Primary sclerosing cholangitis

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Primary sclerosing cholangitis is a rare, chronic cholestatic liver disease characterised by intrahepatic or extrahepatic stricturing, or both, with bile duct fibrosis. Inflammation and fibrosis of bile ducts and the liver are followed by impaired bile formation or flow and progressive liver dysfunction. Patients might be asymptomatic at presentation or might have pruritus, fatigue, right upper quadrant pain, recurrent cholangitis, or sequelae of portal hypertension. The key diagnostic elements are cholestatic liver biochemistry and bile duct stricturing on cholangiography. Genetic and environmental factors are important in the cause of the disease, with the intestinal microbiome increasingly thought to play a pathogenetic role. Approximately 70% of patients have concurrent inflammatory bowel disease and patients require colonoscopic screening and surveillance. Primary sclerosing cholangitis is associated with increased malignancy risk and surveillance strategies for early cholangiocarcinoma detection are limited. No single drug has been proven to improve transplant-free survival. Liver transplantation is effective for advanced disease but at least 25% of patients develop recurrent disease in the graft.

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Clinical presentation

Primary sclerosing cholangitis is a chronic cholestatic liver disease characterised by intrahepatic or extrahepatic (or both) bile duct injury. Clinical presentations reflect the underlying sequence of bile duct injury and fibrosis leading to stricturing, cholestasis, and biliary cirrhosis with progressive liver dysfunction. Primary sclerosing cholangitis is increasingly diagnosed early in the disease course, although this early diagnosis has yet to lead to improved outcomes.

Patients might present with cholestasis (elevation in alkaline phosphatase and γ-glutamyl transferase) after either screening in at-risk patients (typically with inflammatory bowel disease) or general health screening. Alternatively, particularly in patients with inflammatory bowel disease, primary sclerosing cholangitis can be identified through the presence of compatible cholangiographic features even in patients with normal serum biochemistry.[1,2] However, false-positive magnetic resonance cholangiopancreatography (MRCP) findings in this asymptomatic and biochemically normal population might also occur, leaving uncertainty as to the value of MRCP screening in asymptomatic patients with inflammatory bowel disease.

Progressive symptoms, including fatigue, pruritus, and right upper quadrant pain, can develop as the disease progresses. Cholestatic itch can occur in isolation or accompany jaundice. Prolonged cholestasis can lead to fat-soluble vitamin deficiency. Fatigue, autonomic dysfunction, and sleep disturbance can be features of the disease at any stage, whereas hepatic encephalopathy only occurs in advanced stages. Fatigue is typically less common in primary sclerosing cholangitis than in primary biliary cholangitis,[3] and it appears to be worst in patients with intercurrent inflammatory bowel disease. Primary sclerosing cholangitis can be complicated by associated diseases (eg, inflammatory bowel disease, arthropathies, other immune-mediated disorders with shared susceptibility).

Presentation can be with variceal bleeding, ascites, or encephalopathy after progression of occult primary sclerosing cholangitis to end-stage liver disease. Ascites and encephalopathy are less prominent than in hepatitic diseases until late in the disease course. No specific features reliably distinguish primary sclerosing cholangitis from other causes of end-stage disease. Jaundice is a sign of advanced stricturing (typically extrahepatic) and late-stage disease, and it is associated with urine and stool colour changes and can fluctuate in severity. Rapid worsening of cholestatic signs and symptoms should raise concern about cholangiocarcinoma, a complication of primary sclerosing cholangitis. Bacterial cholangitis can complicate stricturing disease and present with pyrexia and rigors. More subtle presentations of cholangitis include non-pyrexial worsening of jaundice and confusion in older people.

Differential diagnosis

The diagnosis of primary sclerosing cholangitis is made according to guidelines published by the European Association for the Study of the Liver,[4] the American Association for the Study of Liver Diseases,[5] and the American College of Gastroenterology.[6] Key aspects are elevated serum markers of cholestasis and bile duct lesions or stricturing on cholangiography, now mainly detected with the use of MRCP, along with compatible

Search strategy and selection criteria

We did a comprehensive search for relevant literature using the relevant health and social care databases (PubMed and other relevant online resources) and meeting records for the past 5 years for the appropriate scientific and clinical meetings. We searched unpublished trial data, on ClinicalTrials.gov, that used the relevant international trial registries. The search terms we used were "primary sclerosing cholangitis", "PSC", "liver cirrhosis", "biliary", "cholangitis", "cholangiocarcinoma", "cholangiopathy", "cholangiography", "biliary epithelial cell", "bile duct", "bile acid", and "cholestasis". Papers in English were selected and no date restrictions were applied to our search.
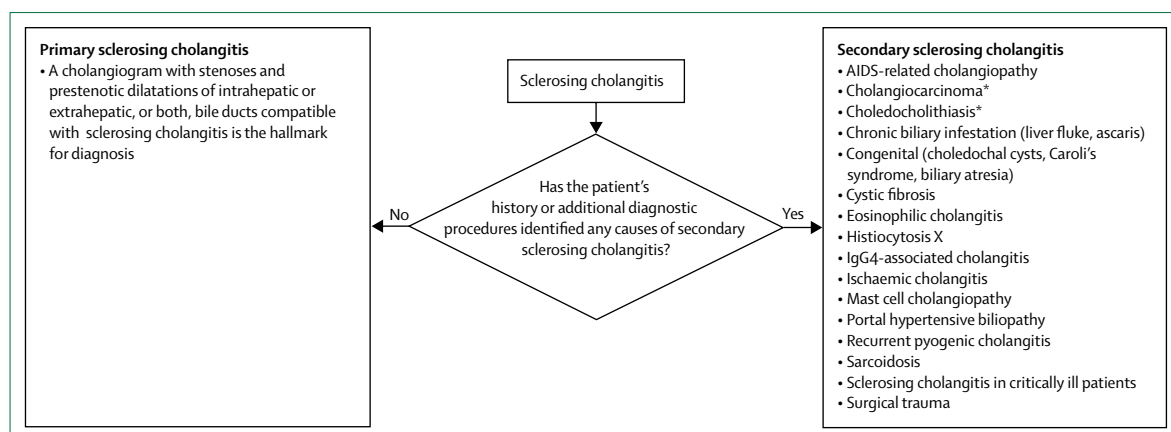
Figure 1: Differential diagnoses for cholangiographic changes that can mimic primary sclerosing cholangitis
*Might be a consequence of primary sclerosing cholangitis.

liver biopsy findings if done. Various forms of secondary sclerosing cholangitis can mimic primary sclerosing cholangitis and constitute important differential diagnoses (figure 1).[4,6,7] Primary biliary cholangitis and autoimmune hepatitis can be differentiated histologically. ABCB4 deficiency can also cause the so-called onion-skin fibrosis of small intrahepatic bile ductules that is classically seen in primary sclerosing cholangitis.

