Seminar

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# Primary sclerosing cholangitis – a comprehensive review

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## Summary

Primary sclerosing cholangitis (PSC) is a rare disorder characterised by multi-focal bile duct strictures and progressive liver disease. Inflammatory bowel disease is usually present and there is a high risk of cholangiocarcinoma and colorectal cancer. Most patients ultimately require liver transplantation, after which disease recurrence may occur. With limited therapeutic options and a lack of proven surveillance strategies, patients currently have significant unmet needs. In the present seminar, we provide a comprehensive review of the status of the field. We emphasise developments related to patient stratification and disease behaviour, and provide an overview of management options from a practical, patient-centered perspective. We survey advances made in the understanding of PSC pathogenesis and summarise the ongoing efforts to develop an effective therapy based on these insights.


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**Key point**

PSC is by formal definition a rare disease, yet the incidence is currently rising due to unknown changes in environmental exposures.

## Introduction

Primary sclerosing cholangitis (PSC) is a chronic liver disease where inflammation and fibrosis lead to multifocal biliary strictures. The close association with inflammatory bowel disease (IBD) is a hallmark of the condition, with IBD present in the majority of patients (Fig. 1).[1,2]

Until the mid-1960s, most published articles were case reports.[3] The broad implementation of endoscopic retrograde cholangiography (ERC) throughout the 1970s led to increasing recognition of the condition and in 1980, three landmark papers from the US, the UK and Norway established a clinical definition.[4–6] Subsequently, the association of PSC with cholangiocarcinoma (CCA),[7] colonic neoplasia[8] and the sub-phenotypes of small-duct PSC,[9] PSC with high immunoglobulin 4 (IgG4) levels,[10,11] and autoimmune hepatitis "overlap syndrome"[12,13] have been described. Disease progression and end-stage liver disease are inevitable in most patients,[14] and in 1983 liver transplantation was established as the only curative treatment option.[15] PSC recurrence after liver transplantation in some patients was noted a few years later.[16]

The pathogenesis of PSC is unknown, but a number of mechanistic theories have been proposed. The concentric fibrosis around the bile ducts in PSC (Fig. 2) is found in a variety of conditions and likely represents a common final pathway for chronic bile duct injury of any cause (Box 1). Defects in mechanisms protecting against bile acid toxicity have been proposed as key players in PSC development.[17–19] The relationship with IBD has also inspired several avenues of research.[20] Passive leakage of pro-inflammatory microbial components to the portal circulation and the possibility of an antigenic trigger of microbial origin were for many years the predominant theories.[21,22] Recruitment of gut-derived T cells to the liver or an insult resulting from disturbances in the gut microbiota have also been proposed.[23,24]

We aim to describe the current understanding of PSC, emphasising recent developments in pathophysiology and clinical management.

## Epidemiology and demographics

PSC conforms to the definition of a rare disease, affecting less than 200,000 individuals in the US and less than 5 per 10,000 inhabitants in the EU (with fewer than 250,000 individuals affected across the EU). Epidemiological studies of PSC, although hampered by the lack of an ICD10 code,[25] report a prevalence rate of around 1 per 10,000 and an incidence rate in Northern Europe and the US of between 0.4 and 2.0 per 100,000 per year.[26,27] There

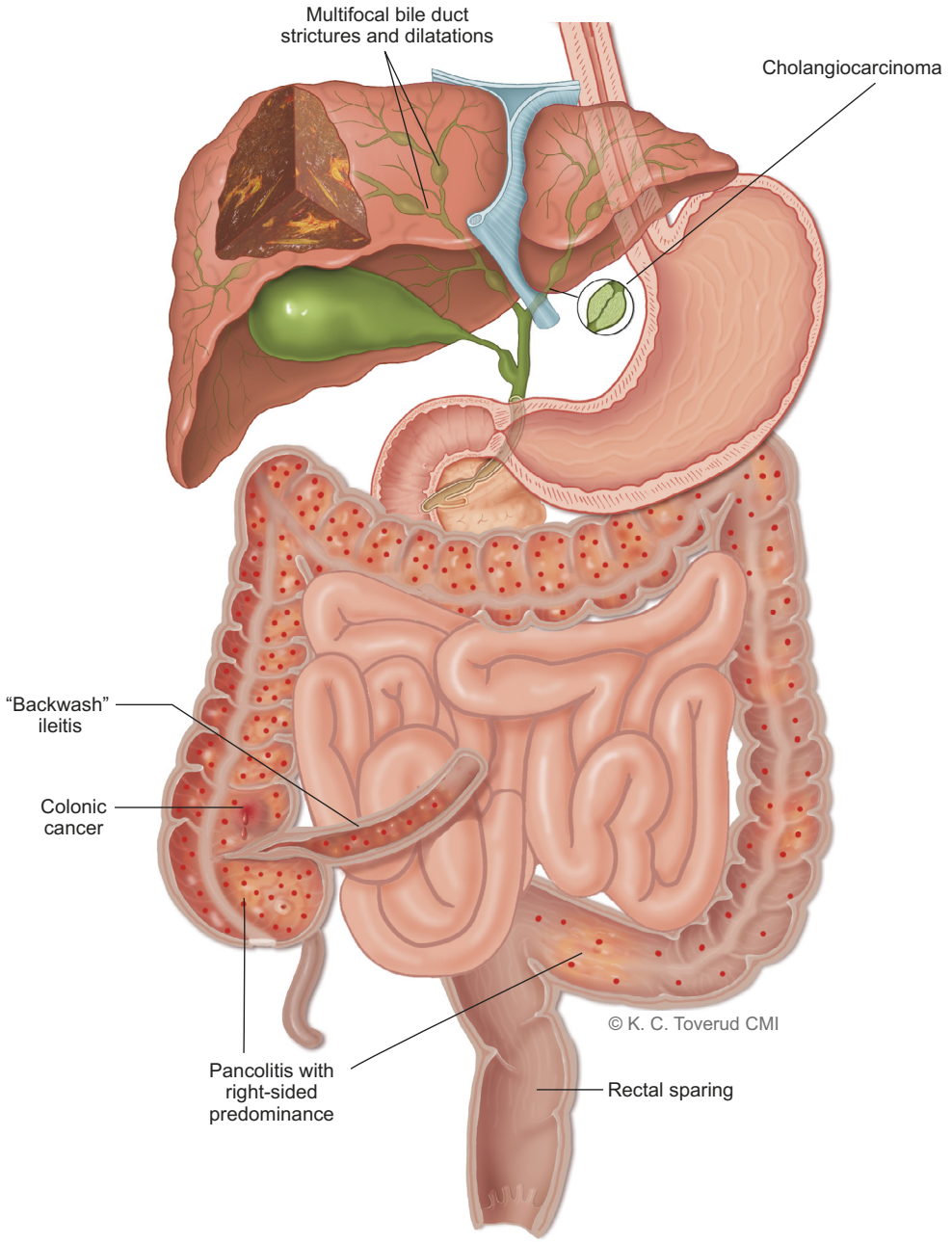


**Fig. 1. Macroscopic bowel and bile duct pathology in primary sclerosing cholangitis (PSC).** PSC is a chronic liver disease where inflammation and fibrosis lead to multifocal biliary strictures. The close association with inflammatory bowel disease (IBD) is a hallmark of the condition, with IBD affecting about two-thirds of patients overall. Colonic involvement is most often classified as ulcerative colitis, but sometimes it is interpreted as Crohn's or indeterminate colitis. Despite the frequently mild symptoms, there is usually pancolitis. Often a right-sided predominance, subtle ileal inflammation ("backwash" ileitis) and rectal sparing are seen. PSC is associated with a considerable risk of gastrointestinal malignancies, mainly cholangiocarcinoma and colorectal cancer. Printed with permission from Kari C. Toverud.

is a geographic gradient towards the South and the East, with studies in Spain, Singapore and Japan reporting approximately 10-fold lower prevalence rates, *i.e.* at 0.022, 0.13 and 0.095 per 10,000, respectively.[28] Childhood-centric assessments have found incidence rates of 0.23 and 0.2 per 100,000 per year.[29,30] Several studies indicate the incidence of PSC is increasing.[31–34] Whilst this may be partly attributable to the application of magnetic resonance cholangiography (MRC) rather than ERC, the clinical features of newly diagnosed patients appear stable over time,[34] which indicates an earlier diagnosis may not explain the increase. A similar increase has been seen in most autoimmune and

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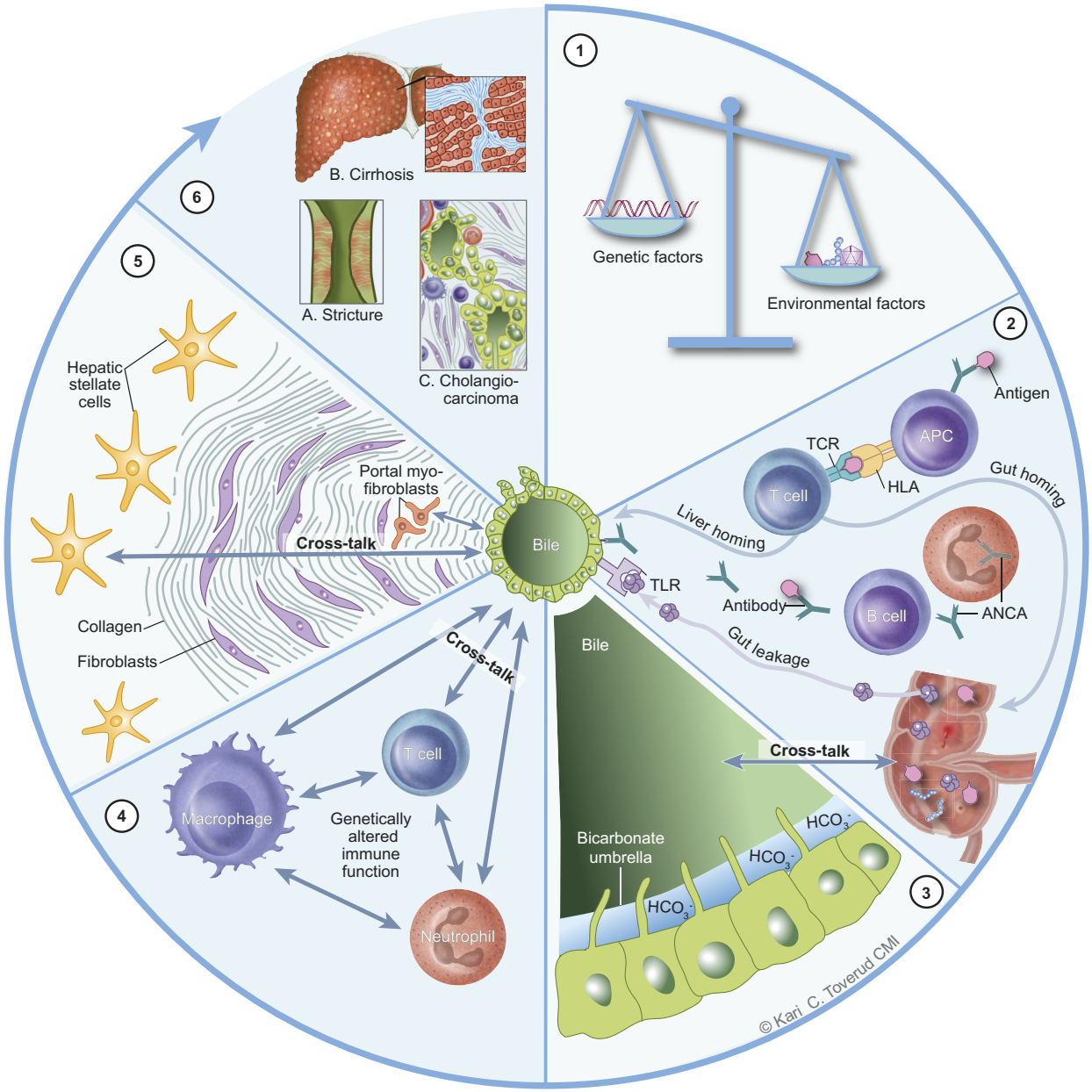


