medical therapies being trialled in PSC with some preliminary beneficial results in Phase II trials. These include the novel bile acid nor-UDCA as well as the FXR agonist, obeticholic acid. Further phase III trials are awaited. Anti-fibrotic therapies are in development for PSC, although the recent trial of an anti-lysyl oxidase like 2 agent failed to reach its primary endpoint. There is some evidence, particularly in children, that antibiotics may be beneficial in PSC, and trials are ongoing, mostly with vancomycin. Distinct intestinal microbiome signatures have been identified in PSC compared with controls, though with differing findings among several studies. This has led to the hypothesis that faecal microbiota transplantation would be beneficial in PSC, and a case report demonstrating this has been published. Prospective clinical trials are awaited. Whilst not currently in routine clinical practice, there is increasing evidence for the use of noninvasive markers of fibrosis as a predictor of clinical outcome. With regards to transient elastography (TE), a cut-off value of >9.9kPa has been associated with worse survival in PSC, and there is a current ongoing prospective clinical trial further evaluating TE as a meaningful prognostic tool. Meanwhile, there is also evidence for the serum biomarker panel, European Liver Fibrosis (ELF) test, for predicting clinical outcomes in PSC. Further validation trials are awaited. However, there is some evidence that if a patient with PSC has normalization of their serum alkaline phosphatase, or reduction to less than 1.5 times the upper limit of normal, they will have a better outcome than if it remains persistently elevated, as measured by clinical endpoints of development of cholangiocarcinoma, liver transplantation, and/or death. There is an urgent need for surrogate markers in PSC which will accurately reflect long-term prognosis in assessing clinical trials of therapy. FURTHER READING Al Mamari S, et al. (2013). Improvement of serum alkaline phosphatase to <1.5 upper limit of normal predicts better outcome and reduced risk of cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol*, 58, 329–34. Björnsson E, et al. (2002). Patients with small duct primary sclerosing cholangitis have a favourable long term prognosis. *Gut*, 51, 731–5. Chapman RW, Williamson KD (2017). Are dominant strictures in pri-

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