A subgroup of children with primary sclerosing cholangitis present with biochemical (markedly elevated transaminases and IgG), serological (characteristic autoantibodies), and histological features typical for autoimmune hepatitis.[8,9] There is no consensus on the nomenclature of this condition (primary sclerosing cholangitis–autoimmune hepatitis overlap syndrome,[4,10] primary sclerosing cholangitis with features of autoimmune hepatitis,[11] autoimmune sclerosing cholangitis[10,11]), but the diagnosis is of clinical relevance because the autoimmune hepatitis component is usually responsive to steroids and patients might benefit from long-term immunosuppression.[12,13] In adults, primary sclerosing cholangitis with features of autoimmune hepatitis is rare, with series reporting[11] a prevalence of 7–14%, and has a worse prognosis than classic autoimmune hepatitis but better prognosis than classic primary sclerosing cholangitis.[14]

The biliary manifestation of IgG4-related disease, IgG4-associated cholangitis, might also mimic primary sclerosing cholangitis.[15] IgG4-related disease is a systemic fibroinflammatory disease[16] with tumour-like swelling of involved organs, a lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, variable degrees of storiform fibrosis, obliterative phlebitis, and often elevated serum IgG4 concentration.[17] IgG4-associated cholangitis can result in marked biliary stricturing with associated autoimmune pancreatitis in over 70% of cases.[18,19] Primary sclerosing cholangitis and IgG4-associated cholangitis are difficult to distinguish between using cholangiography alone.[20] Although both diseases classically affect men, primary

sclerosing cholangitis often occurs in a younger age group than IgG4-associated cholangitis.[18] The prevalence of inflammatory bowel disease is much lower in IgG4-associated cholangitis (5%) than in primary sclerosing cholangitis (70%).[21] IgG4-related disease should be recognised as a separate disease to primary sclerosing cholangitis because biliary stricturing tends to respond well to first-line treatment with corticosteroids.[22]

Primary sclerosing cholangitis needs to be distinguished from secondary sclerosing cholangitis, which might occur after repeated bacterial cholangitis secondary to surgical interventions to the bile ducts or to inherited malformations. Secondary sclerosing cholangitis after intensive care management of critically ill patients and non-anastomotic strictures after liver transplantation are presumably caused by arterial hypoperfusion of the biliary tree.

Epidemiology and prognosis

The prevalence of primary sclerosing cholangitis is up to 16·2 per 100 000 population, being highest in northern Europe and markedly lower in Asia.[23–27] With a prevalence of less than 50 per 100 000, primary sclerosing cholangitis meets the criteria for a rare disease, which brings advantages in drug development through eligibility for orphan status (unless the drug is approved for a more common disease). Primary sclerosing cholangitis is more common in men (65–70%)[24,28] and is most often diagnosed between the ages of 30 and 40 years.[24,28,29]

In a population-based primary sclerosing cholangitis study[24] from the Netherlands, the median survival from diagnosis until liver transplantation or primary sclerosing cholangitis-related death was 21·3 years compared with survival in a combined transplant centres primary sclerosing cholangitis cohort of 13·2 years (p<0·0001).[24] This difference might be due to referral bias with more seriously ill patients in tertiary centres. Notably, 92% of the patients from the population-based Dutch study[24] were given ursodeoxycholic acid.
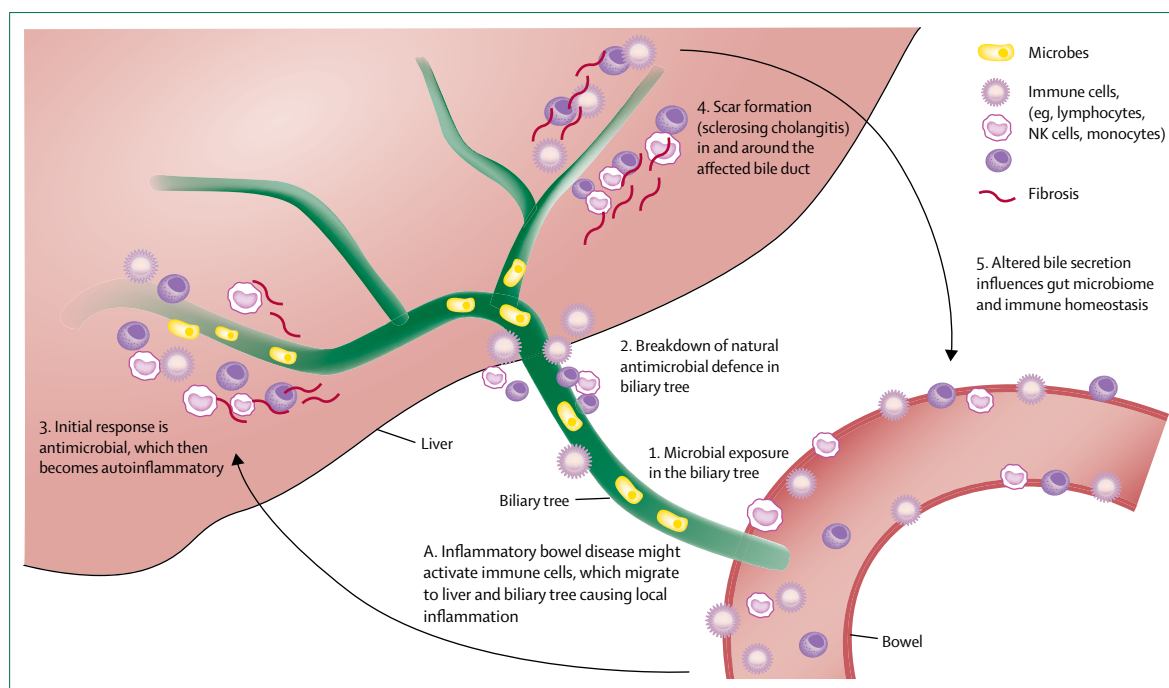
Figure 2: Possible pathogenesis of primary sclerosing cholangitis
Genetic susceptibility and environmental, possibly dietary, factors contribute to pathogenesis, which are not depicted in this figure. A=alternative or additional hypothesis for initiation of the peribiliary inflammatory process. NK=natural killer.