**Fig. 2. Integrated overview of the pathophysiology of primary sclerosing cholangitis (PSC).** Clockwise, the figure illustrates the development from (1) initiating factors (upper right piece) to (6) liver-related complications (upper left piece). (1) There have been considerable advances in understanding the genetics of PSC, with more than 20 susceptibility genes now identified (Table 1). The combined impact of genetic susceptibility factors on overall PSC liability is currently less than 10%, and even accounting for future gene discoveries, environmental risk likely accounts for more than 50%. (2) The relationship between the gut and the liver affection in PSC is not clear. Early theories were concerned with the possible "leakage" of pro-inflammatory bacterial products (*e.g.* lipopolysaccharides, LPS) which would engage innate immune responses (*e.g.* by toll-like receptor signalling). The strong human leukocyte antigen (HLA) associations found in genetic studies however claim a strong involvement of adaptive immune responses, by determining which antigens can be presented to the T cell receptor (TCR). Gut derived antigens are potential triggers of these responses, and activated T cells may migrate to both the liver and gut following clonal expansion because of the overlapping adhesion molecule profiles of gut and liver endothelia (*i.e.* mucosal vascular address in cell adhesion molecule 1 [MadCAM-1] and vascular cell adhesion molecule 1 [VCAM-1] expression along with Chemokine C-C motif ligand 25 [CCL25] secretion).[249] Anti-neutrophil cytoplasmic antibodies (ANCA) are frequently observed in PSC,[250] and may reflect B cell responses to antigens of gut origin.[22] (3) Bile is toxic,[251] and its composition is shaped by involvement of gut-microbial co-metabolism (gut-liver cross-talk).[125] Cholangiocytes are protected against bile acid toxicity by several mechanisms, one of which is the presence of a bicarbonate ($HCO_3^-$) layer ("umbrella") generated by an involvement of the $Na^+$-independent $Cl^-/HCO_3^-$ anion exchanger (AE2) and active $Cl^-$-transporters, most notably the ATP-driven cystic fibrosis transmembrane conductance regulator (CFTR) and the $Ca^{++}$-driven anoctamin 1 channel.[252] The bile acid receptor TGR5 is most likely expressed at the cilia on the biliary epithelium,[253] and may be involved in the regulation of CFTR.[254] Primary or secondary disturbances in bile homeostasis are hypothesised to contribute to pathogenesis of PSC, and are the basis of bile acid based therapies (*e.g.* ursodeoxycholic acid and *nor*ursodeoxycholic acid). (4) Several immune cells are found in the proximity of bile ducts of PSC, most notably T cells, macrophages and neutrophils, all of which are affected by the main genetic findings (Table 1). The exact involvement of each cell type remains unknown, but of key importance is their likely engagement and cross-talk with an activated cholangiocyte phenotype.[87,95,255] (5) Chronic injury converges on common mechanisms of fibrosis development involving hepatic stellate cells and portal myofibroblasts in a hitherto undefined cross-talk with cholangiocytes.[114] The key involvement of cholangiocytes in this cross-talk is given by the "onion skin" features of biliary fibrosis in PSC, but details are unknown. (6) Liver-related complications in PSC are mainly represented by bile duct strictures, liver cirrhosis and cholangiocarcinoma. Printed with permission from Kari C. Toverud.

idiopathic inflammatory conditions over the last decades,[35] either because of decreasing exposure to protective factors ("the hygiene hypothesis") or an increasing exposure to triggers and drivers.

The typical PSC patient is a 30–40 year old male presenting with a diagnosis of ulcerative colitis (UC) or Crohn's colitis and abnormal hepatic biochemistries. In up to 25% of cases, patients may also have other autoimmune diseases.[36] The diagnosis of PSC may precede that of IBD,[37] which may even present after liver transplantation for PSC.[38] Conversely, PSC may present in an IBD patient even after colectomy.[4,39] Therefore, determining which PSC patients do not have IBD is difficult. In Northern Europe and the US, approximately two-thirds of the patients have concurrent IBD. Variable frequencies have been reported in France (60%),[40] Spain (44%),[32] Turkey (43–63%),[41] Iran (62%),[42] India (50%) and Japan (34–37%).[43] It has been suggested that a distinct population of elderly patients without IBD who should be treated and studied separately may exist in Japan.[44] Some of these patients also represent cases of IgG4-associated multi-organ disease (IgG4-associated cholangitis [IAC]), which is hard to demarcate from PSC, even in Western populations. Elevated levels of IgG4 are seen in a subset (~10%) of patients with PSC without comprehensive diagnostic features of an IgG4-associated syndrome (the HISORt criteria).[45]

A Norwegian study has questioned previous epidemiological data in PSC.[46] MRC screening of 322 patients with colitis, after 20 years, identified large-duct PSC in 7.4% of patients, in whom only 2.2% had a prior diagnosis of large-duct PSC. Similar observations have been made in a UK cohort (published in abstract form only).[47] Of note, more than two-thirds of the newly diagnosed asymptomatic patients in the Norwegian study were female, suggesting that PSC occurs as commonly in females as in males, but runs a more clinically quiescent course. This is supported by data from a large multi-centre study of 7,119 patients with PSC, which showed significantly better outcomes for female patients.[48] A milder disease course has also been reported for patients with a diagnosis of Crohn's disease.[48,49] This difference in PSC behaviour, according to clinical presentation of IBD, may also explain why rates of PSC-like changes were comparable in UC and Crohn's disease (6.8% and 9.0%, respectively) at 20 years follow-up in the Norwegian cohort.[46] While the value of identifying subclinical PSC in IBD patients can be questioned, the increased risk of colorectal malignancy and implications for surveillance colonoscopy justify a debate on whether MRC screening of patients with IBD is warranted.

The increased risk of biliary cancer and colorectal cancer in PSC is firmly established and of major clinical importance (Fig. 1). In a multi-centre study of 7,119 PSC patients, hepatobiliary malignancy was diagnosed in 10.9%.[48] This is comparable to the population-derived observations from the Netherlands (CCA diagnosed in 7% of the PSC patients; standardised incidence ratio 398, 95% CI 246–608),[34] and higher than in patients from Southern Europe and Asia (3.3–5.7%).[41,50,51] Up to 50% of CCAs are detected within a year of PSC diagnosis and CCA likely precipitates the diagnosis of PSC in

**Box 1. Diagnosis and differential diagnosis in primary sclerosing cholangitis (PSC).**

| Diagnosing PSC | Diagnostic approach |
|---|---|
| Classical large-duct PSC | Cholestatic serum liver tests (elevated ALP) GGT) and/or cholestatic symptoms (pruritus, jaundice, cholangitis), MRC, diagnostic ERC (occasionally) |
| Small-duct PSC (MRC/ERC normal) | Liver biopsy, IBD confirmed |
| PSC high IgG4 | Serum IgG4, IgG4 staining of relevant biopsy |
| PSC with features of AIH (PSC-AIH overlap) | ANA, anti-SMA, anti-LKM, anti-SLA/LP, IgG, liver biopsy |
| PSC with cholangiocarcinoma | MRI/CT with contrast, EUS, ERC, tissue sampling for cyto- and histopathology |
| **Differential diagnosis and causes of secondary sclerosing cholangitis excluded** | |
| Cholangiocarcinoma | CT/MRI with contrast, EUS, ERC, tissue sampling for cytopathology/histology |
| IgG4-associated sclerosing cholangitis | History, serum IgG4, IgG4 staining of relevant biopsy, PCR based technologies |
| HIV infection | HIV serology, immunological investigations, bile investigations for infections |
| Sarcoidosis | Serum ACE level, serum and 24 h urine calcium, liver biopsy, CXR, pulmonary function tests, FDG-PET CT, cardiac MRI |
| Choledocholithiasis | Ultrasound, MRC/ERC |
| Traumatic or ischaemic biliary injury | History, MRC plus CT/MRI with angiography |
| Papillary stenosis | MRC, ERC +/- biliary manometry |
| Ampullary or pancreatic cancer | MRC, CT/MRI with contrast, duodenoscopy/EUS/ERC, tissue sampling for cytopathology/histology |
| Chronic pancreatitis | History, CT/MRI with contrast, EUS, cytopathology |
| Hilar lymphadenopathy | MRC, CT/MRI with contrast, EUS, histo-/cytopathology |
| Congenital (choledochal cysts, biliary atresia) | MRC, CT/MRI with contrast |
| Chronic biliary infestation (liver fluke or ascaris) | History, serology, MRC, ERC |
| Recurrent pyogenic cholangitis | History, MRC, CT/MRI with contrast |
| Choledochal varices (portal biliopathy) | History, MRC, CT/MRI with contrast |
| Critical illness ischaemic cholangiopathy | History, MRC |

ACE, angiotensin converting enzyme; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ANA, anti-nuclear antibodies; anti-LKM, anti-liver kidney microsomal antibodies; anti-SLA/LP, antibodies against soluble liver antigen/liver pancreas; anti-SMA, anti-smooth muscle antibodies; CT, computerized tomography; CXR, chest X ray; ERC, endoscopic retrograde cholangiography; EUS, endoscopic ultrasound; FDG-PET, fluorodeoxyglucose positron emission tomography; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IgG4, immunoglobulin G4; IgG, immunoglobulin G; MRC, magnetic resonance cholangiography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

**Key point**

PSC affects approximately 8% of patients with IBD and often runs a subclinical course in female patients and Crohn's disease.

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**Table 1. Genome-wide (GW) significant ($p \leq 5 \times 10^{-8}$) risk loci in primary sclerosing cholangitis outside of the human leukocyte antigen (HLA) complex on chromosome 6.**[73–80] Here we display the reported candidate gene(s) within the implicated risk regions, and include the ***P*** value from the first study reporting GW significance for a single nucleotide polymorphism (SNP) within this implicated risk region in PSC. The candidate risk gene(s) at each locus is based on circumstantial evidence, and further studies are needed to link PSC-associated SNPs to distinct genes. In addition to loci shown, four loci showing a ***P*** value $<5 \times 10^{-6}$ and $>5 \times 10^{-8}$ in two genetic studies warrant mentioning: 2q35 (harboring ***TGR5*** and ***CXCR1/2***), 10q24 (harboring ***NKX2-3***), 19q13 (harboring ***FUT2***) and 21q22 (harboring ***ICOSLG***). Only one locus has been reported to influence disease progression in PSC at GW significance (***RSPO3*** at 6q22).[264] *Candidate gene(s) shared with other AIDs refer to the same candidate gene(s) having been reported in both PSC and the listed AID based on mapping of GW significant SNPs to the actual candidate gene(s) in both diseases. Data were obtained from the NHGRI-EBI Catalog of published genome-wide association studies (http://www.ebi.ac.uk/gwas/home). For further reading on the individual gene findings, see reference.[81]

| Chromosome | Candidate risk genes | Lead SNP | *P* value | *P* in other AID* | References | Putative pathophysiological role of candidate gene(s) |
|---|---|---|---|---|---|---|
| 1p36 | *MMEL1, TNFRSF14* | rs3748816 | $2.1\times10^{-8}$ | CeD, MS, RA, UC | Folseraas *et al.* (2012) | *MMEL1*: Potentially involved in neuropeptide degradation.<br>*TNFRSF4:* Molecular switch modulating T cell activation and regulation of immune tolerance. |
| 2q13 | *BCL2L11* | rs6720394 | $4.1\times10^{-8}$ | None | Melum *et al.* (2011) | Apoptosis of B- and T-cells, granulocytes and macrophages and termination of inflammatory response. |
| 2q33 | *CD28, CTLA4* | rs7426056 | $1.9\times10^{-20}$ | AA, CeD, GV, MG, RA, T1D | Liu *et al.* (2013) | *CD28:* Co-stimulatory receptor crucial for T cell activation, survival and proliferation.<br>*CTLA4*: Major negative regulation of T-cell responses by binding to CD80 and CD86. |
| 2q36 | *CCL20* | rs7556897 | $4.7\times10^{-9}$ | PBC, IBD, UC | Ellinghaus *et al.* (2016) | Chemokine. Ligand for chemokine receptor CCR6. Attracts immature dendrittic- and memory T cells. Regulates recruitment of CCR6 positive lymphocytes to liver. |
| 2q37 | *GPR35* | rs3749171 | $3.0\times10^{-9}$ | IBD, UC | Ellinghaus *et al.* (2013) | Member of G-protein-coupled metabolite-sensing receptors expressed on immune cells and a subset of gut epithelial cell. Members of this receptor-family often mediate anti-inflammatory effect. Participates in regulation of IL-4 release from natural killer T cells. |
| 3p13 | *FOXP1* | rs80060485 | $2.6\times10^{-15}$ | None | Ji *et al.* (2017) | Member of forkhead box transcription factor family. Involved in regulation of lymphocyte expansion and differentiation. |
| 3p21 | *MST1* | rs3197999 | $1.1\times10^{-16}$ | IBD, CD, UC | Melum *et al.* (2011) | Serine-threonine kinase. Takes part in the Hippo signaling pathway. Involved in cell morphogenesis, proliferation, apoptosis and stress responses. Regulates inhibitory functions towards macrophages during inflammation. |
| 4q24 | *NFKB1* | rs3774937 | $6.1\times10^{-9}$ | UC, PBC | Ellinghaus *et al.* (2016) | Member of NF-κB family. Controls genes regulating multiple biological processes, including inflammation, tumorigenesis and apoptosis. |
| 4q27 | *IL2, IL21* | rs13140464 | $8.9\times10^{-13}$ | AA, IBD, CeD, T1D | Liu *et al.* (2013) | *IL2*: Broad range of roles in the immune system, among other crucial for T-cell proliferation and regulatory T-cell activity.<br>*IL21*: Inflammatory cytokine. Regulates the activity of multiple target cells in the innate- and adaptive immune response |
| 6q15 | *BACH2* | rs56258221 | $8.4\times10^{-12}$ | CeD, IBD, CD, T1D, VT | Liu *et al.* (2013) | Transcription factor. Inhibits differentiation of effector-memory T-cells and regulates cell differentiation. Implicated in antiviral innate immune response. |
| 10p15 | *IL2RA* | rs4147359 | $1.5\times10^{-8}$ | AA, IBD, CD, MS, RA, T1D, VT | Srivastava *et al.* (2012) | Associates to CD122 and form the high-affinity receptor for IL-2. Binds IL-2 and mediates its signaling effects. |

| | | | | | | |
|---|---|---|---|---|---|---|
| 11q13 | *CCDC88B* | rs663743 | $2.2\times10^{-13}$ | IBD, CD, PBC, SARC | Ji *et al.* (2017) | Member of the hook-related protein family. Regulates maturation and effector functions of T cells during inflammation. |
| 11q23 | *SIK2* | rs7937682 | $3.2\times10^{-9}$ | None | Liu *et al.* (2013) | Serine-threonine kinase. Affects IL-10 in macrophages and NUR77 in leukocytes. |
| 12q13 | *HDAC7* | rs11168249 | $5.5\times10^{-9}$ | IBD | Liu *et al.* (2013) | Class IIa histone deacetylase. Participates in negative selection mechanisms of T cells in the thymus. Essential role in vasculature development. |
| 12q23 | *RFX4, RIC8B* | rs12369214 | $1.3\times10^{-9}$ | None | Ellinghaus *et al.* (2016) | *RFX4*: Transcription factor belonging to the regulatory factor family. Potentially involved in regulation of immune- and infectious responses.<br>*RIC8B*: G-alpha-binding protein. Catalyzes cAMP production |
| 12q24 | *SH2B3, ATXN2* | rs3184504 | $5.9\times10^{-11}$ | CeD, HT, IBD, RA, SLE, T1D, VT | Liu *et al.* (2013) | *SH2B3*: Negative regulator of cytokine signaling and cell proliferation.<br>*ATXN2*: Expressed in hepatocytes and specific neuron populations. Involved in EGFR trafficking, Potentially plays a role in insulin resistance. |
| 16q12 | *CLEC16A, SOCS1* | rs11649613 | $1.3\times10^{-11}$ | CeD, IBD, CD, MS, PBC, SLE, T1D | Ellinghaus *et al.* (2016) | *CLEC16A*: Regulation of B-cell function and autophagy of mitochondria.<br>*SOCS1*: Regulation of cytokine signaling and of thymocyte development. Maintains regulatory T-cell integrity and function. |
| 18q21 | *TCF4* | rs1452787 | $2.6\times10^{-8}$ | None | Ellinghaus *et al.* (2013) | Transcription factor. Regulates plasmacytoid dendritic-, early B- and T cell development. |
| 18q22 | *CD226* | rs1788097 | $3.1\times10^{-8}$ | IBD, RA, T1D | Liu *et al.* (2013) | Co-stimulatory adhesion molecule expressed on immune- and endothelial cells. Enhance cytotoxic function of T cells and natural killer cells. |
| 19q13 | *PRKD2, STRN4* | rs60652743 | $6.5\times10^{-10}$ | T1D | Liu *et al.* (2013) | *PRKD2*: Member of protein kinase D family. Regulation of cell proliferation and the negative selection of T cells.<br>*STRN4*: Involved in cell differentiation, transformation and apoptosis |
| 21q22 | *PSMG1* | rs2836883 | $3.2\times10^{-17}$ | AS, IBC, UC | Liu *et al.* (2013) | Chaperone protein. Important role in ubiquitin-proteasome system. |
| 21q22 | *UBASH3A* | rs1893592 | $2.2\times10^{-12}$ | RA, T1D, VT | Ji *et al.* (2017) | Member of protein tyrosine phosphatase family. Regulates T cell by facilitating apoptosis. |

AA, alopecia areata; AID, autoimmune diseases; AS, ankylosing spondylitis; CD, Crohn's disease; CeD, coeliac disease; Chr, chromosome, GV, Graves' disease; HT; hypothyroidism; IBD, inflammatory bowel disease; MG, myasthenia gravis; MS, multiple sclerosis; PBC, primary biliary cholangitis; RA, rheumatoid arthritis; SARC, sarcoidosis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; UC, ulcerative colitis; VT, vitiligo.

**Key point**

Genome-wide association studies have identified 23 genome-wide significant ($p \leq 10^{-8}$) risk loci that positions autoimmune processes central to the pathogenesis of PSC.

such cases. Thereafter, estimated yearly incidence is 0.5% to 1.5% and late presentations (more than 10 years after the PSC diagnosis) also occur.[34,52–55] The risk of colorectal cancer is fivefold higher than in IBD without PSC and may occur at any point. Hence, colonoscopic surveillance should be performed regularly from the time of diagnosis of PSC, elaborated on later.[56–59] Hepatocellular cancer (HCC) and pancreatic cancer also occur in PSC;[53] HCC possibly at lower frequencies than in cirrhosis from other causes.[60] Whether pancreatic cancer truly occurs at increased frequencies as suggested by some authors,[53] or represents misclassification of CCA in the pancreatic part of the *ductus choledochus* can be debated based on the report on low numbers of pancreatic cancer (ten out of 7,119) in a multi-centre cohort.[48]

Increased frequencies of multiple gallbladder abnormalities including dilatation, cholecystitis, gallstones, and benign and malignant gall bladder lesions are seen in PSC.[61–65] PSC-like gallbladder affection has long been recognised in PSC,[1,66] and seems to occur in up to 15% of patients.[62,67] Gallstones can be found in approximately 25% of patients with PSC,[62] and should be considered part of the normal disease spectrum in otherwise typical cases, rather than excluding the diagnosis.[68,69] Gallbladder mass lesions or polyps have been observed in 4% to 6.5% of patients with PSC, with ~55–75% of these being malignant, leading to reported gallbladder cancer frequencies of 2.5% to 3.5% in the overall PSC population.[61,62] Although a cut-off of 0.8 cm for cholecystectomy has been proposed by some authors,[65] smaller lesions may also harbour neoplasia.[70]

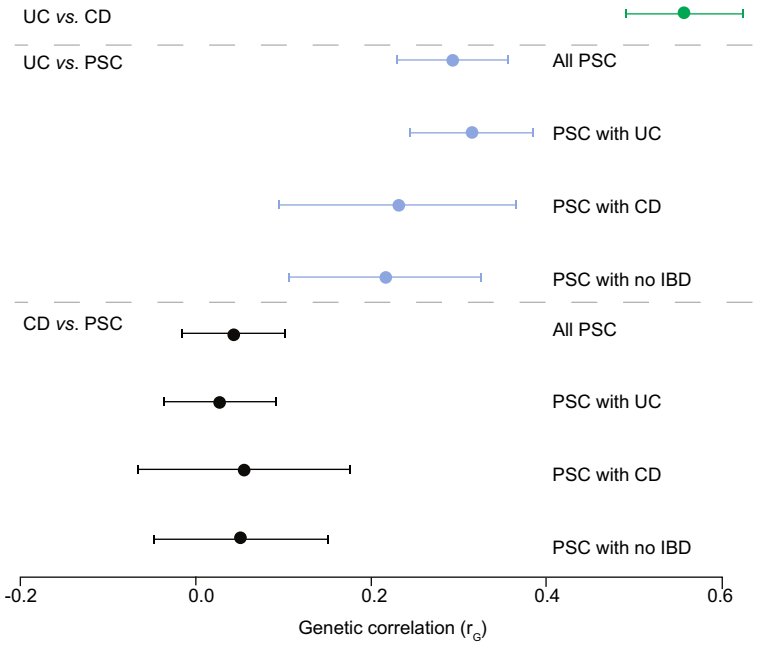


**Fig. 3. Inflammatory bowel disease in primary sclerosing cholangitis (PSC).** PSC has a significantly lower genetic correlation with ulcerative colitis and Crohn's disease (UC and CD; rG = 0.29 and rG = 0.04, respectively) than ulcerative colitis with Crohn's disease (rG = 0.56). This observation supports the clinical notion that inflammatory bowel disease in PSC is a distinct disease entity. Reprinted with permission from reference.[73]

## Aetiology and pathogenesis

A schematic overview of the predominant processes of PSC pathogenesis is shown above (Fig. 2). This overview is based on the various theories of PSC pathogenesis that exist. The story is not currently complete with several contradictions including: a) the lack of efficacy of immunosuppressive drugs pre- and post-liver transplant despite a proposed autoimmune aetiology, b) the progression of PSC after colectomy in the absence of a leaky gut, c) the lack of efficacy of ursodeoxycholic acid (UDCA) and the differing genetic susceptibility of PSC compared to other progressive cholestatic syndromes, despite the proposal that bile acid toxicity causes PSC. However, the clinical observations may partly reflect that these treatments have been applied too late in the disease course, for insufficient duration and/or at an inadequate dose. The pathognomonic lesion in PSC is an "onion skin" scar, referring to concentric layers of fibrosis circumferential to the cholangiocyte lining of the bile ducts. How the cholangiocytes and a few scattered immune cells (mostly T cells, but also neutrophils and macrophages) work with hepatic stellate cells and portal myofibroblasts in the generation of this fibrous obliteration is unknown. Most importantly, the lack of understanding of PSC pathogenesis prevents the development of effective therapies.

The initiating factors for the processes shown in Fig. 2 remain obscure. Siblings of patients with PSC and IBD have an enhanced risk of developing PSC (11-fold and 8-fold respectively) indicating that genetic factors are involved.[71] Genome-wide case-control comparisons of the frequency of genetic variants (genome-wide association studies [GWAS]) have provided a means of dissecting genetic risk in the many human diseases with non-Mendelian patterns of inheritance (so called complex genetic diseases), PSC included (Table 1).[72] The genetic risk in these disorders is dependent on a very large number of disease genes (susceptibility genes), each with a minute impact on overall risk (typically with an odds ratio of 1.2–1.3 or less). The number of susceptibility genes detected for each disease largely reflects the size and phenotypic homogeneity of the available study population, with more than one hundred genes detected in several common diseases where more than 50–100,000 cases and controls have been studied. For PSC, patient populations have been 10-fold smaller,[73–81] with more than 20 robust PSC genes identified.

The main outcome of PSC genetic studies has been the positioning of PSC as an autoimmune disease.[82] The predominant genetic findings localise within the human leukocyte antigen (HLA) complex

on chromosome 6 (odds ratio 3–5), with all other findings much weaker (odds ratio 1.5 and below). The non-HLA findings are almost without exception associated with one or more other immune-mediated or autoimmune condition. Based on the gut leakage and bile acid toxicity centred hypotheses of PSC pathogenesis, one may have anticipated the presence of more non-HLA genes related to innate immunity (similar to Crohn's disease) or bile homeostasis (as observed in paediatric cholestasis syndromes), respectively.[75,79] However, most PSC genes appear to relate to adaptive immune function. Furthermore, there are limited genetic links with IBD, with less than ten out of more than 150 IBD genes showing associations with PSC, and only about half of the PSC genes showing associations with IBD, favouring the hypothesis that the IBD in PSC represents a unique IBD subtype, with genetic features that are distinct from UC and Crohn's (Fig. 3).[73] The other PSC genes show associations to prototypical autoimmune diseases (*e.g.* type 1 diabetes and multiple sclerosis), implying that the genetic susceptibility to PSC extends into autoimmune pathophysiology beyond that represented by IBD.

There are high hopes that the genes identified will provide critical clues to PSC pathogenesis as these findings from patients are likely to be most relevant. The translational research has scarcely started (*e.g.* for *IL2RA* and *CD28*), and will be challenging for many risk loci, since an individual gene has not yet been assigned as causal (*i.e.* it is hard to determine which of a series of neighbouring genes is relevant).[83,84] Even within robustly assigned genes, the causal genetic variant is often unknown, making it impossible to determine whether the variants increase protein function (gain-of-function) or decrease protein function (loss-of-function). Finally, development of an appropriate portfolio of experiments based upon the published literature is biased by studies of gene function that were performed without prior knowledge of a genetic association to PSC. This means tissue- and disease-specific functions may be missed, particularly those relating to cholangiocyte and biliary physiology. Nevertheless, generating hypotheses for how the individual genes identified (Table 1) are involved in PSC pathogenesis is feasible, and now provides a great opportunity for targeted pathophysiological research.