Risk factors and genetics

Primary sclerosing cholangitis is an archetypal complex disease with both genetic and environmental causes. A genome-wide association study[30] (GWAS) of large cohorts has shown a strong association with HLA that is more than 1000 times stronger than any other genetic association.[31] HLA and minor genetic associations detected in the GWAS analyses support a pathogenetic role for T cells.[31,32] The largest GWAS in primary sclerosing cholangitis to date confirmed at least 23 regions of the genome to be associated with disease risk.[33] Despite the marked genetic associations, primary sclerosing cholangitis is only rarely a familial disease. The hazard ratio[34] for a first degree relative to also be affected by primary sclerosing cholangitis is approximately 11. Therefore, environmental factors must also play a major role in disease pathogenesis.

To date, no definitive causal environmental factors have been identified, with no known triggers of disease manifestations. One clue to environmental factors might come from the geographical distribution of the disease with its predominance in northern Europe.[35] Differences in lifestyle, diet, and living conditions are all regionally distributed. Microbial exposure might also play a role in shaping the immune repertoire, particularly during childhood, as a direct infectious disease trigger, or in differences in the intestinal microbiome. Breaking of tolerance to a biliary microbiome might, therefore, be an attractive hypothesis for an immune pathogenesis of primary sclerosing cholangitis (figure 2). Intestinal dysbiosis described in patients with primary sclerosing cholangitis both with and without inflammatory bowel disease, and independent of treatment with urso-deoxycholic acid, supports such a hypothesis,[36] as does demonstration of microbial antigens in liver biopsy samples from patients with this disease, growth of bacteria and fungi from bile cultures taken at initial endo-scopic retrograde cholangiopancreatography (ERCP), and increased T-cell response to microbial antigens.[37]

Inflammatory bowel disease, present in 70% of patients with primary sclerosing cholangitis, is the strongest clinical risk factor for primary sclerosing cholangitis.[38–40] In turn, 5–10% of patients with colitis show or develop primary sclerosing cholangitis. Notably, GWAS analyses disclosed that ulcerative colitis and Crohn's disease were genetically more similar to each other than to primary sclerosing cholangitis, strengthening the argument that primary sclerosing cholangitis-associated inflammatory bowel disease represents a disease entity of its own.[33,41] This argument fits with the clinical observation that primary sclerosing cholangitis-associated inflammatory bowel disease is different from ulcerative colitis and Crohn's disease, frequently showing rectal sparing, right-sided colitis, and (backwash) ileitis but no transmural inflammatory lesions and no fistulae.[42] Even though inflammatory bowel disease and primary sclerosing cholangitis frequently occur in the same patient, temporal association between these two diseases is unusual and unpredictable. To what extent migration of immune cells activated in the large bowel might trigger or contribute to

biliary inflammation is subject to intense study and is an attractive hypothesis for disease pathogenesis.

Pathophysiology

Primary sclerosing cholangitis is characterised by the interplay of inflammation, fibrosis, and cholestasis. The typical fibrosing cholangitis with irregular narrowing and scarring of the biliary tree is probably, in light of genetic associations, immune-mediated and triggered by HLA-restricted T cells leading to release of profibrogenic cytokines (eg, transforming growth factor β). To what extent other immune cells, such as natural killer cells and natural killer T cells, play a role is largely unknown. Inflammation and fibrosis lead to cholestasis and parenchymal injury. Biliary obstruction might facilitate cholangitis. Although primary sclerosing cholangitis in its early stages might be mainly autoimmune mediated, superinfection may represent an important factor for disease progression.[43] Therefore, treating superinfection aggressively and dilating dominant strictures are likely to be effective treatment approaches, particularly in advanced disease.

Cholestasis can become self-sustaining, with the toxic biliary milieu leading to a cycle of progressive injury. The importance of the cholestatic process is indicated by the putative primary sclerosing cholangitis susceptibility genes encoding the apical bile salt receptor TGR5 (also known as *GPBAR1*) and the glycocalyx stabilising enzyme fucosyltransferase 2 (*FUT2*),[30,44] which result in protection of cholangiocytes against potentially toxic bile acids such as glycochenodeoxycholic acid. Cholangiocytes are exposed to bile salt monomers at millimolar concentrations about 1000 times higher than other cells in the body. A so-called alkaline biliary bicarbonate umbrella (figure 3) on the cell surface might keep bile salt molecules in a negatively loaded state preventing protonation and uncontrolled invasion of apolar bile acids into the cholangiocytes with subsequent cell damage and death.[45,46] Additionally, adequate secretion of intracellular bicarbonate protects cholangiocytes from apoptosis that is induced by bile salts, sensitive to bicarbonate, and dependent on soluble adenylate cyclase.[47] TGR5 senses hydrophobic bile salt concentrations and stimulates chloride and bicarbonate secretion thereby stabilising the biliary bicarbonate umbrella. FUT2 is relevant for a stable glycocalyx, a key element of the biliary bicarbonate umbrella in cholangiocytes.[48] Dysfunctional variants of TGR5[30] and FUT2[44] could contribute to the development of a chronic fibrosing cholangiopathy.[45]

Primary sclerosing cholangitis is typically heterogeneous. Particularly in children, the disease can start as a subacute inflammatory hepatitis mimicking autoimmune hepatitis. Therefore, children with autoimmune hepatitis, and all adults with autoimmune hepatitis and cholestatic laboratory features, should undergo MRCP.[4] In most adult patients, hepatitis is mild and the characteristic sclerosing biliary lesions show no evidence of an active autoimmune response.

Portal hypertension is a feature of advanced primary sclerosing cholangitis but may develop before impairment of liver function or cirrhosis is seen.[49,50] Precirrhotic portal hypertension might be induced by biliary scarring leading to venous compression in portal triads more markedly than in portal inflammatory diseases such as chronic viral hepatitis.