The strong HLA association suggests that adaptive immune responses are involved. The HLA class I and/or class II genes are most likely responsible for the findings in PSC[85] – possibly *HLA-B* (class I) and *DRB1* (class II).[77,86] The HLA class I (expressed on all cells) and class II (expressed on antigen-presenting cells) molecules present potentially antigenic peptides, derived from intracellular and extracellular sources, respectively, to the T cell receptor (TCR) on CD8 and CD4 positive T cells. In PSC and most other HLA associated diseases, the antigenic peptides are unknown. In coeliac disease and drug-induced liver injury, equally strong HLA associations are complementary to exogenous gluten and drugs, respectively, suggesting the presence of a similar mechanism behind HLA associations in autoimmunity.[87] Data also suggest the presence of PSC specific TCR clones in the livers of patients,[88] but as for the PSC associated HLA variants, their antigen specificity is unknown. It is currently unknown whether the gut and liver co-morbidity in PSC is caused by exposure to a similar antigenic trigger at both sites,[89] or by the recruitment to the liver of T cells that have been primarily activated in the gut.[90] The latter possibility is favoured by the presence of similar lymphocyte homing mechanisms for the liver and the gut.[91]

The predominant cell type in the portal inflammatory infiltrate in liver biopsies from patients with PSC is the T cell.[92,93] It has been suggested that there is cross-talk between cholangiocytes and T cells, facilitating their recruitment to the portal areas.[94,95] How the potentially T cell related susceptibility genes (*e.g. IL2/IL21*, *IL2RA*, *HDAC7*, *SIK2*, *PTPN2*, *SH2B3*, *CTLA4/CD28*, *IL2/IL21*, *MMEL1/TNFRSF14*, *CCL20*, *CD226*, *FOXP1*, *CCDC88B* and *PRKD2*) exert their pathogenicity in the context of this cellular infiltrate is unknown. Many of them are relevant both to development, activation and key effector functions of several T cell subsets. Other cell types, notably macrophages and neutrophils, are found in the portal areas.[96,97] By investigating bile, a strong protein signature (*e.g.* IL8, S100A8), supporting the involvement of one or both of these cell types has been found.[98–100] Some of the susceptibility genes (*e.g. PRDX5*, *TGR5, PSMG1*, *NFKB1* and *REL*) may also play a role in innate immune responses related to these observations, but details are unknown. Regarding the potential triggering of innate immune responses by gut-derived bacterial components, similar to cholangiopathy in the *Cftr*$^{-/-}$ mouse model,[101] there is currently limited human data supporting the occurrence of simple "leakage" of LPS and other bacterial components in PSC.[102]

Some of the PSC susceptibility loci harbour genes that are potentially involved in bile acid homeostasis (*e.g. TGR5* on chromosome 2 and *HDAC7* on chromosome 12),[103,104] but there is currently no data to support involvement of genes causing Mendelian cholestasis syndromes (*e.g. ABCB4* and *BSEP*) in PSC. This does not mean bile acid toxicity and alterations to protective mechanisms (including the $HCO_3^-$-producing machinery, which involves both CFTR and TGR5)[19] are irrelevant, but rather it implies such mechanisms are downstream of the initiating events (Fig. 2). Bile formation is a complex physiological process.[105] A broad avenue of research in the bile acid field has developed in close relationship with therapeutic developments. The widespread prescription of UDCA has inspired research into the mechanisms of action behind the potential protective effects of bile acid interventions in

**Key point**

The role of the gut in PSC development is as of yet undefined, and the interplay between the gut microbiota and host immunology and bile acid physiology are rapidly growing research fields.

PSC.[106] New therapeutic applications have been derived from this research in the form of *nor*UDCA, which appears to enhance general resistance to bile acid induced biliary injury, via a bicarbonate rich choleresis, along with local effects in the bile ducts by cholehepatic shunting.[107–110] Additionally, research following the same logic has expanded knowledge on a broad range of nuclear receptors that respond to cholestasis and are involved in normal bile acid homeostasis (*e.g.* farnesoid X receptor; FXR, retinoid X receptor; RXR, peroxisome proliferator-activated receptor alpha; PPARalpha and pregnane X receptor; PXR).[111] These receptors are currently under scrutiny as therapeutic targets in early phase clinical trials (*e.g.* trials of the FXR agonist obeticholic acid).

The biliary epithelium shows an activated phenotype in PSC,[112] including an expansion of the peribiliary gland system.[113] Although the details are not clear, this activation is likely important for peribiliary fibrosis development and subsequent cirrhosis, through interactions with hepatic stellate cells,[114] portal myofibroblasts,[115] or both. Persistent exposure to effector molecules of chronic inflammation and regeneration (*e.g.* interleukin 6 and WNT signalling),[116,117] along with a co-carcinogenic effect from accumulated bile acids during chronic cholestasis,[118–120] are probably important for the malignant transformation of cholangiocytes. Further research into bile homeostasis and cholangiocyte biology is being facilitated by better experimental tools (*e.g.* biliary organoids and new animal models).[121,122] Furthermore, there is increasing appreciation of the co-metabolic functions of the gut microbiota in bile homeostasis,[123,124] whereby gut bacteria either directly (*e.g.* by conjugation) or indirectly (*e.g.* via altered FXR signalling[125,126]) influence biliary physiology.

The composition of the gut microbiota in PSC has been described using 16S rRNA sequencing technologies.[20] Overall, the composition of the gut microbial community is altered, with an overall reduction in bacterial diversity and altered abundance of certain bacteria compared with the healthy state.[24,127–132] The loss of microbial diversity observed in a variety of disease states, PSC now included, is a major outcome of studies so far.[133] Yet, this observation raises the problem of "the chicken or the egg", which cannot currently be resolved. To date, most studies performed in human diseases have analysed mucosal or stool samples from diseased individuals, in whom observations can be a consequence, as much as a cause of the disease. However, data from other diseases, suggests that reduced bacterial diversity occurs prior to and independent from clinical disease manifestations.[20] By what mechanisms bacterial diversity and other gut microbial changes may be pathogenic remains to be established for any disease. For PSC, several hypotheses can be made, ranging from immunolog-

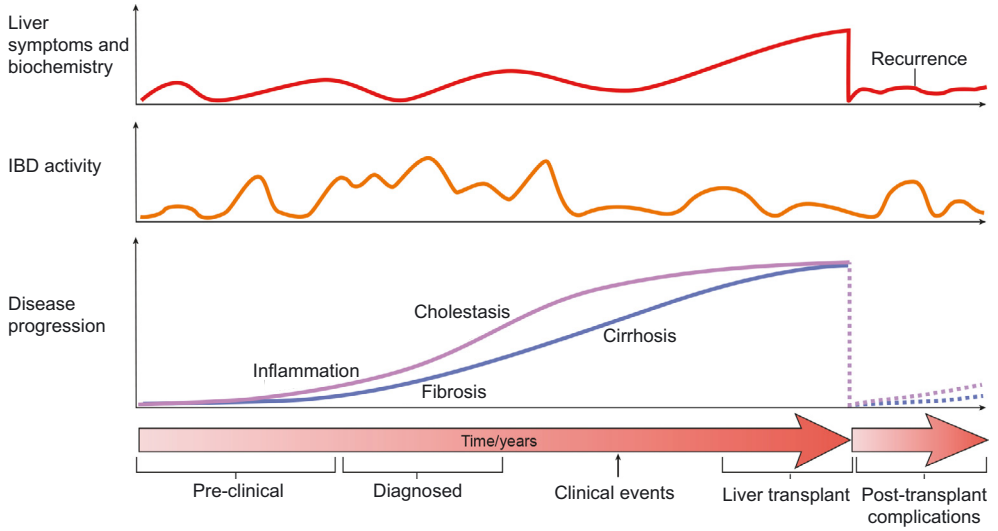


**Fig. 4. Natural history in primary sclerosing cholangitis (PSC).** Disease course assessed by hepatic biochemistries and symptoms typically fluctuate (upper panel). Inflammatory bowel disease (IBD) disease behavior (middle panel) is also variable and does not correlate with liver manifestations. Liver disease progression is inevitable in most patients, with fibrosis and cirrhosis due to inflammatory and cholestatic processes (Fig. 2). As illustrated in the bottom timeline, the high fraction of asymptomatic patients at diagnosis raises suspicion that there is often a long preclinical phase and diagnostic lead-time. The lack of tools to accurately evaluate disease activity and stage in PSC is a challenge in the follow-up of patients and in determining clinical efficacy of new drugs in clinical trials (Table 2 and Box 5). Clinical events frequently warrant specialist consultation (Box 3). Liver transplantation is the only curative treatment option, but timing varies according to local practice, which involves symptomatic indications (*e.g.* recurrent cholangitis, intractable pruritus) and cholangiocellular dysplasia in addition to end-stage liver disease. Finally, as shown in the right part of the figure, a number of post-transplant issues occur in PSC, including a high frequency of acute cellular rejections, disease recurrence as well as IBD exacerbations (which must be demarcated from transplant related bowel complications, such as cytomegalovirus colitis and mycophenolate colitis). Printed with permission from Kari C. Toverud.

ical mechanisms (*e.g.* altered innate immune activation status, antigenicity of microbial products) to metabolic factors (*e.g.* relating to bacterial co-metabolism of bile acids). Gene findings (*e.g.* the *FUT2* associations[79,134,135]) support the involvement of the gut microbiota in initiating events of PSC pathogenesis, which as suggested from the pilot data on antibiotic therapy may also hold therapeutic prospects.[136]

## Diagnostic definitions

A practical guide to diagnostic considerations when PSC is suspected is provided (Box 1). PSC requires a radiological diagnosis made upon the exclusion of known causes of sclerosing cholangitis (secondary sclerosing cholangitis, Box 1). The modality of choice for making a diagnosis of PSC is now MRC, with acceptable sensitivity and specificity (0.86 and 0.94, respectively) and cost-effectiveness compared with ERC for initial screening.[137,138] Serum liver tests typically show a cholestatic profile, but it is important to be aware that alkaline phosphatase (ALP) levels are naturally fluctuating in PSC (Fig. 4), and may be normal in a significant fraction of patients. Clinical, endoscopic (*i.e.* type and distribution of lesions), radiological and histological examinations are required to establish a diagnosis of either UC or Crohn's disease in patients with PSC.[139,140] The IBD associated with PSC is phenotypically (Fig. 1) and genetically[73–75] distinct from patients with IBD in the absence of PSC. Since pathognomonic features of IBD in PSC do not exist, standard IBD definitions should still be used, whilst making sure particular features (*e.g.* "backwash" ileitis, rectal sparing etc.) are adequately captured and described. Definition of PSC subtypes (Box 1) and CCA (Box 2) often poses similar clinical considerations, since normal diagnostic criteria and definitions are often not directly applicable to patients with PSC.

### *IgG4-associated sclerosing cholangitis*

The distinction between IAC and PSC with elevated IgG4 is important as the cholangiographic changes of IAC may resolve completely upon corticosteroid treatment and IAC is not pre-malignant. However, PSC patients with elevated IgG4 are less responsive and data suggest they may progress more rapidly than other PSC patients.[10,11] Patients are diagnosed using an adaption of the HISORt criteria for autoimmune pancreatitis, on the basis of two or more main manifestations (elevated serum IgG4, suggestive pancreatic imaging findings, other organ involvement and bile duct/ampullary biopsy with >10 IgG4 positive cells/high power field) combined with a significant response to corticosteroid treatment.[141] However, many centres are reluctant to perform bile duct or ampullary biopsies because of the perceived risk of cholangitis or pancreatitis and low yields. Serum IgG4 measurement has insufficient accuracy and established cut-off values are lacking; slight elevations up to 5 g/L or 4×ULN occur in patients with PSC not fulfilling IAC criteria. Additional evaluation of IgG4/IgG1-ratio (>0.24 indicates IAC) or blood IgG4/IgG RNA ratio using real-time PCR (elevated in IAC) has been reported to improve delineation of IgG4 disease and could enhance the diagnostic algorithm.[45,142] Moreover, IgG4 may be directly involved in the pathogenesis of IAC, as suggested by the excellent clinical response upon treatment with the anti-CD20 antibody, rituximab, in IAC patients,[143] as well as the induction of disease in neonatal mice upon injection of IgG4 and IgG1 from patients with IAC.[144]

**Box 2. Diagnosis of cholangiocarcinoma and bile duct dysplasia in primary sclerosing cholangitis (PSC).**

| Diagnostic features | Cholangiocarcinoma | Bile duct dysplasia |
|---|---|---|
| Indicative findings | | |
| 1. Clinical: | • Rapid clinical deterioration (features of biliary obstruction, weight loss, abdominal pain) | • None |
| 2. Biochemical: | • Cholestatic liver function tests<br>• Continuously elevated CA19-9 after biliary decompression<br>• Elevated CA-125 (65%) | • None |
| 3. Non-invasive imaging (MRI/MRC, CT, US) | • Mass lesion (iCCA)<br>Hilar stricture (pCCA)<br>Distal bile duct stricture (dCCA)<br>± biliary duct dilatation, extrahepatic metastasis | • Bile duct stricture |
| 4. Invasive imaging: (ERC, POCS, IDUS) | • Bile duct stricture or polypoid lesion | • Bile duct stricture |
| Confirmatory findings | | |
| 5. Cytological: ± DIA or FISH | • High grade dysplasia or carcinoma<br>• Cellular aneuploidy | • Low to high grade dysplasia |
| 6. Histological: (FNAC, biopsy, surgical specimens) | • Carcinoma (adenocarcinoma >95% of cases) | • Low to high grade dysplasia |

CT, computerized tomography; dCCA, distal cholangiocarcinoma; DIA, digital image analysis; ERC, endoscopic retrograde cholangiography; FISH; fluorescent *in situ* hybridisation; FNAC, fine needle aspiration cytology; iCCA, intrahepatic cholangiocarcinoma; IDUS, intraductal ultrasound; MRI/MRC, magnetic resonance imaging/magnetic resonance cholangiography; pCCA, perihilar cholangiocarcinoma; POCS, peroral cholangioscopy; US, ultrasound.

**Key point**

Demarcating IgG4-associated cholangitis and features of autoimmune hepatitis in patients with PSC have therapeutic implications.

### *Small-duct PSC*

The continuous improvement in MRC technology (*e.g.* the use of higher magnetic fields) means that the likelihood of an abnormal ERC in patients with normal MRC is small. If MRC is normal and PSC is suspected, it is reasonable to consider patient referral to centres with known technical expertise in MRC as a first step. If high-quality MRC is normal, most experts would perform a liver biopsy, unless ERC is indicated (*e.g.* suspected gallstone disease).

Seminar

A diagnosis of small-duct PSC is made upon histological findings characteristic of PSC and concurrent clinical and biochemical abnormalities strongly suggestive of PSC.[145] It is not clear if small-duct PSC represents an early-stage of PSC, a mild variant of PSC or a separate disease entity with an aetiology distinct from large-duct PSC. The HLA associations with IBD in small-duct PSC resemble those of large-duct PSC, and suggest shared aetiologies between large-duct PSC and small-duct PSC in the presence of concomitant IBD.[146] In small-duct PSC without IBD, a heightened suspicion of other biliary diseases (*e.g.* primary biliary cholangitis [PBC]) or secondary sclerosing cholangitis (*e.g.* related to genetic cholestasis resulting from *ABCB4* mutations) is warranted.

*Autoimmune hepatitis in patients with PSC*

Biochemical and histological features of autoimmune hepatitis are apparent in 7–14% of patients with PSC. This poorly demarcated patient group has previously been denominated "overlap patients" or patients affected with "overlap syndrome". However, current understanding is that rather than reflecting a distinct entity, the observed autoimmune features in PSC form a continuous spectrum with higher activities typically seen in younger patients.[147] Accordingly, a position paper published from the International Autoimmune Hepatitis Group (IAIHG)[148] argues in favour of abandoning the term "overlap syndrome". Rather, the consensus is that each diagnosis should be considered separately, and a diagnosis of PSC made based on standard criteria. If features of autoimmune hepatitis are also detected, the patient has PSC with features of autoimmune hepatitis. Importantly, diagnosis and treatment of autoimmune hepatitis in the context of PSC is complex and the IAIHG scoring systems for autoimmune hepatitis are less useful. Elevated transaminases and IgG may indicate autoimmune hepatitis, but may also be elevated as part of the biliary disease, meaning histological evidence is generally required for the diagnosis of the combined entity and therapeutic decision-making. Immunosuppressive therapy following standard guidelines for treatment of autoimmune hepatitis is recommended for patients with PSC and features of autoimmune hepatitis, although literature regarding treatment outcome is scarce.[149] The treatment response seems less pronounced than in autoimmune hepatitis without a primary diagnosis of PSC, and the risk of side-effects, particularly bone disease, often prompts discontinuation in difficult-to-treat cases.

**Key point**

Ursodeoxycholic acid has a positive impact on surrogate markers for PSC activity and is widely prescribed for treatment of PSC, but should not be used at high doses.

## Stratification and prognostication

The natural history of PSC is progressive, evolving through biliary fibrosis to liver cirrhosis and end-stage liver disease or CCA in the vast majority of patients (Fig. 4).[150] Asymptomatic patients have been shown to have a better prognosis than patients with symptoms at diagnosis, but often develop symptoms given time.[151,152] PSC has a highly variable natural history. Furthermore, the naturally fluctuating course of liver biochemistry tests, ALP and bilirubin (where transient elevations may be caused by cholangitis, biliary calculi or dominant strictures), adds to the difficulty of assessing disease stage and prognosis. Currently there are no established prognostic tools that reliably estimate prognosis in the individual patient.

*Clinical risk models and histology*

Several attempts have been made to develop a PSC specific risk stratification or prognostic model, to predict clinical outcome in early PSC. The first PSC specific model was presented by the Mayo Clinic in 1989,[153] with several models subsequently developed (Table 2). Over time, liver biopsy was abandoned because of its invasive nature and inherent sampling variability in PSC.[151,154,155] Subjective variables (*e.g.* splenomegaly and hepatomegaly) were also excluded in later models. Time-dependent models are considered to capture risk more accurately, as biochemical parameters may change according to disease stage.[156] The PSC specific revised Mayo risk score is the most widely used model (Table 2); however, its relatively short horizon (four years), as well as a flat-running survival estimate curve in early-stage disease, yields limited discriminant information. Moreover, the notable failure of the model in forecasting the adverse outcomes observed in high-dose UDCA treatment trials was a disappointment.[157]

The observation that ALP reduction after UDCA treatment can predict outcomes (liver transplantation and death) in PBC[158] has inspired studies into the association between ALP reduction and clinical outcome after UDCA treatment in PSC.[159–163] However, study design varies and attempts to cross-validate suggested criteria in subsequent studies have failed. For instance, a cut-off value of 1.5xULN proved discriminatory at two years in one study (Oxford cohort), but was only found predictive when applied at six and 12 months by others (Heidelberg and UK-PSC series, respectively). In addition, unlike in PBC, ALP has a naturally unpredictable fluctuating nature in PSC which, on the individual level, may limit the value of single measurements at any point in time for patient follow-up or clinical trials alike. Thus, further studies are warranted to clarify the relevance of ALP for treatment response stratification in PSC.

As typical cholangiographic changes define the diagnosis of PSC, prognostic scoring systems have been based on imaging of bile duct changes in PSC. The cholangiographic classification of intra- and extrahepatic biliary duct lesions using ERC in the

**Table 2. Prognostic indices in primary sclerosing cholangitis (PSC).** This table provides an overview of biomarkers and clinical scores predicting prognosis in PSC, including serum-based biomarkers, imaging and clinical features, as well as composite scores often based on natural history studies. Currently, the revised Mayo risk score is most widely used in PSC, while the Child-Pugh score is widely used in cirrhosis staging in chronic liver diseases in general. Model for end-stage liver disease (MELD) score is frequently employed as a liver transplant allocation tool, although with caveats discussed in the text. No single biomarker or score has been definitively established for clinical use at the individual level in PSC.

| Prognostic indice | Details | Comments | References |
|---|---|---|---|
| Age | Increased age | Age is consistently associated with prognosis across studies and included in many risk models | 151,153–156,257,258 |
| Albumin | Low albumin | Albumin is inversely associated with prognosis and a component of several clinical risk scores; sign of advanced, decompensated liver disease, low sensitivity in early disease | 156,257,258 |
| ALP | ALP as continuous variable | ALP is consistently associated with prognosis across studies; however, the naturally fluctuating course of ALP in PSC complicates its use in individual patients. | 159–163 |
| | ALP normalization (any time) | | |
| | ALP reduction to <1.5×ULN (any time or one year) | | |
| | ALP normalization, OR 50% reduction, OR <1.5×ULN within six months | Variable criteria have been applied across studies, and findings from individual studies have not been confirmed in others (*e.g.* ALP <1.5×ULN at one or two years not confirmed in subsequent studies). Sub-optimal study design (post-hoc analyses of UDCA trials) in some of the studies | |
| | ALP normalization OR 40% reduction at one year | | |
| Anti-GP2 | Pancreatic autoantibody | Anti-GP2 positivity was associated with poor LTX-free survival in two independent patient panels; long FU; association with CCA | 259 |
| Bilirubin | Bilirubin | Bilirubin elevation is consistently associated with a worse prognosis across studies, as incorporated in 8/9 clinical predictive scores. Transient elevations due to cholangitis, biliary obstruction, etc. complicate the use of single measurements of bilirubin; elevation >3 months proposed by some to overcome this | 151,153,155,156,257,258,260,261 |
| | Elevated bilirubin >3 months | | |
| Dominant stenosis | Bile duct diameter 1.5 mm smaller than that of the common duct or 1.0 mm smaller than that of a hepatic duct (within 2 cm of the bifurcation at ERC) (poorly defined) | Associated with adverse prognosis. Endoscopic treatment of dominant stenosis has been demonstrated to improve revised Mayo–risk predicted LTX-free survival | 195 |
| ELF test | Based on three direct components of fibrogenesis: HA, TIMP-1, PIIINP | ELF test is a strong predictor of prognosis (LTX, death) independent of the revised Mayo risk score. Validation of results in several independent patient panels, yet all retrospective | 171,172 |
| IgG4-high PSC | Elevated IgG4 and/or IgG4/IgG1 ratio; IgG4 disease excluded | Elevated IgG4 in PSC is associated with a shorter LTX-free survival | 10 |
| IL8 | Inflammatory marker | IL8 predicted clinical outcome in two independent patient panels in a single-centre study | 100 |
| INR | Represents liver failure | Component in some clinical risk scores; sign of advanced, decompensated liver disease, low sensitivity in early disease | 260 |
| Small-duct PSC | Characteristic histology for PSC despite normal cholangiogram | Associated with better prognosis and not associated with increased risk of CCA; however, the risk of converting to large-duct PSC over time is not well documented | 34 |
| Vap-1 | Vascular adhesion protein-1 | Vap-1 predicted clinical outcome in two independent PSC patient panels from two different centers in one study | 262 |
| ***Invasive*** | | | |
| Histological stage | Histologic staging by either the Nakanuma, Ishak or Ludwig score | Associated (in descending order) with LTX or liver-related death | 167,168 |
| Amsterdam score | Based on scoring of intrahepatic and extrahepatic changes on ERC cholangiograms | One large single-center study (n = 174), long FU; invasive nature (ERC) limits utility in clinical FU | 164 |
| Calprotectin (bile) | Calprotectin in bile (from ERC) | Parallels use of faecal calprotectin in IBD, underscoring relationship between PSC and IBD. Requires invasive procedure for sampling, reducing utility in clinical FU | 99 |
| ***Non-invasive imaging*** | | | |
| MRI | Arterial peribiliary hyperenhancement | One small study (n = 62) found association with increased revised Mayo risk score, LTX and death | 165 |
| MR elastography | Liver elasticity | One large single-center, retrospective study (n = 266) showed association with liver decompensation. Not universally available; currently too costly and time-consuming for routine clinical use; not applicable if iron overload. Further studies warranted. | 179 |

(*continued on next page*)

**Table 2** (*continued*)

| Prognostic indice | Details | Comments | References |
|---|---|---|---|
| Transient elastography | Liver stiffness (elasticity), using Fibroscan®; baseline values or change | Retrospective, single-center, large study;[168] both baseline values and change in liver stiffness predicted clinical outcome (LTX, death or liver decompensation). Impact of severe cholestasis/cholangitis uncertain. Not applicable in ascites or (severe) obesity. The findings were validated in an independent study from a different center. | 173,175 |
| Ultrasound | Spleen size (>120 mm) | Associated with prognosis (LTX, death, liver decompensation); single-center (n = 126), retrospective study, validation in independent cohort. | 175,263 |
| ***Clinical scores*** | | | |
| Child-Pugh score | Bilirubin, albumin, INR, encephalopathy, ascites | General cirrhosis score; 2-year survival in end-stage liver disease | 260 |
| Mayo score | Age, bilirubin, histological stage, haemoglobin, IBD | Includes liver biopsy (invasive); subjective elements (IBD) | 153 |
| King's College score | Age, histological stage, hepatomegaly, splenomegaly, ALP | Includes liver biopsy (invasive); subjective elements (hepatomegaly, splenomegaly) | 154 |
| Multicenter model | Age, bilirubin, histological stage, splenomegaly | Includes liver biopsy (invasive); subjective elements (splenomegaly); large panel (n = 426) mainly based on the cohorts from the studies by Wiesner and Farrant | 155 |
| Scandinavian model | Age, bilirubin, histological stage | Large cohort (n = 305); includes liver biopsy (invasive) | 151 |
| Revised Mayo risk score | Age, bilirubin, albumin, AST, variceal bleeding | Most commonly used model. Multi-center, large cohort (n = 405) and validation in independent cohort (n = 124). Based on existing data from the Multicenter study + 103 new patients. Relying mainly on factors reflecting advanced disease, insufficient discriminatory power in early disease. | 257 |
| MELD score | Bilirubin, creatinine, INR | General LTX allocation instrument; predicts 3-month mortality in end-stage liver disease | 261 |
| Time-dependent score | Age at diagnosis, bilirubin, albumin | Large multicenter cohort (n = 330); internal cross-validation | 156 |
| PSC score | Age, albumin, bilirubin elevation >3 months, hepatomegaly, splenomegaly, dominant bile duct stenosis, intra- and extrahepatic bile duct changes | Large cohort (n = 273); long FU; includes both clinical variables (some of affected by subjectivity) and cholangiographic changes (invasive) | 258 |

ALP, alkaline phosphatase; AST, aspartate aminotransferase; CCA, cholangiocarcinoma; ELF, Enhanced Liver Fibrosis test; ERC, endoscopic retrograde cholangiography; FU, follow-up; GP2, glycoprotein 2; HA, hyaluronic acid; IBD, inflammatory bowel disease; IgG4, immunoglobulin 4; IL8, interleukin 8; INR, international normalized ratio; LTX, liver transplantation; MELD, model for end-stage liver disease; MRC, magnetic retrograde cholangiography; MRI, magnetic resonance imaging; PIIINP, propeptide of type III procollagen; TIMP-1, tissue inhibitor of metalloproteinases-1; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; VAP-1, vascular adhesion protein-1.