Primary sclerosing cholangitis should be considered a premalignant disease.[51] 10–20% of patients with primary sclerosing cholangitis develop cholangiocarcinoma, which can be the first disease manifestation in patients with subclinical primary sclerosing cholangitis. For this reason, the malignancy incidence is highest in the first year of disease follow-up. Primary sclerosing cholangitis-induced cholangiocarcinoma is thought to be an inflammation-induced cancer. The toxic environment of bile could conceivably be a cofactor accelerating carcinogenesis in primary sclerosing cholangitis. Additional genes might also contribute because patients also have an increased risk of extrahepatic cancers including of the colon (particularly in primary sclerosing cholangitis-associated inflammatory bowel disease), gallbladder, and pancreas. Intriguingly, the risk of hepatocellular carcinoma, even in cirrhosis, appears to be lower than in other chronic liver diseases.[52]

Diagnostic investigations

Primary sclerosing cholangitis is diagnosed in patients with cholestatic liver blood test results when MRCP or ERCP show characteristic bile duct changes. Patients with histological features compatible with primary sclerosing cholangitis, but a normal cholangiogram, are classified as having small duct primary sclerosing cholangitis.[4]

Serum biochemical tests

Although alkaline phosphatase elevation is characteristic, elevation in transaminases (eg, alanine transaminase, aspartate transaminase) might suggest a more inflammatory disease manifestation termed primary sclerosing cholangitis–autoimmune hepatitis overlap syndrome or primary sclerosing cholangitis with features of autoimmune hepatitis. Elevated serum bilirubin concentrations suggest the possibility of more advanced disease, cirrhosis, or dominant biliary strictures.

Serum autoantibodies

Primary sclerosing cholangitis has no diagnostic serum autoantibody test. Atypical perinuclear antineutrophil cytoplasmic antibodies are positive in 26–94% of patients with primary sclerosing cholangitis,[4] but they are not disease specific and do not reflect prognosis.[29,53,54] Positive antinuclear antibodies, smooth muscle antibodies, or elevated concentrations of total immunoglobulins and immunoglobulin subsets should alert clinicians to the possibility of autoimmune hepatitis, IgG4-related
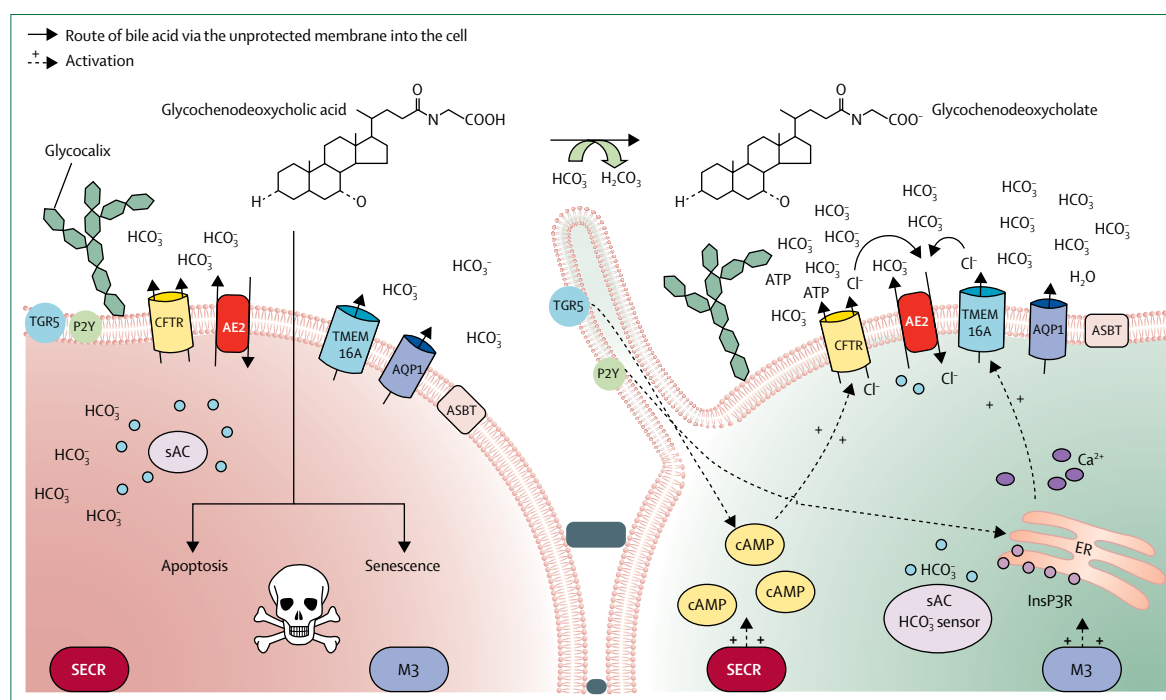
Figure 3: The biliary bicarbonate umbrella hypothesis[45-48]
Dysfunction of TGR5 (involved in HCO_3^- secretion) or the glycocalyx-stabilising enzyme FUT2 (involved in umbrella formation) have been discussed as weakening the biliary HCO_3^- umbrella in some[30,44] but not all cohorts of patients with primary sclerosing cholangitis. AE2=anion exchanger 2. AQP1=aquaporin-1. ASBT=apical sodium-dependent bile acid transporter. Ca^{2+}=calcium ion. cAMP=cyclic adenosine monophosphate. CFTR=cystic fibrosis transmembrane conductance regulator. Cl^-=chloride ion. ER=endoplasmic reticulum. H_2O=water molecule. HCO_3^-=bicarbonate. H_2CO_3=carbonic acid. InsP3R=inositol trisphosphate receptor. M3=muscarinic receptor type 3. P2Y=purinergic G protein-coupled receptors. sAC=soluble adenylyl cyclase. SECR=secretin receptor. TGR5=G-protein-coupled bile acid receptor. TMEM16A=transmembrane member 16A (a calcium-dependent chloride channel).