Amsterdam score was proposed to estimate medium- and long-term prognosis in PSC,[164] but the invasive procedure reduces applicability in clinical practice. One study reported that early peribiliary hyperenhancement on MR imaging (MRI) was associated with the Mayo risk score, as well as clinical outcome (liver transplantation-free survival),[165] but others conclude that correlation between MRI/MRC findings and survival is unclear.[166]

Liver biopsy offers direct assessment of pathologic processes and traditionally played a central role in the evaluation of PSC, providing histologic assessment of disease grade and stage as gauged by the extent of inflammation and fibrosis, respectively. The Ludwig's score of fibrosis has been regarded as a reference standard in PSC, defining four progressive stages of disease. Histology was included in several early risk models for PSC (Table 2) and increasing Ludwig stage is associated with poorer survival.[153] Staging by either of three histological scoring systems: the Nakanuma system (developed for PBC), Ishak scoring, and Ludwig and Batts' scoring, was demonstrated to associate with transplant-free survival.[167,168] More objective continuous measures of the amount of fibrosis, such as collagen proportionate area may further improve the performance of liver histology, avoiding interobserver variability in the staging of PSC. Histology may be subject to considerable sampling variability in PSC,[169] although the clinical importance of the sampling error is disputed by some.[170] Nevertheless, the invasive nature and associated risk of adverse events, despite low procedure-related mortality, limit routine applicability of liver biopsy in PSC.

### *Noninvasive tests*

In recent years, there has been much interest in the development of noninvasive tests of liver fibrosis for stratification and prognostication in PSC. Serum tests of liver fibrosis reflect fibrogenesis either indirectly (*e.g.* APRI, Fib4 score) or directly. The

Enhanced Liver Fibrosis (ELF®) test, a direct marker panel of liver fibrosis based on three components of fibrogenesis and matrix remodelling, has been demonstrated to be a strong predictor of clinical outcome, independently of the Mayo risk score, in several independent PSC panels, underscoring the potential of liver fibrosis markers as prognosticators in PSC.[171,172] Since liver fibrosis potentially differs depending on aetiology, it is conceivable that tailoring of a specific liver fibrosis marker panel for PSC may yield improved predictive power.

Imaging offers alternative ways of assessing fibrosis. Liver stiffness measurement (LSM) by transient elastography (TE) has been extensively validated for the assessment of liver fibrosis in a range of chronic liver diseases. LSM as assessed by TE has been shown to correlate well with the degree of liver fibrosis in PSC, performing best at the extremes of histological stage.[173,174] An association between clinical outcome and both baseline LSM and change in LSM over time has been demonstrated for TE.[173,175] This finding has attracted substantial interest and TE is listed as one of the preferred candidates for surrogate endpoints in PSC, in a position paper by the International PSC Study Group (Box 5), although further validation is warranted.[176] Cholestasis is a confounder when measuring liver stiffness and case reports and small patient series have shown that LSMs improve following stricture treatment.[177,178] MR elastography (MRE) was explored in one retrospective study of 266 patients with PSC, suggesting that liver stiffness as assessed by MRE was associated with progression to decompensated liver disease.[179] MRE may be performed in conjunction with MRC, however it is expensive and not broadly available.

## Clinical events and patient management

PSC patients are subject to a number of significant events throughout a fluctuating and highly variable disease course (Fig. 4). Treatment recommendations are limited by the lack of robust data, but the current consensus is summarised in Box 3. Clinical experience is crucial given the complexity of the condition. We believe gastroenterologists and hepatologists at referral centres, with a significant experience base, should see patients with PSC at least annually and on the development of new symptoms.

### *Symptoms and quality of life*

Approximately 50% of patients with PSC are reported to have symptoms in recently published patient series; however, patient surveys report a higher prevalence, with fatigue, pain and pruritus the most common.[180] A limited number of studies have now been published interrogating the quality of life experienced by patients with PSC, utilising a

**Box 3. Practical management of clinical challenges in primary sclerosing cholangitis (PSC).**

| | |
|---|---|
| **Symptomatic treatment** | |
| Pruritus | Cholestyramine, rifampicin, naloxone/naltrexone, sertraline, nasobiliary drainage, plasmapheresis, Molecular Adsorbent Recirculation System, phototherapy, liver transplantation |
| Cholangitis | Antibiotics, prophylactic rotating antibiotics, ERC for flow-limiting strictures, liver transplantation |
| Fatigue | No evidence-based treatments |
| Bone disease | Vitamin D if needed, osteoporosis managed according to standard practice |
| **Liver disease modifying treatment** | |
| PSC | No current Level 1 evidence of treatments that alter the natural history of PSC |
| Recurrent PSC after liver transplantation | No current Level 1 evidence of treatments that alter the development of recurrent PSC |
| Features of autoimmune hepatitis | Predniso(lo)ne, azathioprine |
| PSC patients with high IgG4 levels | Predniso(lo)ne *ex juvantibus* in selected cases where IgG4 associated sclerosing cholangitis cannot be excluded |
| End stage liver disease with portal hypertension | Complications of cirrhosis managed according to standard practice |
| **Inflammatory bowel disease treatment** | |
| 5-aminosalicylic acid | Oral, suppository, enema |
| Corticosteroids | Predniso(lo)ne, budesonide |
| Anti-metabolite | Azathioprine, 6-mercatopurine |
| Anti-tumor necrosis factor-α | Adalimumab, infliximab, golimumab |
| Anti-integrin | Anti-α4β7 integrin (vedoluzimab), anti-α4 integrin (natalizumab) |
| Endoscopic | For ALM and DALM considered endoscopically resectable |
| Surgery (proctocolectomy with ileostomy or ileo-anal pouch) | For medically refractory colitis, DALM and ALM considered unsuitable for endoscopic resection, high grade dysplasia and colorectal cancer |
| **Dominant strictures treatment** | |
| ERC | Balloon dilatation, temporary short-term (1–2 weeks) plastic stent insertion |
| Percutaneous transhepatic biliary access | For selected cases of failure to cross stricture during ERC |
| **Liver surgery and transplantation** | |
| Resection extrahepatic biliary tree | Sometimes considered in selected low surgical risk patients with dominant stricture where endoscopic therapy has failed and liver transplantation is not available |
| Liver resection | Cholangiocarcinoma unsuitable for liver transplantation |
| Liver transplantation | For patients with decompensated cirrhosis, poor quality of life, refractory to medical therapy. In some centres patients with severe symptomatic disease, biliary dysplasia and localised hilar cholangiocarcinoma after neoadjuvant therapy. Normally cholangiocarcinoma should be excluded. |

ALM, adenoma-like mass; DALM, dysplasia associated lesion or mass; ERC, endoscopic retrograde cholangiography; IgG4, immunoglobulin G4.

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range of measures.[181–187] In only one study has the impact of coexistent IBD been considered with the Short IBD Questionnaire.[187] These studies have consistently demonstrated restrictions in quality of life across multiple domains. However, there are limitations to these findings, as the tools used are either generic quality of life measures or have been developed for other medical conditions (*e.g.* PBC-40). Poor quality of life, caused by severe refractory symptoms from recurrent cholangitis and pruritus unresponsive to standard therapy, may qualify patients for liver transplantation in some transplant programs.[188] While fatigue is common, with demonstrable associated autonomic dysfunction, there is a dearth of effective therapies and fatigue should not serve as the indication for liver transplantation outside the context of end-stage liver disease.[186,189]

*Bacterial cholangitis*

Bile cultures from patients with PSC show a wide range of bacteria, in patients with and without prior biliary interventions. Cholangitis occurs frequently but symptoms may be atypical and standard definitions for cholangitis (*e.g.* according to Billharz[190]) are not applicable. Empirical antibiotics are typically effective, and some patients require antibiotics to be readily available should features develop. Prophylactic antibiotics should be administered prior to and following biliary interventions.[191] The onset of acute cholangitis necessitates assessment for flow limiting biliary strictures by MRI and when necessary biliary intervention. Positive bacterial cultures of bile in patients undergoing ERC for dominant stenosis is not associated with worse prognosis in PSC, provided the dominant stenosis and infection are treated. However, *Candida* infection of bile may be associated with significantly worse prognosis.[192] Occasionally, late-stage patients may require long-term, rotating antibiotics for recurrent cholangitis.

Clinically apparent recurrent cholangitis may be a debilitating clinical problem for patients with PSC, but it is not associated with a worse prognosis for patients awaiting liver transplant, hence additional exception points are not warranted within MELD-based allocation systems.[193] This has called into question whether recurrent cholangitis should be an accepted indication for liver transplantation given the limited organ supply. There is a wide variation in practice internationally with 17% of patients with PSC transplanted for this indication in Norway,[188] while less than 5% of patients with PSC are registered for this indication in the UK.

**Key point**

Prognostication in PSC is likely to improve upon implementation of non-invasive tests for disease severity and disease stage; elastography and protein markers in particular.

*Dominant strictures*

The term dominant stricture is used to describe a clinically significant stenosis within the extrahepatic biliary tree in PSC detected at ERC. The generally accepted, yet arbitrary, definition is a stenosis of ≤1.5 mm in the common bile duct or ≤1 mm in the hepatic duct within 2 cm of the hilum.[194] Associated jaundice and/or cholestatic liver dysfunction are not part of the definition, although they do indicate the clinical relevance of the stenosis, which justifies invasive evaluation and therapy.[59] The ERC definition of a dominant stricture is not validated for MRC, which lacks hydrostatic pressure and spatial resolution in the extrahepatic ducts. However, MRC offers utility by providing a road map for subsequent ERC and may identify relevant mass lesions. Limited data exist regarding the natural history of untreated dominant strictures. A single retrospective study reporting dominant stenosis in 45% of patients, demonstrated similar change in liver biochemistry from baseline at two months and one year after diagnosis, whether a dominant stenosis was present or not.[195] This suggests that dominant stenoses do not result in worse short-term outcomes and questions whether biliary intervention is justified in the absence of worsening cholestasis.

The reported incidence of complications associated with ERC in PSC is 4–18%.[196–201] In one of three studies that had a control group the incidence of complications was increased compared to patients without PSC.[201] This justifies an approach whereby ERC is undertaken by the most experienced available operator. Peri-procedural antibiotics and standard strategies for prevention of pancreatitis (*e.g.* rectal NSAIDs and occasional prophylactic pancreatic stenting) are recommended per existing guidelines.[59] For the management of dominant strictures in PSC, balloon dilatation is the approach for which most evidence exists.[202] However, smaller studies report the short-term efficacy of plastic stent insertion (1–2 weeks).[202,203] In a recent randomised trial, both treatments were of equal clinical benefit, but with more frequent side-effects in the stenting group.[204]

*Cholangiocarcinoma*

It can be difficult to distinguish between the symptoms and findings of early stages of CCA complicating PSC, from PSC alone, although in the majority of cases, the early stages of CCA are asymptomatic (Fig. 1).[205] While rapid deterioration of liver function, abdominal pain, weight loss and increasing jaundice in patients with PSC should elicit suspicion of CCA, equally they may be caused by benign complications or progression of PSC, and when related to malignancy often reflect advanced CCA.