disease, or an overlap syndrome. Serum IgG4 elevations are not specific to IgG4-related disease and have been reported in primary sclerosing cholangitis. Serum IgG4 of more than four times the upper limit of normal strongly suggests IgG4-associated cholangitis as does an IgG4:IgG1 ratio of more than 0·24.[55] Identification of highly specific IgG4+ B-cell clones in IgG4-associated cholangitis (but not primary sclerosing cholangitis or cholangiocarcinoma) with next generation sequencing[56] has allowed reliable distinction between IgG4-associated cholangitis or IgG4-related disease, primary sclerosing cholangitis, and biliopancreatic malignancies.[57] A quantitative PCR test measuring the ratio of IgG4:IgG1 RNA in blood has been developed[57,58] and is being validated in non-European cohorts.[59]

Imaging
Abdominal ultrasound is helpful in excluding biliary calculi, which can complicate stricturing disease, and might also identify portal hypertension (splenomegaly) and gallbladder enlargement.[60] Ultrasound surveillance (every 6–12 months) is recommended for gallbladder polyps.[4] Data on the use of intraductal ultrasonography in distinguishing primary sclerosing cholangitis and IgG4-associated cholangitis are scarce.[61] Cross-sectional imaging with contrast CT is used for the diagnosis

and staging of suspected cholangiocarcinoma, but its sensitivity is low. Cholangiography by MRCP is the standard investigation for the diagnosis of primary sclerosing cholangitis.[62] A beading appearance caused by short multifocal strictures of the intrahepatic or extra-hepatic bile ducts, or both, is characteristic (figure 4). ERCP, with its recognised risk of complications, is reserved for therapeutic intervention or assessment of bile duct strictures (brush cytology, biopsy). Meta-analysis of prospective studies comparing MRCP with ERCP reported a sensitivity of 86% and specificity of 94% for the diagnosis of primary sclerosing cholangitis by MRCP,[63] although invasive cholangiography might be more sensitive in detecting early disease (97% overall diagnostic accuracy compared with 90% for MRCP).[64] Data on liver stiffness, as assessed by transient elastography, are promising, suggesting that liver stiffness is associated with outcome.[65] Splenomegaly on ultrasound, a parameter for portal hypertension, seems to have similar predictive values to transient elastography.[66,67] The enhanced liver fibrosis test might have the potential to distinguish between mild and severe disease.[68]

Liver biopsy
Liver biopsy in primary sclerosing cholangitis is controversial. The need for liver biopsy in the diagnosis
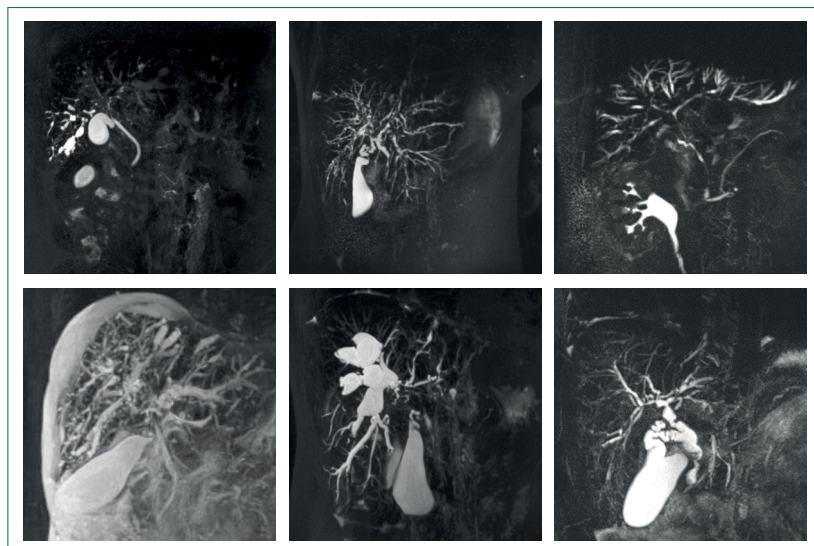
Figure 4: **Typical features of large duct primary sclerosing cholangitis**
Three-dimensional-gated T2 turbospinecho magnetic resonance cholangiopancreatography maximum intensity projection images showing typical features of large duct primary sclerosing cholangitis with irregular narrowing of bile ducts, stenoses, and focal dilatation of bile ducts. Reproduced with permission from Christine Baudouin and Ben Hall, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK.

of large duct primary sclerosing cholangitis has been challenged,[69] but it is valuable when cholangiography is normal. Liver biopsy might be helpful in assessing the degree of interface hepatitis suggestive of primary sclerosing cholangitis with features of autoimmune hepatitis, and it might also help to decide if immuno-suppressive therapy is indicated. The classic histological hallmark of primary sclerosing cholangitis is concentric, so-called onion-skin periductal fibrosis (figure 5), but this feature is often not found in biopsy specimens particularly in early disease. Some degree of bile-duct damage, however, should be identified. Molecular pathology approaches, such as tissue transcriptomics, informing stratified models for treatment, might increase the value of biopsy-based assessment approaches in the future.

Management of primary sclerosing cholangitis
Medical management
No single drug or treatment has been proven to prolong transplant-free survival in primary sclerosing cholangitis. The hydrophilic bile acid, ursodeoxycholic acid, has been extensively studied. However, evidence to show long-term benefit of ursodeoxycholic acid is unclear and its use remains controversial. Early studies with low doses of 10–15 mg/kg showed improvement of liver blood tests results and liver histology (when analysed by a multi-parametric histological score).[70] Most studies are restricted to analysis of liver blood tests, and only one under-powered trial,[71] with a mean follow-up of 2·2 years, studied outcome by death or liver transplantation. A 5-year placebo-controlled trial[72] of moderate dose urso-deoxycholic acid (17–23 mg/kg) showed a trend towards improved transplant-free survival although it was, again,

underpowered. A landmark large multicentre study[73] of high dose ursodeoxycholic acid (28–30 mg/kg) was stopped early because of a poorer outcome in the ursodeoxycholic acid group than the placebo group, and guidelines advise against the use of high doses in primary sclerosing cholangitis.[4,6] Nonetheless, ursodeoxycholic acid, typically at moderate doses of 15–20 mg/kg daily, remains widely used.[4,24,38,74,75] Large-scale studies and meta-analyses do not support a reduced cancer risk in patients with primary sclerosing cholangitis receiving ursodeoxycholic acid.[73,76]

Immunosuppressive therapy has not been shown to improve outcome in classic disease. However, the trial evidence for drugs such as prednisolone,[77] budesonide,[78] azathioprine,[79] tacrolimus,[80] methotrexate,[81] mycophenolate mofetil,[82] colchicine,[83] penicillamine,[84] and antitumour necrosis factor antibodies[85] is limited by small numbers and often old studies with uncontrolled assessments. None of these therapies can be recommended.

Small series in patients with IgG4-related disease show marked improvement in liver blood tests results and IgG4 concentrations and resolution of biliary stricturing on cholangiography within 2–4 weeks of corticosteroid treatment.[86] When IgG4-related disease is suspected, a short-term trial of corticosteroid therapy might be indicated. However, in the absence of a prompt clinical or biochemical response, treatment should not be prolonged. Patients with good evidence of associated autoimmune hepatitis features should be treated with the use of immunosuppressive treatment algorithms similar to those used for classic autoimmune hepatitis.[8,87,88]

The use of a combination of ursodeoxycholic acid and metronidazole has shown an improvement in liver blood tests but not in disease progression.[89] Benefit with vancomycin has been reported in small studies in paediatric and adult populations with primary sclerosing cholangitis.[90,91] Drugs, such as sirolimus, that have both antimitotic and antifibrotic properties remain attractive theoretically but no evidence supports their use.[92]

Fibrates, peroxisome proliferator-activated receptor agonists that show anticholestatic properties synergistic with ursodeoxycholic acid, have a biochemical benefit in primary biliary cholangitis.[93] The combination of fibrates and ursodeoxycholic acid is attractive for treating patients with primary sclerosing cholangitis who have a poor biochemical response to ursodeoxycholic acid alone. Outcomes from small studies suggest improvement in liver blood tests but little effect on disease progression.[94]

Endoscopic management
The reported incidence of dominant strictures varies, with one report[95] of 106 patients with a median follow-up of 5 years describing dominant stenoses in 53 (50%) patients. This result might, however, reflect the challenge of defining what constitutes a dominant stricture and referral bias. A dominant stricture has been defined as a narrowing to less than 1·5 mm in the common bile duct or less than

1 mm in the right and left hepatic ducts.[5,95,96] With this definition, a single UK study[39] from a tertiary referral centre with a specialist interest in endoscopic therapy reported dominant strictures in 80 (63%) of 128 patients. Patients with dominant strictures, even if cholangiocarcinoma is excluded, have a substantially worse prognosis than those without.[39] ERCP with brush cytology or biopsy are most commonly used in the diagnostic process of differentiating benign from malignant strictures.

Endoscopic intervention for dominant biliary strictures in patients with symptomatic disease appears beneficial.[95,97] A multicentre randomised trial[98] of 65 patients confirmed the findings from a previous study[99] that short-term stenting is not superior to balloon dilatation and is associated with higher treatment-related complications. Primary sclerosing cholangitis guidelines recommend balloon dilatation as first-line endoscopic treatment.[4,5,100]

The role of metal stents, which are fully covered, removable, and self-expandable, in primary sclerosing cholangitis is yet to be established.[101,102] When considering ERCP or any endoscopic biliary intervention, the clinician should be alert to the risk of bacterial cholangitis, and prophylactic antibiotics should always be given according to local antibiotic resistance profiles.[103] Bile sampling at the beginning of ERCP, then giving antibiotic prophylaxis, might be a prudent approach.[104,105]

Varices screening should be offered if evidence suggests cirrhosis or suspicion of portal hypertension.[49] Patients with primary sclerosing cholangitis might develop varices before cirrhosis is evident.

A total colonoscopy with segmental mucosal biopsies is advised to exclude inflammatory bowel disease once primary sclerosing cholangitis is diagnosed. For patients with confirmed colitis, annual (or biennial in some individuals) colonoscopic surveillance for colorectal dysplasia or neoplasia is recommended.

Liver transplantation

The timing and selection of patients with primary sclerosing cholangitis for liver transplantation remains a challenge. Primary sclerosing cholangitis is a well established indication for liver transplantation in patients with decompensated liver disease, intractable pruritus, or recurrent bacterial cholangitis.[106,107] The European Liver Transplant Registry reported short-term and long-term survival in 3710 patients who had received transplants between 2001 and 2015 at 91% at 1 year, 82% at 5 years, and 74% at 10 years (Karam V, Centre Hépato-Biliaire Paul Brousse, personal communication). Early referral to a transplant unit is recommended if evidence suggests liver synthetic dysfunction or complications. Indications for liver transplantation include a UK Model for End-Stage Liver Disease score of more than 49 or a Model for End-Stage Liver Disease score of more than 14 (outside UK).[108,109] In Nordic countries, biliary dysplasia is

an indication for pre-emptive liver transplantation. Cholangiocarcinoma remains a contraindication to liver transplantation in most countries. However, a few centres have reported good recurrence-free survival with neo-adjuvant chemoradiation in highly selected patients with unresectable hilar cholangiocarcinoma.[110–112] Results of further studies are awaited.
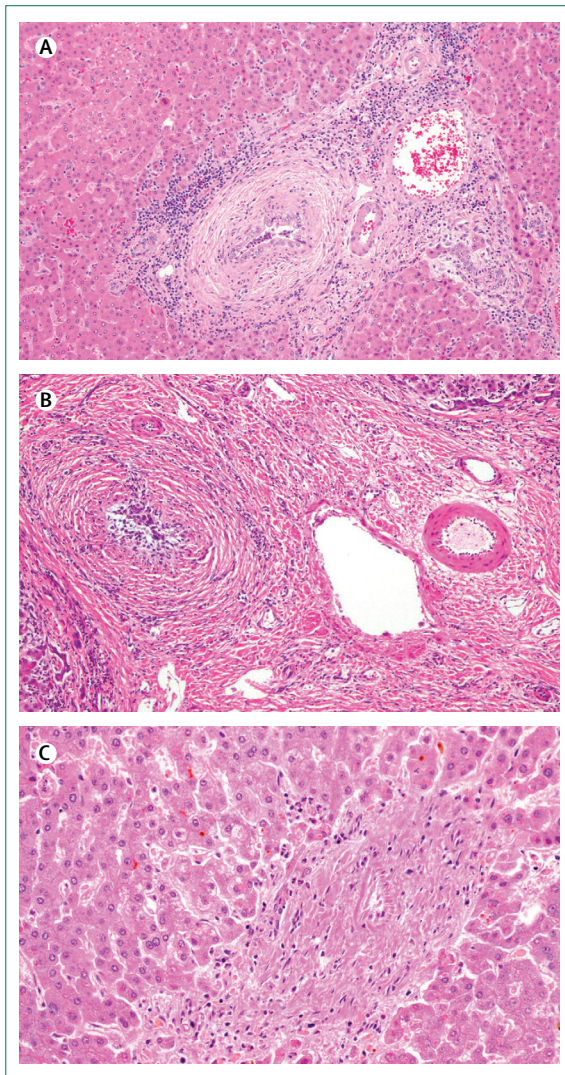