Diagnosing CCA in PSC relies on a combination of tumour marker CA19-9, various imaging modalities, biliary brush cytology, including cytogenetic testing if available and histology (Box 2).[56,57,206] A utility of CA19-9 is only seen in combination with other modalities, as it lacks sensitivity (low levels may be observed in advanced CCA) and specificity

(elevated levels may be observed with cholangitis or other malignancies).[207] Genetic variants in the fucosyltransferases 2 and 3 (*FUT2*/*FUT3*) influence CA19-9 levels.[208] MRI and computerised tomography may visualise early features of CCA in PSC, but difficulties in distinguishing inflammatory, benign and malignant lesions lead to suboptimal diagnostic accuracy. Combined MRI/MRC has the highest sensitivity (sensitivity 89%, specificity 75%),[205] and is preferred for the detection of small lesions.[209] PET scan does not provide higher diagnostic accuracy in diagnosing early-stage CCA, but can be of value in the staging of CCA diagnosed by another modality.[210] Invasive imaging techniques including ERC, endoscopic extra- or intraductal ultrasound and cholangioscopy are complementary to noninvasive imaging modalities as they afford the opportunity to obtain cytological and histological samples required for definitive diagnosis of dysplasia or CCA in PSC. Endoscopic ultrasound (EUS) with fine needle aspiration has shown utility in establishing the diagnosis of CCA, particularly in patients with negative brush cytology and no mass on cross-sectional imaging,[211] but as for transcutaneous biopsies, concerns have been raised over the risk of needle track tumour cell seeding. For this reason, and based on availability and local experience, practices differ regarding the use of endoscopic ultrasound with tissue sampling.[59] Peroral cholangioscopy using a thin, flexible catheter-type endoscope that allows for direct visualisation of extrahepatic bile duct strictures has shown improved diagnostic accuracy in identifying malignant strictures in sporadic CCA, but focused studies in PSC-CCA have not been performed.[59] The utility of single-operator cholangioscopy (*e.g.* SpyGlass®, Boston Scientific, USA) has been evaluated in a case series including 47 patients with PSC, where the procedure enabled targeted biopsies from otherwise inaccessible strictures, but where only one out of a limited number of three patients with CCA were diagnosed by the procedure (sensitivity 33%, specificity 100%).[212]

Given limitations in available evidence and availability of EUS and second generation cholangioscopy, ERC with biliary brushings remains the standard for obtaining tissue samples on suspected CCA in PSC (Fig. 5). While biliary brush cytology has a high specificity (97% in meta-analysis) for malignancy in PSC, it has limited sensitivity (43% in the same series).[213] The addition of fluorescent *in situ* hybridisation (FISH) for PSC increases the sensitivity (68% in meta-analysis) at the expense of specificity (reduced to 70%).[214]

Lack of accurate diagnostic modalities for detection of early stages of CCA (Box 2) and insufficient treatment strategies for advanced stages of CCA currently restrict the ability to perform effective CCA surveillance (Box 4).[215] Clinical practice varies, but proposals advise an interval surveillance strategy with annual MRI or ultrasound in combination with CA19-9 followed up by ERC, with biliary brush cytology and FISH (if available), in cases where there is a suspicion of CCA clinically and/or on imaging. Particular vigilance is required in newly diagnosed patients with PSC. The indication for and timing of liver transplantation in patients with dysplasia and no signs of CCA remain controversial.[56] Presence of dysplasia of any grade has been reported in 83% of explant livers with PSC-CCA, compared with 36% of those without CCA.[216] However, about one-third of patients with biliary dysplasia have been reported not to have CCA on follow-up and the time interval for progression from dysplasia to carcinoma is unpredictable.[216]

Liver transplantation or surgery with complete resection represent the only treatments with curative intent for CCA.[217] Liver transplantation following neoadjuvant therapy, including external beam radiotherapy combined with radio-sensitizing chemotherapy, endoluminal brachytherapy and maintenance chemotherapy can be considered in highly selected patients with unresectable, perihilar early-stage (I-II) CCA.[218] Systemic chemotherapy remains the mainstay palliative treatment modality for patients not eligible for surgery. A meta-analysis performed in overall CCA, combining the results from two randomised trials (ABC-02 [phase III], and BT22 [phase II]), provides supportive evidence for the use of gemcitabine combined with cisplatin as first-line treatment.[219–221] Chemotherapy improves the progression-free and overall survival, but the median overall survival is still only approaching one year in metastatic CCA.[219] Other palliative treatment strategies include endoscopic stenting and photodynamic therapy.[222]

**Key point**

Cholangiocarcinoma and colon cancer are dreaded complications in PSC and malignancy is currently the single most common cause of death in patients.

### *Cirrhosis*

There is presently no medical therapy proven to delay the development of liver cirrhosis in patients with PSC. There has been extensive debate as to the efficacy of UDCA,[56,57] leading to inconsistent prescription practices around the world. Whilst high-dose UDCA (28–30 mg/kg/day) is likely to be harmful,[157] there is insufficient evidence to argue for or against prescription of low-dose (13–15 mg/kg/day) UDCA.[223] In some centres, a six month trial period of low-dose (13–15 mg/kg/day) UDCA prescription is utilised, whereby a decrease in ALP levels is used as the basis for potential long-term prescription.[224] Immunosuppression may be efficacious in the subset of patients with concurrent autoimmune hepatitis. However, this is not evidence-based and any observed benefit must be weighed against the risk of side-effects. Paediatric series have documented progression of liver disease in approximately half of patients with PSC and concurrent autoimmune hepatitis.[225] Documented IAC should be treated with corticosteroids, but it is doubtful whether immunosuppression is effective

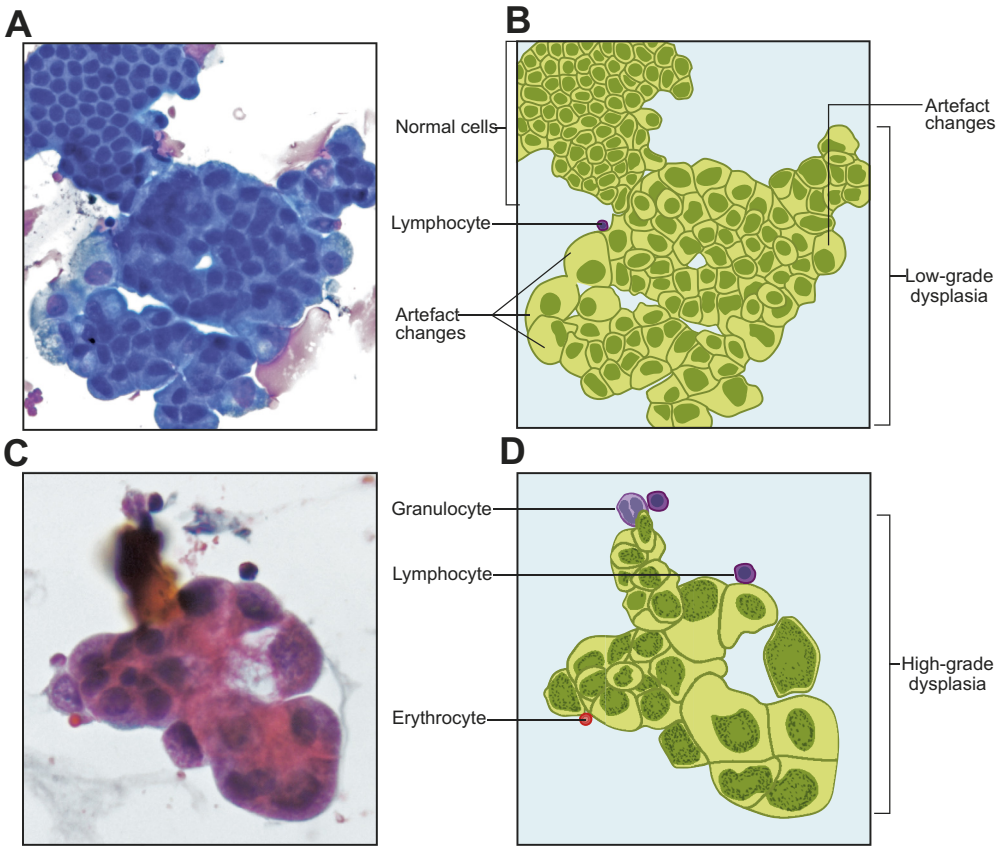



**Fig. 5. Cholangiocellular dysplasia and brush cytology in primary sclerosing cholangitis (PSC).** The classification of cholangiocellular dysplasia in PSC is mostly done according to Riddel's classification.[256] The reason for this is that the BilIN classification partly accounts for architecture, which cannot be assessed by brush cytology. Furthermore, the reproducibility of brush cytology assessments by Riddel's classification may be better, particularly for less experienced observers. Riddel's classification involves normal epithelium (upper right of top panels), indefinite for dysplasia, low grade dysplasia (lower left of top panels) and high-grade dysplasia (including adenocarcinoma) (bottom panels). As described elsewhere,[256] normal epithelium is comprised of "cobblestone" sheets of cells in monolayer with even, relatively dense chromatin pattern and no nucleoli. Low-grade dysplasia is characterised by sheets and clusters of cells with nuclear/cellular overlapping ("non-monolayer" growth), smooth nuclear shape and moderately increased nuclear/cytoplasmic ratio. High-grade dysplasia exhibits typical cell clusters with marked increases in nuclear/cytoplasmic ratio, nuclear/cellular overlapping and crowding; the nuclear membranes are irregular with signs of moulding; the nuclei show coarse chromatin with distinct and prominent nucleoli. Upper panel is stained by May-Grünwald-Giemsa, lower panel is stained by Papanicolaou. Printed with permission from Kari C. Toverud.

in patients with PSC, mild elevation of IgG4, and no IAC.

The appearance of the liver on imaging can be very abnormal in PSC, with marked atrophy of a liver lobe (usually the right) and compensatory hypertrophy of the remainder of the liver with regenerative nodules.[226] Hence, making a diagnosis of cirrhosis in PSC has largely been dependent on the finding of clinical and/or imaging features of portal hypertension or the development of complications of cirrhosis. The management and surveillance strategies used for PSC cirrhosis are similar to those used for other causes of cirrhosis and should be undertaken per standard clinical practice and guidelines. That said, the risk of HCC in PSC and PSC cirrhosis appears to be low, raising the question of surveillance intervals in PSC cirrhosis.[60] In addition, newer surveillance strategies for the development of varices dependent on TE cut-offs have not been validated in PSC and monitoring the hepatic venous pressure gradient is not recommended to assess prognosis in cholestatic cirrhosis. The presence of cirrhosis and portal hypertension in PSC may pose significant challenges to the management of associated conditions, *e.g.* colectomy and surgical resection of CCA.

### *Liver transplantation*

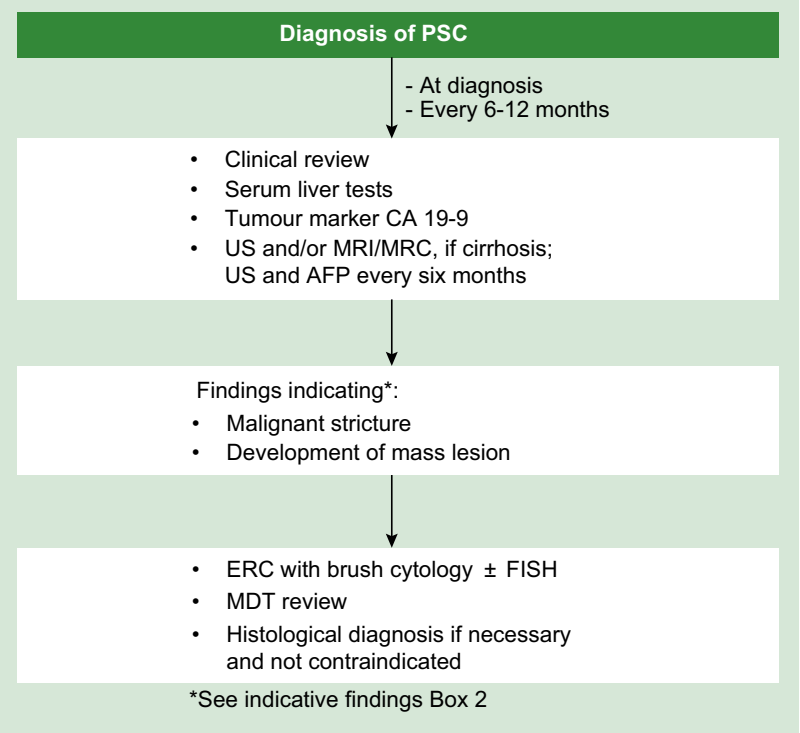
The indications for liver transplantation in PSC are similar to other liver diseases with the majority listed and transplanted with a qualifying MELD (or similar) score in a patient with cirrhosis.[227] Regional variations in practice exist. In Scandinavian practice,

liver transplantation is offered to patients with cholangiocellular dysplasia, whilst some US centres undertake liver transplantation for highly selected patients with hilar CCA. An analysis of UNOS outcomes demonstrated that patients with PSC had a lower mortality and were less likely to be removed from the list (too sick) than patients listed for other indications despite similar MELD scores.[228] This suggests that MELD may overestimate the severity of liver dysfunction in patients with PSC. Conversely, it has been argued that whilst MELD predicts waitlist mortality, the actual need for liver transplantation is poorly reflected for some patient groups (PSC included) for which MELD introduces a systematic disadvantage.[228–230] PSC patients frequently experience a poor quality of life and increased risk of disease-specific adverse outcomes, including recurrent or intractable cholangitis and the development of biliary malignancies, all poorly reflected by MELD-score based risk prediction.[228]