Figure 5: **Histology of primary sclerosing cholangitis**
Reproduced with permission from Yvonne Bury, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK. (A) A medium-sized portal tract with bile ducts surrounded by periductal onion-skin concentric fibrosis and oedema with a mild portal inflammatory cell infiltrate (haematoxylin and eosin stain [H&E]; reduced by 25% from ×100 magnification). (B) The bile duct epithelium shows degenerative and atrophic changes and the bile ducts assume an irregular outline. Such characteristic lesions are present only in fewer than half of biopsy specimens because such medium-sized to large ducts are sampled uncommonly in biopsy specimens (H&E; reduced by 25% from ×100 magnification). (C) Progressively, bile ducts are lost and portal tracts contain unpaired arteries without an associated bile duct. This represents ductopenia when seen in more than half of portal tracts. Ductopenia is present in the later stages of primary sclerosing cholangitis and is commonly associated with portal, periportal, or bridging fibrosis (H&E; reduced by 25% from ×200 magnification).

At least 25% of transplanted patients will develop recurrent disease after transplant.[106,113,114] Inflammatory bowel disease with an intact colon is a risk factor for recurrent primary sclerosing cholangitis, implicating gut–liver axis factors in disease recurrence.[113,115] No evidence supports specific post-transplant immunosuppression regimens having an effect on recurrence.

Symptom management

The most tractable symptom is pruritus. Dominant strictures should be sought and actively managed. First-line medical therapy is with the bile acid sequestrant cholestyramine. Second-line therapies include rifampicin and naltrexone. Pruritus in advanced disease is often refractory to medical management. At present, no specific therapies for fatigue exist.

Patients with primary sclerosing cholangitis have an increased risk of osteoporosis[116] and might also be deficient in vitamin D and other fat-soluble vitamins.

Follow-up and outcomes

Bacterial cholangitis

Bacterial cholangitis might occur spontaneously or be precipitated by ERCP[96,117] and may contribute to disease progression.[118] Urgent biliary decompression is mandatory for patients with acute cholangitis in the context of a dominant biliary stricture.

Cholangiocarcinoma and gallbladder carcinoma

Hepatobiliary malignancies are a common cause of mortality in patients with primary sclerosing cholangitis.[119] Patients with dominant strictures are at highest risk of cholangiocarcinoma (with up to 76% being perihilar),[39] whereas patients with small duct primary sclerosing cholangitis are at low risk.[30,37,38] Cholangiocarcinoma might be the presenting feature of primary sclerosing cholangitis with up to 50% of primary sclerosing cholangitis-associated cholangiocarcinoma being identified within 1 year of presentation.[39,51,120] The lifetime risk of cholangiocarcinoma in patients with primary sclerosing cholangitis is up to 20% with an annual incidence of 0·6–1·5% and prevalence of 6–13%.[29,39,38,39,120] Alkaline phosphatase returning to normal or up to 1·5 times the upper limit of normal within 1 or 2 years after diagnosis suggests a better outcome and reduced risk of cholangiocarcinoma in one study.[3,31–36]

Cancer screening is a key part of follow-up monitoring. Biliary brush cytology is the standard investigation for suspicious strictures but a review[121] reported the sensitivity for diagnosing cholangiocarcinoma in primary sclerosing cholangitis to be only 43%.[96,117,121–123] A meta-analysis found that with the use of fluorescence in-situ hybridisation (FISH), sensitivity can be improved to 68% (51% for FISH polysomy)[124] and specificity to 70% (93% for FISH polysomy)[124] for cholangiocarcinoma diagnosis.[124] Cost, however, limits its use. Technical advances in biliary endoscopy, endoscopic ultrasound, and cholangioscopy (SPYGLASS) to obtain tissue are becoming widespread and suggest promise for the future.[125–130]

Carbohydrate antigen (CA19-9) and carcinoma embryonic antigen (CEA) measurements are widely used for cancer screening. However, they are not sufficiently sensitive or specific to allow effective screening, although evidence suggests utility in combination with imaging modalities.[5,131,132] Elevated CA19-9 might be useful as part of the overall clinical picture suggesting cholangiocarcinoma, but it should not be used in isolation for screening or diagnosis of cholangiocarcinoma.

MRCP, combined with contrast-enhanced MRI of the liver, is the imaging modality used in some centres for annual assessment. Many centres still use ultrasound, although no evidence supports this use. Studies of novel biomarkers in bile are ongoing with the goal of improving screening accuracy. Volatile organic compounds and bile lipid profiles measured at bile aspiration, including oxidised phosphatidylcholines, are promising with improved sensitivities but require further analysis.[133] Malignancy in gallbladder polyps is reported in 3% of patients from large studies from Scandinavia and the USA[4] and might occur in small polyps (<1 cm).[134,135] As a result, patients should undergo ultrasound surveillance of the gallbladder every 6–12 months and cholecystectomy has been recommended if polyps are greater than 0·8 cm (although lower thresholds have been suggested as well).[6] Pancreatic cancer is also reported more frequently in patients with primary sclerosing cholangitis than in the general population[41] and hepatocellular carcinoma has a prevalence of 2–4% in patients with primary sclerosing cholangitis and cirrhosis.[39,136]

Colonic cancer

Primary sclerosing cholangitis-associated inflammatory bowel disease is associated with a higher risk of colorectal cancer (with a 10-year reported risk of 14% and 20-year reported risk of 31%) than primary sclerosing cholangitis without inflammatory bowel disease (10-year reported risk of 2% and 20-year reported risk of 2%).[51] In another study[51,137] of primary sclerosing cholangitis-associated inflammatory bowel disease, the absolute risks of developing colorectal dysplasia or carcinoma were 9% after 10 years, 31% after 20 years, and 50% after 25 years of disease. The corresponding risks in ulcerative colitis alone were 2%, 5%, and 10%. Cancers are more commonly right sided than left sided (67% vs 36%) in primary sclerosing cholangitis-associated inflammatory bowel disease.[138] Guidelines advise annual surveillance colonoscopy with segmental mucosal biopsies in patients with primary sclerosing cholangitis and inflammatory bowel disease.[4,139] For patients without confirmed inflammatory bowel disease, many clinicians repeat a colonoscopy with mucosal biopsies in 5 years. Patients found to have colonic dysplasia or polyps should be managed according to current guidelines.

Prognostic scoring systems

Several scoring systems (appendix) have been developed that incorporate some clinical factors (panel). However, these scoring systems are often more appropriate for trials than for normal clinical management. The generic Child-Pugh score was studied in primary sclerosing cholangitis[150] and yielded 7-year survival of 90% for class A, 68% for class B, and 25% for class C. Some evidence suggests that the Mayo risk score might perform better in early stage disease than the Child-Pugh score.[151]

Controversies and uncertainties

Appropriate settings for management

Inter-observer variability is substantial in terms of interpretation of cholangiographic and histological findings, leading to inaccurate diagnoses for some patients. In small centres, which do not manage many patients, the radiology and pathology departments often have limited experience of interpreting these tests. The false-positive (and similarly false-negative exclusion) diagnosis of primary sclerosing cholangitis has great implications for an individual. We suggest that the investigations (even if not the patients themselves) should be reviewed centrally by expert centres. What level of clinical activity or exposure should people making the diagnosis undertake to have confidence in their practice? Audit of correct diagnostic rates as proven by long-term follow-up should allow adequate quality control for diagnostic services in the future. The paucity of clear guidelines as to what surveillance is appropriate might mean that patients benefit from management by centres with experience of larger cohorts. Management of dominant strictures is also an area with a paucity of evidence and cases should be discussed in multidisciplinary forums in large centres to review whether endoscopic assessment and intervention is appropriate.

Optimal approach to screening for cholangiocarcinoma

The optimal method for surveillance for cholangiocarcinoma is unknown.[62] Imaging techniques or biomarkers for early detection of this type of cancer are inadequate. Cholangiocarcinoma remains a huge challenge, with an estimated lifetime risk of 10–20% in patients with primary sclerosing cholangitis. In the absence of clear evidence, guidelines suggest screening for cholangiocarcinoma with 6–12 monthly imaging with ultrasound or MRI and CA19-9 measurements.[6]

Colonoscopy

Most patients with primary sclerosing cholangitis (but not all of them) have inflammatory bowel disease, which is asymptomatic in a fair proportion of those affected. Diagnosis in these patients can only be made by colonoscopy with multiple biopsies because colitis might be purely microscopic. It is not clear if these patients also have a similarly raised risk for colonic cancer and require yearly colonoscopic screening, or if it is sufficient to

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Panel: Prognostic factors in primary sclerosing cholangitis

Good prognostic factors
- Younger age at diagnosis[140]
- Female sex[140]
- Reduced or normal alkaline phosphatase concentrations (whether given ursodeoxycholic acid or not)[141-146]
- Small duct disease[140,147,148]
- Primary sclerosing cholangitis with features of autoimmune hepatitis (worse than classic autoimmune hepatitis, better than classic primary sclerosing cholangitis)[12,13]

Poor prognostic factors
- Extensive intrahepatic or extrahepatic biliary strictures
- Dominant strictures[149]
- Recurrent cholangitis[39]
- Ulcerative colitis (as opposed to Crohn's disease)[140]
- Evidence of liver synthetic dysfunction
- Cirrhosis with portal hypertension

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examine and regularly screen those with clinically apparent inflammatory bowel disease.

Transplantation as a treatment approach

Liver transplantation remains the only curative treatment for primary sclerosing cholangitis albeit with a substantial risk of disease recurrence. Many questions remain relating to transplantation in this disease on appropriate timing, whether patients with biliary dysplasia or cholangiocarcinoma should be excluded, and type of donor organ used. The ideal timing for transplantation is not known and is more influenced by availability of donor organs rather than evidence. Early transplantation carries its own risks because graft survival is relatively low, especially in patients with primary sclerosing cholangitis. Transplantation for cholangiocarcinoma does not reach the requirements for potential long-term survival to suggest transplant improves outcome in this context. However, data from the USA suggest that neoadjuvant chemoradiotherapy combined with transplantation for early cancers is showing improved outcomes.[152,153]

Outstanding research questions

The predominant outstanding research question in primary sclerosing cholangitis is how to prevent or reverse disease progression to avoid end-stage liver disease and the development of malignant and other complications. Despite much work, there remains no licensed therapy. An effective therapy programme will require the development and validation of appropriate predictive surrogate disease markers (the slowly progressive nature of the disease makes use of hard disease endpoints difficult in placebo-controlled trials) and improved trial design. Although studies show that a lower alkaline phosphatase concentration is associated with better outcomes, the study of the use of high dose ursodeoxycholic acid showed lowering of alkaline

phosphatase concentration but did not improve outcomes. These conflicting results suggest that additional biomarkers of clinical improvement, such as liver elastography, are urgently needed. Future trials need a stratified approach including anatomical (intrahepatic *vs* extrahepatic *vs* small duct disease), mechanistic (antifibrotic *vs* anticholestatic *vs* anti-inflammatory), and staging aspects. Unstratified so-called all-comer trials potentially fail to show a link between biomarkers and outcomes because of inclusion of low-risk patients who would not reach an endpoint within the observation period. A collaborative approach is also crucial given that no single centre has enough patients to undertake a large study.

Another key area for research is the accurate identification and optimal management of clinically relevant dominant strictures and whether dilating stenoses, in parallel with the aggressive treatment of biliary tree infection, might improve outcomes in large duct disease.

Interest has increased from clinicians and industry for trials (appendix).[154,155] The diversity of approaches and treatment reflects the uncertainties in primary sclerosing cholangitis. Combination medical treatment targeting different aspects of disease pathogenesis might offer new opportunities.[156] Liver transplantation clearly changes the natural history of disease and some data suggest that other treatment interventions that effectively improve cholestasis might affect disease course; however, this approach needs further investigation.

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