Overall <5% of transplants in the US are done on the basis of PSC while about 15% of those in Scandinavia are undertaken for PSC, reflecting both differences in practice and prevalence. Relatively high rates of transplantation for a rare disease like PSC reflect the progressive nature of the condition and the current lack of disease modifying treatments. Patients with PSC experience excellent outcomes after liver transplantation compared to other indications. When compared to other primary liver diseases, patients with PSC achieve the second best life expectancy after transplantation partially accounted for by the younger age of patients with PSC being transplanted.[231]

There are a number of specific management issues relevant to patients with PSC through the transplant process, including management of colitis, graft selection, anticoagulation, type of biliary anastomosis and disease recurrence. Pre-operative remission of colitis is recommended, as active disease at transplantation has been reported to predict subsequent graft failure.[232] In the MELD era, patients with PSC in the US have experienced increased waiting times for deceased donor transplantation and more frequently undergo live donor liver transplant (LDLT) compared with other indications.[233] The same group have demonstrated that patients with cholestatic liver disease have better patient and graft survival with LDLT compared to recipients from deceased donors, which would be further enhanced in an intention to treat analysis by accounting for the shorter waiting time afforded by LDLT.[234] Patients with PSC have increased peri-transplant hypercoagulability,[235] but the implication of this finding on thrombotic events remains to be established. A further peri-operative consideration is the type of biliary anastomosis, where a trend from hepatico-jejunostomy with a Roux-en-Y towards hepaticoduodenostomy and duct-to-duct has been seen. A meta-analysis of published case-control studies suggested lower rates of cholangitis in patients with a duct-to-duct anastomosis compared to patients undergoing a bilio-enteric anastomosis.[236]

**Box 4. Suggested surveillance algorithm for cholangiocarcinoma in primary sclerosing cholangitis (PSC).** At present no validated algorithm for cholangiocarcinoma surveillance in PSC has been established. The suggestion is not evidence-based and the topic in sore need for further research. See main text for established surveillance strategies for colorectal- and gallbladder carcinoma in PSC.




AFP, alpha-fetoprotein; ERC, endoscopic retrograde cholangiography; FISH; fluorescent *in situ* hybridisation; MDT, multidisciplinary team, MRI/MRC, magnetic resonance imaging/magnetic resonance cholangiography; US, ultrasound.

In keeping with other autoimmune liver diseases, early and late cellular rejection are more common after liver transplantation for PSC,[237] hence immunosuppression combining long-term steroids, a calcineurin inhibitor with a third agent (*e.g.* azathioprine or mycophenolate) is used in many transplant programmes. However, evidence-based guidance regarding the optimal immunosuppressive regimen in PSC is lacking, and informal surveys have revealed large variations in current practice (ranging from mono to triple immunosuppression long-term). With recent advances in HCV treatment, PSC is now the most common disease to recur after liver transplantation. Variable frequencies of recurrent PSC after liver transplantation have been reported in the literature (range 6–60%), however, a frequency of around 20% is most commonly seen.[237] An observation that colectomy prior to liver transplantation is associated with a lower risk of PSC recurrence has been reported from multiple UK centres.[238] Although many other single centre reports have been made, no single factor has consistently been reported to impact on the risk of recurrent PSC.[237,239] As for PSC *per se*, no medical

**Key point**

The optimal regimen for immunosuppression in PSC patients after liver transplantation is not clear, and disease recurrence and IBD exacerbations often occur.

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**Box 5. Suggested surrogate endpoints for clinical trials in primary sclerosing cholangitis (PSC).**

| Rank | Surrogate marker | Comments | Strength of recommendation |
|---|---|---|---|
| 1 | ALP | ***Potential surrogate endpoint:*** Several observational studies suggest that ALP is a surrogate marker for transplant-free survival. ALP has been employed in all clinical trials in the past two decades (primary endpoint in over 40% of studies), but outcomes are conflicting with regard to the utility as a surrogate parameter for clinical efficacy of ursodeoxycholic acid. ALP is deemed a useful parameter for stratification of patients in clinical trials, although thresholds need to be clarified. | Level 4, RG D |
| 2 | TE | ***Potential surrogate endpoint:*** Two independent studies have demonstrated that baseline measurements and rate of progression of liver stiffness measurements by TE were strongly and independently linked with patients' outcomes, suggesting that TE may be an attractive surrogate endpoint. | Level 2b, RG C |
| 3 | Histology | ***Potential to be a robust surrogate endpoint:*** Histology has been used as an outcome parameter in 12 of 26 studies in the past 20 years. Histology is considered less undulating than serum tests; the impact of sampling variability is debated. The invasiveness of the procedure is a disadvantage, whereas its potential for revealing the mechanism of action of the investigational drug is an advantage. Available data indicate that histology is a useful stratification tool for clinical trials in addition to its value as an outcome parameter. | Level 2b, RG B |
| 4 | ALP + histology | ***Explorative surrogate endpoint:*** In the absence of a convincing single-surrogate endpoint, combining multiple endpoints (either as composite or co-primary endpoints) is considered advisable and should be explored further. | Level 5, RG D |
| 5 | Bilirubin | ***Unlikely to be suitable:*** Serum bilirubin is part of several prognostic scoring systems and consistently associated with clinical outcome in PSC. However, it only rises permanently in late-stage disease and temporary increases may be due to intercurrent events not reflecting long-term outcome. Hence, it was deemed unlikely to be suitable for clinical trials. | Level 2b, RG C |

Through a Delphi process of reiterating consensus rounds, experts in the field within the International primary sclerosing cholangitis (PSC) Study Group (IPSCSG) in 2016 produced and published a shortlist of suggested surrogate endpoints for clinical trials in PSC.[176] Ranking was determined by the top three preferences of each panelist among the original 19 endpoints. The proposed surrogate endpoints were scored according to an acknowledged hierarchy of surrogate endpoints (Level 1: True clinical-efficacy measure; Level 2: Validated surrogate endpoint; Level 3: Non-validated surrogate endpoint, yet established to be reasonably likely to predict clinical benefit; Level 4: Correlate that is a measure of biological activity, but not established to be at a higher level) and the OCEBM grades of recommendation (RG; A: Consistent level 1 studies; B: Consistent level 2 or 3 studies or extrapolations from level 1 studies; C: Level 4 studies or extrapolations from level 2 or 3; D: Level 5 evidence or troubling inconsistent or inconclusive studies of any level). ALP, alkaline phosphatase; TE, transient elastography.

interventions are currently available to prevent the progression of recurrent PSC, which is ultimately associated with significantly reduced graft and patient survival.[238]

*IBD and colorectal neoplasia in PSC*

PSC-IBD, whether considered UC or Crohn's (Fig. 3), is almost universally colonic (usually a pancolitis), with a right-sided predominance, backwash ileitis and rectal sparing (Fig. 1).[240] Thus, a complete ileocolonoscopy is warranted in all patients with PSC. Current guidelines recommend 5-yearly colonoscopies to survey for colitis in patients with PSC and without known colitis, with routine biopsies recommended to increase the detection of IBD.[56,59] In the absence of more specific guidelines, patients with PSC-IBD should receive medical treatment according to general IBD guidelines.[57] That said, because of the milder symptoms associated with PSC-IBD there may be a tendency to underestimate the extent and activity of mucosal inflammation. Hence, IBD associated with PSC may be an undertreated condition. Whilst limited data exists, there is currently no evidence of harm associated with the available therapies for IBD (including biological therapies) to contraindicate their use in PSC. The role of UDCA as chemoprophylaxis against colorectal cancer in PSC-IBD remains unsettled.[56,57]

The increased risk of colorectal cancer in PSC-IBD justifies a strict surveillance strategy of yearly colonoscopy from the time of diagnosis for patients with PSC-IBD.[59] Dye-based chromoendoscopy is being increasingly recommended to facilitate detection of flat lesions with dysplasia.[56,57,209,241,242] In addition to targeted biopsies, non-targeted four-quadrant biopsies from all colonic segments and the terminal ileum should, in general, be performed, but can be omitted in follow-up ileocolonoscopies conducted by appropriately trained hands in the situation of quiescent disease and adequate bowel preparation.[241,243]

Surgical management of PSC-IBD may be required before or after liver transplantation. Both pancolectomy with ileostomy and colectomy with ileal pouch anal anastomosis are feasible and effective. While pouchitis is more common for patients with PSC-IBD, compared to patients with UC alone,[240,244] both short and long-term outcomes are favourable and many patients find an ileo-anal pouch more acceptable. The alternative of pancolectomy with ileostomy is associated with a risk of peristomal varices. Surveillance of the rectal stump is mandatory if not resected. After transplantation, approximately one-third experience deterioration in their IBD with the remainder having no change or an improvement.[245] Pre-transplant colectomy cannot be recommended routinely, but the increased risk of malignancy and potential role of active disease in development of PSC recurrence warrant considerations when colectomy may otherwise be indicated.

*Osteoporosis*

Cholestatic diseases predispose patients to metabolic bone disease and bone mineral density examinations are recommended at diagnosis and regular intervals thereafter by the European Association for the Study of the Liver (EASL) and the American Association for the study of Liver Diseases (AASLD) guidelines.[56,57] Dietary supplementation with vitamin D and calcium may be considered in patients with PSC, in the lower normal-range of vitamin D concentrations (<50 nmol/l). Treatment of osteoporosis follows general guidelines and specific evidence pertaining to efficacy in patients with liver disease is scarce.[246]

*Cause of death in PSC*

There was a fourfold increased risk of mortality in patients with PSC compared to the general population in a large population based cohort.[34] The median survival until liver transplantation or PSC-related death in this cohort was of 21.3 years, as opposed to 13.2 years in a tertiary referral cohort from the same geographical area.[34] The most frequent causes of PSC-related death were CCA (32%), liver failure (15%), transplant-related complications (9%) and colorectal cancer (8%), demonstrating that a major impact on life expectancy is imposed by the increased risk of malignancies in PSC.

## Summary and future directions

PSC remains a considerable clinical challenge despite the many scientific advances made over recent years. The lack of effective medical therapy to arrest disease and manage symptoms necessitates invasive treatment (endoscopy and liver transplantation) as the mainstays of management. Co-morbidities add to disease burden, particularly IBD and the unpredictable risk of cancer. Diagnostic tools to gauge disease activity and cholangiocellular dysplasia would be extremely helpful, but are currently in their infancy. Research is needed in many areas, including biliary and bowel complications after liver transplantation. These unmet needs make PSC one of the major remaining challenges in hepatology.

Whilst genetic studies have positioned PSC alongside other autoimmune diseases, the translational value of this observation remains unclear. The possibility of an environmental driver of the autoimmune features, similar to coeliac disease, remains a possibility.[87] PSC-centred studies on the individual gene findings are awaited to clarify whether the wealth of biologics currently available for other autoimmune and immune-mediated diseases might hold re-purposing opportunities in PSC. It is a time of particular activity for clinical trials in PSC with the majority of clinical trials focussed on cholestatic and fibrotic targets (*e.g.* *nor*UDCA, anti-LOXL2, obeticholic acid and other FXR agonists, ASBT inhibition), with some emerging interest in therapeutic targeting of the gut microbiota (*e.g.* faecal transplantation, long-term non-absorbable antibiotics) and T lymphocyte homing (*e.g.* anti-VAP1, vedolizumab). The *nor*UDCA phase II trial demonstrated a dose-dependent reduction of ALP in patients receiving 500–1500 mg *nor*UDCA compared with placebo.[247] The results from the simtuzumab trial have been published in abstract form and were essentially negative.[248] The effects of the other interventions are currently unknown. As shown in Fig. 2, the complex multistep process ultimately resulting in PSC is likely to involve all aspects currently being targeted. The outcomes of the ongoing clinical trials may help determine which principle approaches are likely to be most effective. The different pathophysiological components may also need targeting in parallel for efficacy to be obtained, meaning that ultimately a combination of conceptually different drugs is potentially needed.

We can only predict incremental discoveries in science. In the near future, implementation of biomarker research and advances in imaging technologies (both MRI and ultrasound) are likely to address major limitations related to diagnosis, prognostication, surveillance and the gauging of treatment effects in PSC. Studies of the gut microbiota in PSC are rapidly evolving,[20] and are likely to open up major new areas of research, improving our understanding of PSC pathophysiology. Game-changing discoveries will elucidate the causes of PSC and its associated malignancies, but where among the candidate areas (Fig. 2) such discoveries should be sought is speculation. Together, the many challenges create considerable research opportunities for clinical and basic scientists alike, and will keep a small and enthusiastic specialist community busy for years to come.

**Key point**

Ongoing clinical trials in PSC target different mechanistic compartments (*e.g.* bile acid therapies, anti-fibrotics, biologics, antibiotics) and may provide proof-of-concept for future development of an effective therapy.

## Conflict of interest

TK, TF, DT declare no conflict of interests in relation to this manuscript. MV reports personal fees from Intercept.

Please refer to the accompanying ICMJE disclosure forms for further details.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2017.07.022.

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